Medical Radiology
Radiation Oncology
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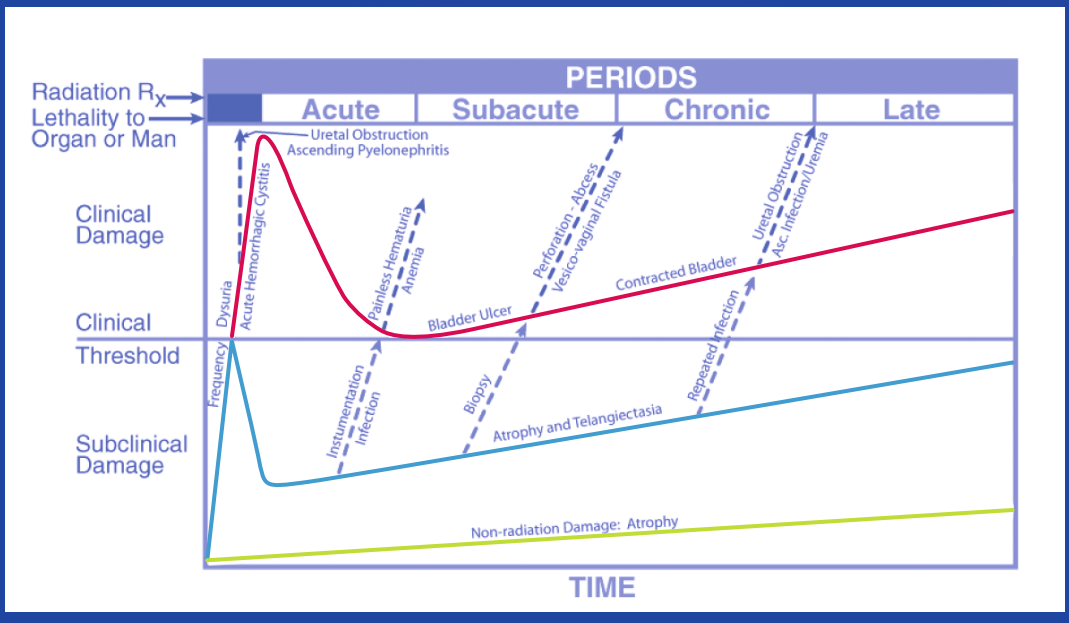
Editors

ALERT – Adverse Late Effects of Cancer Treatment

Volume 2: Normal Tissue Specific Sites and Systems



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ALERT – Adverse Late Effects of Cancer Treatment

Volume 2: Normal Tissue Specific Sites and Systems

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This volume recognizes our patients…
Cancer Survivors who have benefited from the treatment and lived with its consequences

"To save one life is to save the whole world"

Talmud

I dedicate this book to my long-time friend Mayer Mitchell (Bubba), who recently succumbed to cancer and the late effects of cancer therapy. Mayer's life epitomized the challenges of a cancer survivor. He had stage IV Hodgkin's disease, Breast cancer, Prostate cancer, Urinary Bladder cancer, and Rectal cancer. Each cured cancer was followed by a radiation/ chemotherapy-associated complication. Nevertheless, he endured and, with his brother Abe, built thousands of homes, shopping centers in five southern states over five decades.

Philip Rubin

I dedicate this book to my many teachers and mentors. My parents were both teachers in the NYC public schools and I grew up with a strong sense of respect for teachers. As I have always been drawn to the physical sciences, I have particularly fond feelings towards many instructors in math, chemistry, physics and engineering. At the completion of my third year of medical school at the University of Rochester (in New York), I could not envision practicing in any one of the core clinical specialties; I missed the quantitative aspects of the physical sciences. While I was contemplating a career change to become a math teacher, my then girl friend (now wife) Caryn, who

was also a medical student at Rochester, said to me, "I heard a talk today from someone who is a radiation oncologist, you should go talk to them, I think you might like that field." Serendipity. And she was right! My subsequent visit to the radiation oncology department started my >30 year relationship with Dr. Rubin. As a student at Rochester, I have fond memories of shadowing Dr. Rubin on Wednesday afternoons. As I remember it, he used to see all of the patients under treatment in his department each week. So, the patients all had two "weekly checks"; one with their primary treating radiation oncologist, and a second with Dr. Rubin. He used to take great pride in explaining the rationale for the radiation treatment, and always emphasized the need to understand the risks of the radiation treatment when choosing fields and doses. Over the next three decades, Dr. Rubin proved to be a great mentor, role model, and friend. He has supported and nurtured my interests in radiation-induced normal tissue injury; e.g. getting me involved with his LENT-SOMA initiatives and helping me to formulate ideas and projects. Helping to write a book with Dr. Rubin, who has helped our field understand so much about the effects of radiation, has been and honor. Thank you Phil. Thanks also to Sandy Constine- a long-time friend and colleague. Sandy has made tremendous contributions to better understand the effects of radiation, particularly in children. Your dedication to ameliorating pediatric late effects is inspiring. I am glad that we were able to help Phil with this book- published approximately 35 years after Phil's landmark contribution Clinical Radiation Pathology (published with George Casarett). This book proved to be a labor of love for us all.

I am thankful to all who contributed to this book; the authors, editors, administrative assistants, and our publisher. Your efforts and expertise are much appreciated. Thank you to my many excellent teachers and mentors throughout school, including college (Cooper Union), medical school (University of Rochester), internship (Sinai Hospital of Baltimore) and residency (Mass General). Thanks also to my many colleagues at UNC and Duke for providing a fertile and productive environment, and for serving as teachers and mentors. Special thanks to Drs. Leonard

R. Prosnitz, Edward C. Halperin and Gustavo S. Montana for their mentorship and guidance. Thank you to my family for their support: to my parents (Hyman and Helen Marks), to my wife Caryn- whose love, caring and encouragement are ongoing sources of strength, and to our three children (Noah, Samuel and Benjamin).

Lawrence B. Marks

"For the person fighting cancer, each day is precious and must be faced with courage. For the physician, each patient is an inspiration. For the survivor of cancer, the world is full and each day is a celebration."
I wrote these words many years ago, and continue to reflect on the many sources of inspiration that grace my life. I feel tremendous gratitude for my good fortune to work in a field and live a life that refreshes my spirit on a daily basis. This book honors the memory of our patients who did not survive cancer, but also those who have faced mortality but found a way to embrace all that life offers. A friend of mine once said: "That is the essence of surviving cancer—making your life a passionate statement instead of just marking time."
I am surrounded by individuals who have helped me understand the wonder of my life, and afforded me the opportunity to contribute what I can. Philip Rubin, a giant in our field, towers above all others in my professional life. On a snowy night in Rochester 32 years ago he persuaded me to join his faculty by clearly outlining my future…one in which he would work with me to fulfill whatever personal destiny I might have. He defined the trait that I value above all others, curiosity. He combined that with enthusiasm and creativity, and a drive to benefit others. I have strived to emulate this great man. I have been fortunate to have other mentors who also demonstrated these qualities, notably John Felstiner who was my English teacher at Stanford, Leigh Thompson who was a professor at The Johns Hopkins medical school, Archie Bleyer during my fellowship in Pediatric Oncology at the University of Washington, Sarah Donaldson during my residency in radiation oncology at Stanford, and Edward Halperin and Larry Marks who have been friends and colleagues during many

of these years. However, I am also appreciative of the many young physicians, nurses, social workers, and others who are focused on improving the lives of cancer patients and enable me to do my job.
My personal life has been graced by the lady who I met 42 years ago, and then married 41 years ago. Sally has a spirit of giving to others that cannot be extinguished, and on a daily basis rekindles my flame. The joy that we both receive from our remarkable children, Alysia and Josh, fills us and affirms the relevance of our lives. For me, they demonstrate the gifts that life affords, and foster my dedication to provide my patients with the opportunity to live their lives as fully as possible.

Louis S. Constine

Foreword

The publication in 1968 of the book by Rubin and Casarett entitled *Clinical Radiation Pathology*, in Volumes I and II, represented a hallmark statement regarding the late effects related to radiation therapy.

The new text by Rubin and his co-workers comprehensively documents contemporary understanding of the adverse late effects of cancer treatment in a coherent, multidisciplinary approach related to the care of cancer survivors. All major organs are affected by the treatment program, whether it be radiation, chemotherapy, or surgical treatment, and these impacts must be taken into consideration in any discussion on what might be the most appropriate treatment in cancer management. Modern cancer treatment is clearly based on safe intensification of radiation therapy, chemotherapy, and biologic modifiers. Not only has this resulted in a significant general increase in survivorship (e.g. to 64 %) for cancer overall, but the survival rate is considerably higher for selected malignancies, such as 87 % for breast cancer and 80 % for childhood cancers. Malignancies resistant to therapy have necessitated the utilization of aggressive treatment approaches associated with improvement in survivorship but also with increased risk of normal tissue complications. Late effects can occur years after the cessation of the treatment regimen, tending to arise earlier with radiation therapy than with chemotherapy. The present text, reflecting more recent publications, offers landmark statements with regard to the potential for such effects, the general concepts and principles relating to their development, and the dynamic interplay among molecular cytologic and histopathologic events. There is now much greater awareness that modern cancer treatment leads to not only physiologic and metabolic abnormalities, but also clinical manifestations that dictate the need for innovative new aggressive programs of management.

Without question the present text represents a dramatic step forward from the original Rubin/Casarett text, with more emphasis on the contemporary situations that each oncologist faces in their practice on a day-to-day basis. The efforts on the part of Rubin and his colleagues have borne fruit. This new book provides readers with significant information about late effects and how they might be managed. It is recommended for inclusion on the shelf of every oncologist and should be at the forefront of practitioners' minds when considering the various treatment regimens.

Luther W. Brady, MD
Hans-Peter Heilmann, MD
Michael Molls, MD
Carsten Nieder, MD

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The editors are grateful for the tremendous effort of Sisi Lisa Chen, our managing editor. She indeed was the glue that held all the pieces of this effort together. She nurtured the elements through their gestation and now its birth.

Global Acknowledgements

The editors sought to create a comprehensive book covering a wide array of information. As such, we relied heavily on prior works addressing similar topics, including many works that we helped to create. Portions of this book were adopted, with permission, from the following sources:

Special Issue of the Int J Radiat Oncol Biol and Phys from March 30, 1995 dedicated to the SOMA (subjective, objective, management, analytic) system to assess Late Effects of Normal Tissues (LENT). This initiative aimed to better standardize the manner in which normal tissue effects are quantitatively scored.

Special Issue of the Int J Radiat Oncol Biol and Phys from March 1, 2010 dedicated to QUANTEC (quantitative Analysis of normal tissue effects in the clinic). This initiative aimed to summarize the available dose/volume/outcome data for normal tissue effects.

Rubin and Casarett's textbook, Radiation Pathology, from 1968. This book offered a comprehensive summary of the effects of radiation on normal tissues.

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Zhang, Shu-Xin. An Atlas of Histology. New York: Springer-Verlag Inc.; 1999. Dr. Marks is supported by NCI Grant CA69579.

Updated and Supplemental Information

Interested readers are encouraged to view additional information from other sources including:

Common Terminology Criteria for Adverse Events (CTCAE) from the U.S. Department Of Health And Human Services (National Institutes of Health and National Cancer Institute). This report provides a grading system for the common toxicities. It is updated periodically with the last update, version 4.03, published June 14, 2010. Available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

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Introduction

Our country formally declared war on cancer four decades ago. While many skirmishes have been won, the battle rages on. Far too many patients still succumb to cancer. Nevertheless, an increasing number of patients are successfully treated, and the population of cancer survivors is increasing. An estimated 13.7 million Americans (almost 4 % of the United States population) were living with a history of cancer on January 1, 2012. By January 1, 2022 that number is expected to increase to nearly 18 million (Siegel et al. 2012). Overall, approximately 65 % of adults will survive their malignancy, and this is much higher for selected cancers such as breast and the lymphomas.

Living beyond cancer should be cause for celebration. However, cancer survivors are vulnerable to the late effects of their therapy. They have complicated needs including physical problems, financial obstacles, and mountains of emotions that must be addressed. All of these hurdles can compromise the quality of life of cancer survivors and their family.

The modern era of cancer therapy is predicated on the safe intensification of radiation, chemotherapy, and biologic adjuvants. Malignancies resistant to therapy have demanded an aggressive treatment approach that often resides on the edge of normal tissue tolerance, or even exceeds tolerance to some "acceptable" degree. Clearly, the potential to ameliorate or prevent such normal tissue damage, or to manage and rehabilitate affected patients, requires an understanding of tissue tolerance to therapy. Because "late effects" can manifest months or years after cessation of treatment, therapeutic decisions intended to obviate such effects can be based only on the probability, not the certainty, that such effects will develop. In making such decisions, the balance between efficacy and potential for toxicity should be considered and may be influenced by host-, disease-, and treatment-related risk factors. The determination of the frequency and pathogenesis of late effects is difficult for several reasons: (a) patients must survive long enough for damage to develop, (b) the number of patients both affected and unaffected by therapy must be known, and (c) the latent period to the manifestation of damage compromises discernment of the responsible component of multimodality therapy. Further complicating our understanding of organ tolerance to therapy is that tumor and host factors interact with therapy in the causation of late effects.

This book represents a monumental effort by numerous experts on the adverse consequences of radiation and chemotherapy. It was inspired by our patients, both those fortunate enough to have survived, but also those who did not. For our survivors, it is our responsibility to understand, mitigate, treat, and prevent their "late effects." However, this book was also inspired by our mentor, Philip Rubin. With George Casarett (Rubin and Casarett 1968), he pioneered the field of radiation-associated normal tissue damage. At a time when many radiation oncologists were satisfied to be effectively combating cancer, Phil Rubin recognized that the *quality* of survival after cancer was paramount. He was driven to teach his colleagues and emerging oncologists the critical need to appreciate normal tissue toxicity and the pathophysiology by which it evolved. At the University of Rochester, he successfully obtained a succession of program project grants to study normal tissue toxicity. It has been his lifelong goal to educate future generations of oncologists about the power and also the consequences of cancer therapy. His motto was always:

"there is no free lunch." Finally, he encouraged numerous protégé to follow in his footsteps. His inspiration to oncologists, pathologists, and biologists throughout the world has allowed for the safe treatment of an uncountable number of patients.

Louis S. Constine, MD, FASTRO
Lawrence B. Marks, MD, FASTRO

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Brain and Cranial Nerves

Susannah Yovino, Young Kwok, and William F. Regine

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Abstract

- *Anatomy*: Gross examination of the CNS reveals two distinct types of tissue (gray and white matter), which are also easily visible on MRI.
- *Histology*: Population of pluripotent neural stem cells (capable at least in vitro of dividing into neurons, astrocytes, and oligodendroglia) exists throughout the brain and spinal cord.
- *Pathophysiology*: No discrete lesion is pathognomonic for radiation injury to the CNS, which is classically associated with pathologic changes common to most other mechanisms of CNS injury, including demyelination, malacia (decrease in white and gray matter volume), gliosis (scarring), and vascular damage.
- *Pathogenesis*: Damage to endothelial tissue within the CNS appears to play a key role in post-radiation demyelination. This was elegantly demonstrated by a boron neutron capture experiment.
- *Biology*: An increase in vascular endothelial growth factor (VEGF) production, triggered by blood–brain barrier (BBB) disruption, appears to play a key role in the pathogenesis of white matter lesions.
- *Clinical Syndromes*: Brain radiation has been frequently cited as the major cause of neurocognitive decline in cancer patients. All were treated in a fashion that would significantly increase the risk of late radiation toxicity, i.e., large daily fractions and concurrent radiosensitizer.
- *Special Topics*: Exposure of the fetal nervous system to ionizing radiation between the gestational ages of 8–25 weeks is associated with microcephaly and mental retardation. An exposure of 1 Gy at the most sensitive gestational age of 8–15 weeks is associated with an estimated 43 % risk of mental retardation. Neurocognitive and neuropsychologic consequences of brain radiation in children may occur in up to 50 % of children who undergo brain radiation. Radiation-induced dementia associated with diffuse leukoencephalopathy is

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characterized by depression, emotional lability, and deficits in memory and attention which progress to gait disturbance and incontinence in approximately 80 % of patients.

- *Detection Diagnosis*: Magnetic resonance imaging (MRI) is a sensitive imaging modality for white matter lesions. Both the incidence and severity of white matter lesions in the brain are directly related to increasing RT dose and worsen with time.
- *Diagnosis*: CNS radionecrosis is a focal, well-circumscribed lesion that develops in regions of the brain near the primary tumor that have received high doses of radiation.
- *Management*: Corticosteroids are the mainstay of treatment for many radiation-induced CNS toxicities, including radiation necrosis, cranial nerve palsy, and peripheral neuropathy.

Abbreviations

ALL	Acute lymphoblastic leukemia
BBB	Blood–brain barrier
COWAT	Controlled oral word association test
CNS	Central nervous system
CTCAE	Common terminology criteria for adverse events
HVLT	Hopkins verbal learning test
HBO	Hyperbaric oxygen
LENT–SOMA	Late effects normal tissue task force–subjective, objective, management, and analytic
MRI	Magnetic resonance imaging
MMSE	Mini-mental status exam
NHL/CLL	Non-Hodgkin lymphoma and chronic lymphocytic leukemia
PNS	Peripheral nervous system
POMS	Profile of mood states short form
TMT	Trail making test
WM	White matter
VEGF	Vascular endothelial growth factor

1 Introduction

Radiation toxicity in the central nervous system (CNS) is potentially devastating. Recent advances in imaging, treatment planning, and molecular biology have increased our understanding of the pathophysiology of this complex process. This chapter will review the anatomy and biology, pathophysiology, imaging characteristics, and clinical findings characteristic of radiation-induced neurotoxicity. The biocontinuum of radiation-induced acute, subacute, chronic, and late effects is illustrated in Fig. 1.

2 Functional Anatomy and Histology

2.1 Anatomy

The nervous system is primarily divided into the central nervous system (CNS), which consists of the brain and spinal cord, and the peripheral nervous system (PNS). Gross examination of the CNS reveals two distinct types of tissue (gray and white matter), which are also easily visible on MRI. Gray matter is made up of neuronal cell bodies and their supporting glial cells and is concentrated in the cerebral cortex, cerebellum, and interior of the spinal cord. Within the white matter, clusters of gray matter form islands such as the basal ganglia, thalamus, cranial nerve nuclei, and multiple other critical structures. White matter consists primarily of axons, with glial cells interspersed among the axonal processes, and gains its white color from the axons' myelin coating.

The brain is further subdivided into the cerebrum, cerebellum, and brainstem (Fig. 2). The cerebrum controls voluntary movement, sensory processing, speech, memory, and cognition, while the cerebellum is involved in the integration of motor and sensory function as well as balance and motor coordination. The brainstem controls involuntary vital functions such as respiration, plays a role in the regulation of consciousness and the sleep/wake cycle, and contains the nuclei of cranial nerves III–XII. All neural pathways between the brain and spinal cord also pass through the brainstem. The spinal cord is divided craniocaudally into 31 spinal nerves which carry motor and sensory innervation to the entire body, with the exception of the territories in the head and neck supplied by the 12 cranial nerves. The spinal cord is also functionally separated in the axial plane into ascending (sensory) and descending (motor) pathways.

The peripheral nervous system is comprised of all other neural structures outside the spinal cord and includes the somatic nervous system (supplying voluntary motor control to the muscles and returning sensory information to the spinal cord and brain) and the autonomic nervous system (responsible for regulation of involuntary functions such as heart rate, respiration, blood pressure, and digestion).

2.2 Histology

The neuron is well established as the primary structural and functional cell of the nervous system. A variety of glial cells exist as "support cells" in both the central and peripheral nervous system. Oligodendrocytes and Schwann cells are the myelinating cells of the CNS and the PNS, respectively. Our understanding of the role of astrocytes, the most numerous type of glial cells, continues to evolve, but they

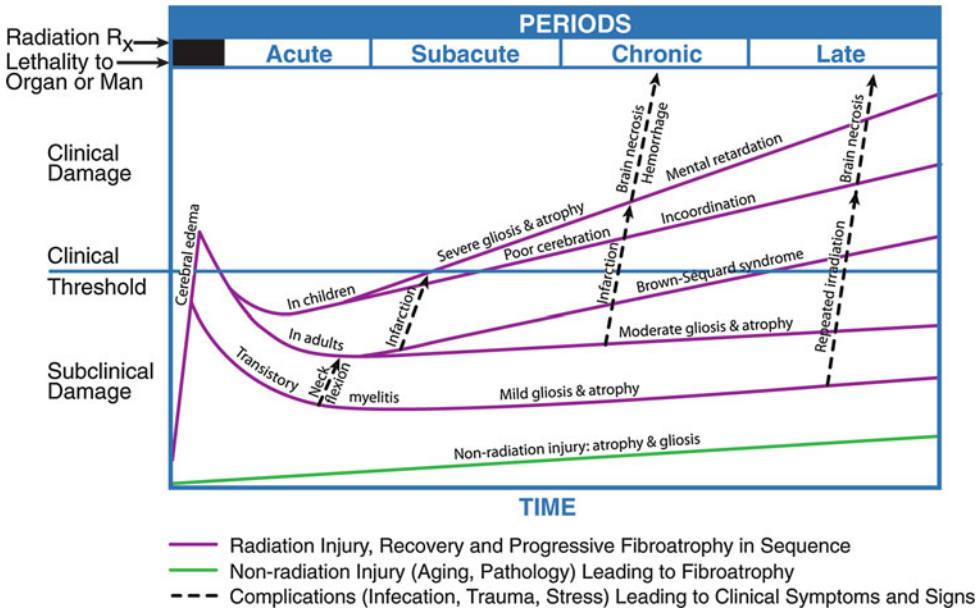


Fig. 1 Biocontinuum of radiation induced acute, subacute, chronic, and late effects in the CNS (with permission from Rubin and Casarett 1968)

have an established function as part of the blood–brain barrier (BBB), as mechanical support cells within the CNS, in the metabolism of neurotransmitters and ions such as calcium and potassium, and as the main mediators of gliosis, the response to injury in the brain parenchyma. Ependymal cells line the ventricles of the brain as well as the central canal of the spinal cord and produce cerebrospinal fluid (CSF). Microglia, derived from a monocytic (hematopoietic) cell lineage, are the primary phagocytes of the CNS and play a role in acute brain injury (Fig. 3a, b).

Although neurons themselves are likely incapable of mitotic division, the adult human brain has recently been established to have a neuron-generating stem cell compartment, contradicting previously held dogma. Neurogenesis has been constitutively demonstrated within the dentate gyrus of the hippocampus as well as the subventricular zone and olfactory bulb, and a population of pluripotent neural stem cells (capable at least in vitro of dividing into neurons, astrocytes, and oligodendroglia) exists throughout the brain and spinal cord. Regenerative neurogenesis in response to injury has been demonstrated in the corticospinal tract, neocortex, and striatum. These cell populations are the subject of intense research (Emsley et al. 2005).

3 Biology, Physiology, and Pathophysiology

3.1 Radiobiology of the Central Nervous System

The pyramidal cells are the major neurons of the brain. They are considered post-mitotic cells and as such are unable to be replaced. However, there is evidence of a stem cell region in the brain, located in the hippocampus, which may be capable of regenerating neurons (as illustrated in Fig. 4).

Classical radiobiology teaches that CNS tissue is a "late-responding" tissue, characterized by a low α/β ratio, delayed manifestation of radiation injury, and extreme variability in response as the fraction size is altered (Hall 2006a). Recovery of neural tissue from radiation injury was predicted by this model to be extremely limited. This has been contradicted by a landmark study in rhesus monkeys published by Ang et al. (2001). Rhesus monkeys were re-irradiated at varying doses (44 Gy followed by either 57.2 or 66 Gy) at varying time intervals (1 or 2 years). The animals were then observed for up to 66 months. Histologic studies of the monkey spinal cords suggested significant repair at one year, with recovery continuing to increase through the third year following reirradiation. A dose-response relationship predictive for myelopathy was also observed. From these data, the authors extrapolated conservative estimates of human spinal cord recovery from myelopathy, following an initial dose of 45 Gy, as 50, 60, and 65–70 % at 1, 2, and 3 years, respectively.

Structural differences between the brain and spinal cord result in a major difference in radiation tolerance between the two tissues. Within the brain, islands of eloquent tissue are intermingled with large areas of brain parenchyma which can be significantly damaged or even removed without compromising essential functions. Consequently, many areas of the brain can tolerate high doses of focal radiation without the development of catastrophic damage. In contrast, the spinal cord is a tightly compacted cable of tissue, nearly all of which is functional. Transection or damage to one segment of the spinal cord results in loss of

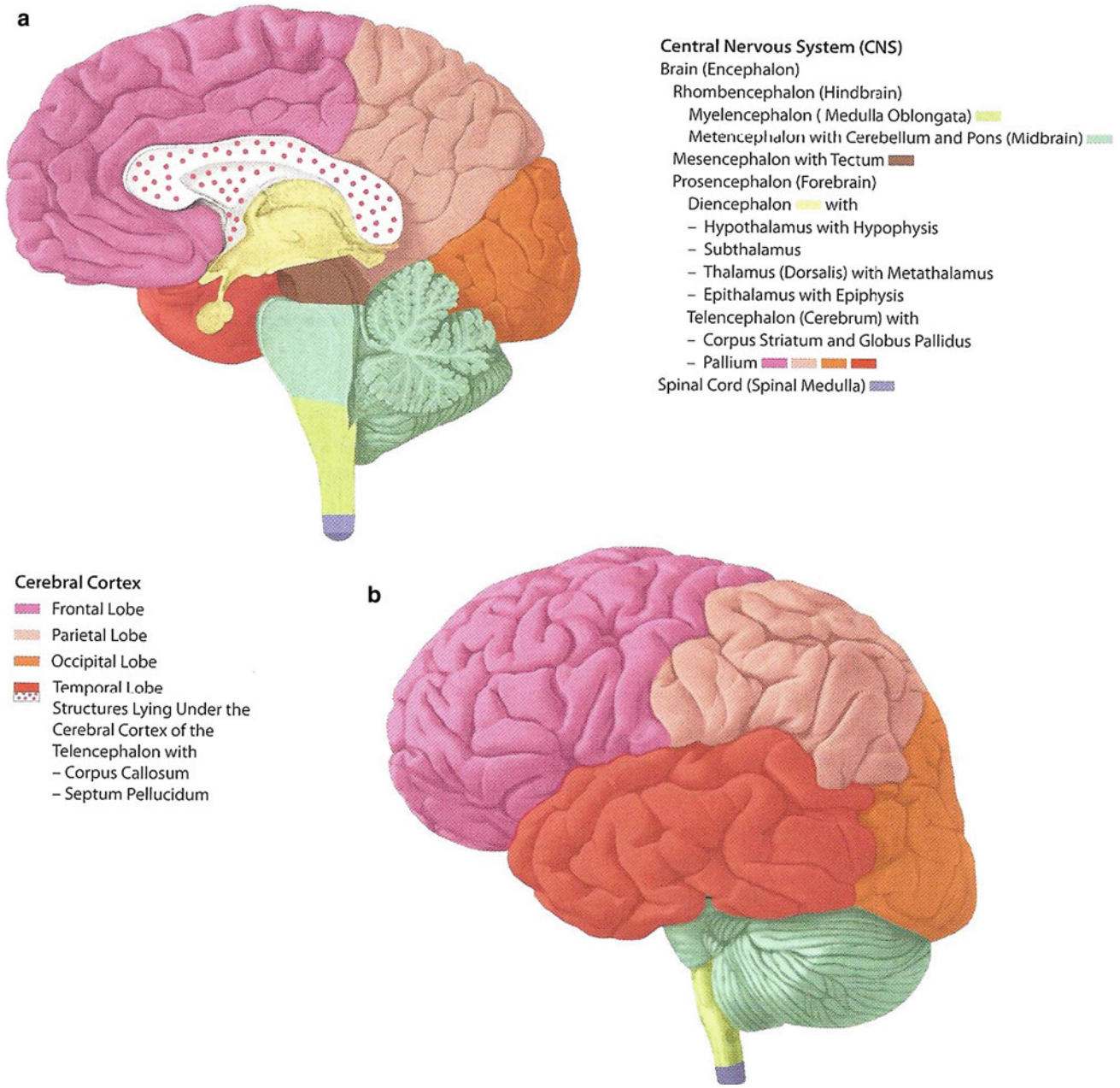


Fig. 2 Different regions of the brain are shown. **a** Medial view: Median sagittal section; **b** Left lateral view (with permission from Tillman 2007)

all downstream function of the cord, which has important implications for radiation dose prescription and treatment planning (Fig. 5).

3.2 Pathology and Pathophysiology of Radiation Damage Within the Nervous System

No discrete lesion is pathognomonic for radiation injury to the CNS, which is classically associated with pathologic changes common to most other mechanisms of CNS injury, including demyelination, malacia (decrease in white and gray matter volume), gliosis (scarring), and vascular damage. Foci of liquefactive necrosis associated with significant edema and gliosis may develop in areas receiving high doses of radiation. Figure 6a, b illustrates key features of radiation necrosis. Glial and endothelial cells appear to be the key target cells for radiation damage in the CNS. Because adult neurons are not actively dividing cells, radiation damage to neurons at typical therapeutic doses is therefore unlikely to contribute significantly to CNS toxicity. However, increasing evidence suggests that neural stem cells, an actively dividing cellular compartment, may be

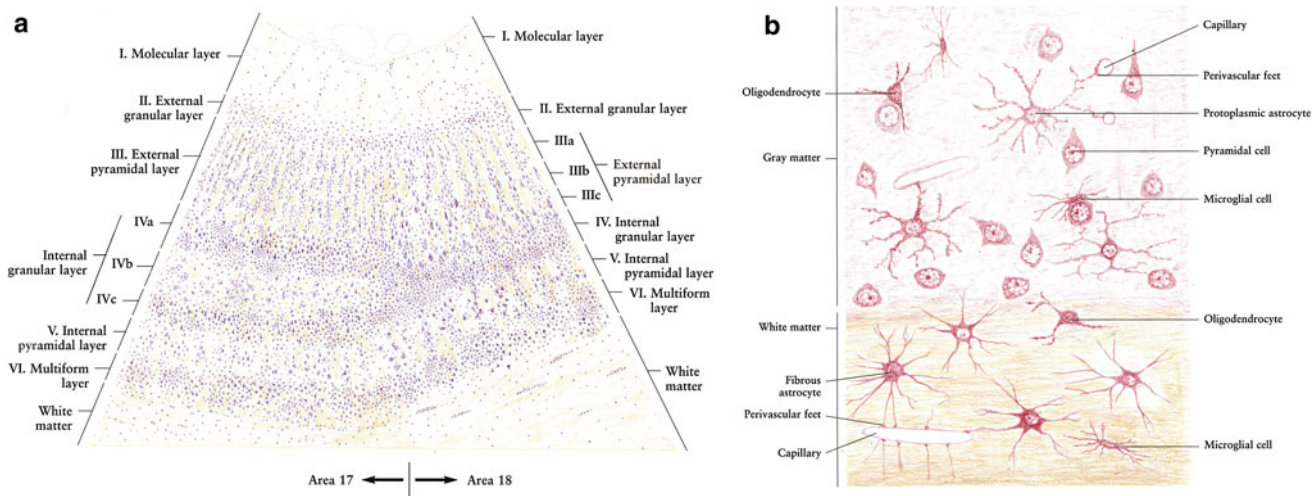


Fig. 3 Histology. **a** Low power magnification. **b** High power magnification of the human cerebrum with different cell types marked (with permission from Zhang 1999)

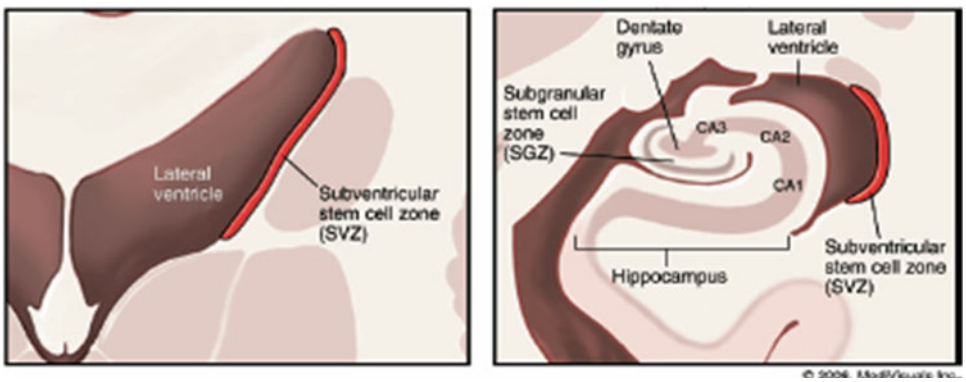
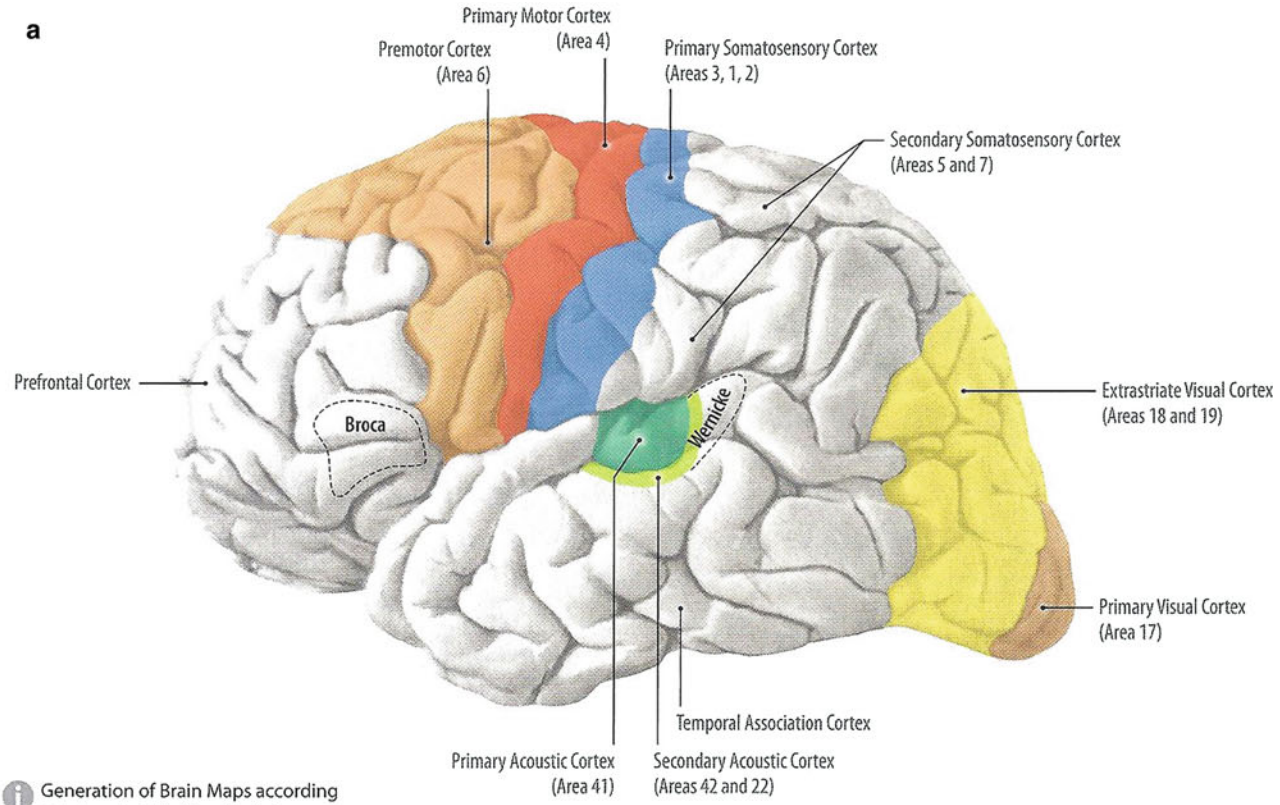


Fig. 4 Distribution of stem cells in the adult human brain (adapted with permissions from Barani et al. 2007)

subject to radiation damage and play a significant role in late radiation toxicity, particularly with respect to neurocognitive effects.

Clinically, radiation toxicity in the CNS is divided into three phases (acute, early delayed, and late), which correlate with different pathophysiologic mechanisms (Kim et al. 2008). In the acute phase, acute inflammation related to cytokine activity and disruption of the BBB dominates. Acute radiation toxicity within the CNS is characterized by headache, fatigue, and, in severe cases, signs of increased intracranial pressure. Transient demyelination is thought to be responsible for early delayed reactions in the CNS. The primary manifestation of early delayed CNS reaction is the somnolence syndrome, which is seen most frequently in children who receive whole brain radiation and intrathecal methotrexate; it typically occurs approximately 6–12 weeks following the completion of whole brain radiation therapy. The hypersomnolence is typically self-limited and its correlation with the development of late neurotoxicity is controversial (Ch'ien et al. 1980; Berg 1983). The manifestations of late neurotoxicity (developing at least 3 months after radiation exposure) are highly variable, ranging from subtle cognitive deficits to severe encephalopathy associated with diffuse white matter damage. Radiation necrosis, variably associated with cerebral edema and focal neurologic deficits, may develop in areas of the brain receiving high (>60 Gy) radiation doses. Late neurotoxicity is mediated by a combination of vascular lesions, cytokine-induced tissue damage, impaired neurogenesis, and reactive oxygen species.

One of the most consistent features of late radiation damage in the CNS is white matter damage (necrosis and demyelination). Oligodendrocytes are responsible for



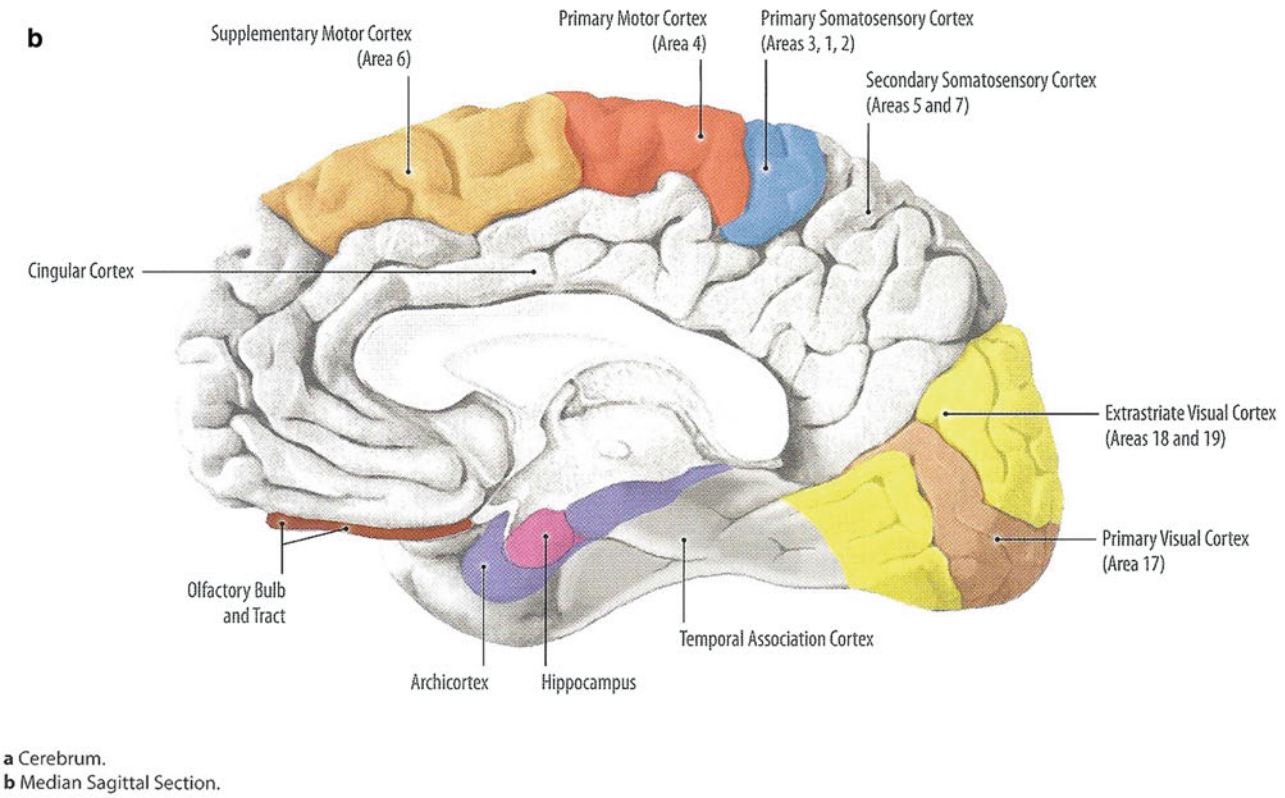


Fig. 5 Physiology: coarse distribution of functions within the brain, **a** Left lateral view; **b** Medial view of the right section (with permission from Tillman 2007)

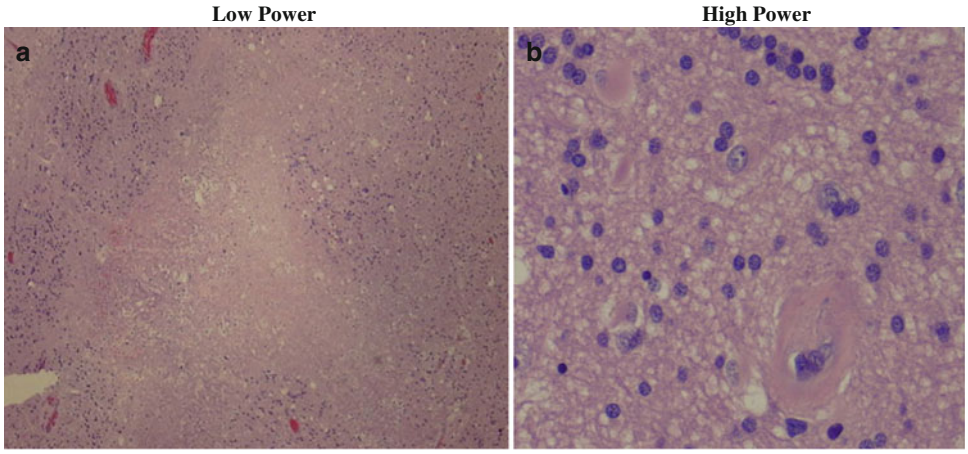


Fig. 6 Radiation Necrosis—Histology. Low power image on the left demonstrates central necrosis with surrounding hypercellular gliosis. High power magnification on the right demonstrates hypercellularity, arteriosclerosis (5 o'clock), and scattered reactive astrocytes, **a** Low power; **b** High power

myelinating neurons and appear to be the most radiosensitive glial cells (Barbarese and Barry 1989; Vrdoljak and Bill 1992). Damage to oligodendroglia was thus hypothesized to be the primary mechanism of radiation-induced demyelination. However, damage to endothelial tissue within the CNS appears to play a key role in post-radiation demyelination. This was elegantly demonstrated by a boron-neutron-capture experiment in which the borated compound (BSH) was unable to cross the BBB. Due to the extremely short range of the alpha particles generated by boron neutron capture therapy, the endothelium was selectively irradiated while brain parenchyma was spared. White matter necrosis and demyelination were nonetheless observed, suggesting that glial cells are not the primary target cells in the development of these lesions (Coderre et al. 2006).

An increase in vascular endothelial growth factor (VEGF) production, triggered by BBB disruption, appears to play a key role in the pathogenesis of white matter lesions. In rodent models, radiation damage to the BBB occurs in two phases. Acute apoptosis of endothelial cells is observed within 24 h of radiation, with regeneration of the endothelium complete approximately 14 days after a single fraction of radiation is administered (Li et al. 2006). The late phase of BBB disruption is associated with increasing vascular permeability beginning approximately 3 months after radiation (in the mouse model) (Yuan et al. 2006). Because VEGF itself causes increased vascular permeability, a positive feedback loop is created which ultimately results in significant local edema, inflammation, and hypoxia. Although VEGF levels eventually rise to a level sufficient to trigger angiogenesis, the structure of the BBB in irradiated areas does not return to normal. The loss of normal endothelium is thought to contribute significantly to the development of late white matter necrosis. Anti-VEGF therapies such as bevacizumab are the subject of active investigation as possible modulators of this late response (Gonzalez et al. 2007).

Reactive oxygen species are responsible for approximately 2/3 of X-ray induced DNA damage. Although radiation-generated ROS are themselves short-lived, radiation damage is associated with a prolonged ROS cascade in the damaged normal tissue and chronic oxidative stress. A variety of mechanisms contribute to chronic oxidative stress in irradiated areas. In areas of the CNS which have been damaged by radiation, the BBB is disrupted and the production of pro-inflammatory cytokines (e.g., TNF-α, INF-γ, ICAM-1) is upregulated (Belka et al. 2001). Activated leukocytes as well as CNS microglia are recruited to the area and release large quantities of ROS as they participate in the local inflammatory reaction. Neuronal excitotoxicity is also associated with the release of ROS, as is chronic hypoxia resulting from damage to small blood vessels.

As noted above, certain areas of the brain (primarily the hippocampal dentate gyrus and the subventricular zone) retain constitutive neurogenic stem cell activity throughout life. Memory and learning abilities appear to be correlated with stem cell activity in these regions, at least in available rodent models, and damage to NSC's in irradiated adults is likely partly responsible for post-radiation neurocognitive deficits (Barani et al. 2007). Neurogenic stem cells appear to be significantly radiosensitive, (Peissner et al. 1999) with rapid and prolonged loss of cell population in the stem cell compartment following radiation (Tada et al. 2000). Juvenile rats have a higher density of active NSC's and thus appear to be at higher risk for neurocognitive sequelae of brain radiation (Fukuda et al. 2005). This correlates well with the inverse relationship between age at irradiation and the severity of cognitive deficits observed clinically in humans.

4 Clinical Syndromes

4.1 Clinical Syndromes

Exposure of the CNS to radiation results in a variety of clinical manifestations. In an attempt to standardize the evaluation and reporting of neurotoxicity, formal scoring

Table 1 LENT–SOMA grading criteria for CNS toxicity (Emsley et al. 2005)

Brain	Grade 1	Grade 2	Grade 3	Grade 4
Subjective signs				
Headache	Occasional, minimal	Intermittent, tolerable	Persistent, intense	Refractory and excruciating
Somnolence	Occasional, able to work or perform normal activity	Intermittent, interferes with work or normal activity	Persistent, needs some assistance for self care	Refractory, prevents daily activity, coma
Intellectual deficit	Minor loss of ability to reason and judge	Moderate loss of ability to reason and judge	Major loss of ability to reason and judge	Complete loss of reasoning and judgement
Functional competence	Perform complex tasks with minor inconvenience	Cannot perform complex tasks	Cannot perform complex tasks	Incapable of selfcare/ supervision, coma
Memory	Decreased short term, difficulty with learning	Decreased short term, loss of short term	Loss of short and long term	Complete disorientation
Objective signs				
Neurologic deficit	Barely detectable neurologic signs, able to perform normal activities	Easily detectable neurologic abnormalities, interferes with normal activities	Focal motor signs, disturbances in speech, vision, etc.interfering with daily activities	Hemiplegia, hemisensory deficit, aphasia, blindness, etc. requires continuos care, coma
Cognitive functions	Minor loss of memory,reason and/or judgement	Moderate loss of memory,reason and/or judgement	Major intellectual impairment	Complete memory loss and/or incapable of rational thought
Mood and personality changes	Occasional and minor	Intermittent and minor	Persistent and minor	Total disintegration
Seizures	Focal, without impairment of consciousness	Focal with impairment of consciousness	Generalised, tonioclinic or absence attack	Uncontrolled with loss of consciousness >10 mn
Management				
Headache, somnolence	Occasional nonnarcotic medication	Persistent nonnarcotic medication intermittent low dose steroids	Intermittent high dose steroids	Parental high dose steroids, mannitol and/or surgery
Seizures	Behavioural modification	Behavioural modification and occasional oral medication	Permanent oral medication	Intravenous anticonvulsive medication
Cognition, Memory	Minor adaptation	Psychosocial + educational intervention	Occupational and physiotherapy	Custodial care
Analytic				
MRI	Focal white matter changes; dystrophic cerebral calcification	White matter changes affecting <1 cerebral lobe; limited perilesional necrosis	Focal necrosis with mass effect	Pronounced white matter changes; mass effect requiring surgical intervention
CT	Assessment of swelling, oedema, atrophy			

tables for the evaluation and description of acute and late neurotoxicity have been developed. Table 1 summarizes the Late Effects Normal Tissue Task Force–Subjective, Objective, Management, and Analytic (LENT–SOMA) and the National Cancer Institute CTC (V.4) Common Terminology Criteria for Adverse Events (CTCAE) grading systems for neurotoxicity. The clinical expression depends on a host of factors, including total dose, fraction size, treated volume, treatment time, and age of the patient. Other factors contribute to CNS toxicity in many patients undergoing radiotherapy to the brain and spinal cord. These include surgery, medications (e.g., steroids, opioids, benzodiazepines, anticonvulsants), chemotherapy, and pre-existing medical comorbidity). The importance of recurrent or persistent malignancy as a contributor to neurological and neurocognitive sequelae in patients undergoing radiation therapy for brain tumors also should not be underestimated.

Table 2 Representative clinical endpoints: arbitrarily segregated into subgroups as shown

	Focal	Global
Subclinical	1. Radiologic abnormality	1. Modest declines in IQ 2. Diffuse EEG findings
Clinical	1. Dysmobility of a limb 2. Focal loss of sensation 3. Aphasia 4. Visual field cut 5. Inability to form new memories	1. Clinically evident neurocognitive problems 2. Mental retardation

The clinical endpoints are summarized in Table 2 as Focal and Global events. Late CNS toxicity may be broadly, and somewhat arbitrarily, segregated into categories as shown.

4.1.1 Cerebrovascular Syndrome

Acute exposure to high total body doses (≥20–30 Gy) causes the cerebrovascular syndrome. Fatal within 24–48 h, this syndrome is associated with systemic loss of vascular permeability and the rapid onset of cerebral edema and multiorgan failure. The few reported human cases have been associated with prodromal symptoms including fever, confusion, and weakness. These are followed by a brief (5–6 h) latent period where recovery of mental status and blood pressure may occur. This latent phase rapidly progresses to the final stage of the cerebrovascular syndrome, associated with fever, diarrhea, refractory hypotension, and progressive cerebral edema causing worsening mental status and death (state when death usually occurs) (Hall 2006b; Waselenko et al. 2004).

4.1.2 RT-Induced Neurocognitive Deficits in the Adult Population

Brain radiation induces late cognitive changes in the adult brain as well. The precise evaluation of these changes is complicated by a number of factors. Many patients with disorders (brain metastases, malignant glioma) requiring brain RT have a limited lifespan, and do not survive long enough to develop late neurocognitive changes, which can develop years after cranial RT. Surgery, chemotherapy, medications, and disease recurrence also cause neurotoxicity, further complicating the precise evaluation of radiation's contribution to cognitive deficits (see above). Finally, accurate assessment of neurocognitive deficits requires serial neurocognitive testing for years following radiation, which frequently is not feasible (Crossen 1994). The RTOG has investigated a battery of previously validated neurocognitive tests which can be administered in 45 min, shown in Table 3 (Regine et al. 2004).

Table 3 Battery of neurocognitive tests assessed in RTOG BR-0018

Test name	Functions assessed
Mini-mental status exam (MMSE)	Memory, attention, cognition
Hopkins verbal learning test (HVLT)	Memory
Verbal fluency/Controlled word association test (COWAT)	Executive functioning, verbal learning, working memory, and vocabulary
Ruff 2 and 7	Selective attention
Trail making test A and B (TMT-A, TMT-B)	Focused attention and speed performance
Profile of mood states short form (POMS)	Tension, depression, anger, vigor, fatigue, confusion

Radiation-induced dementia associated with diffuse leukoencephalopathy is characterized by depression, emotional liability, and deficits in memory and attention which progress to gait disturbance and incontinence in approximately 80% of patients, as shown in Fig. 7. An important differential diagnosis is normal-pressure hydrocephalus. Spontaneous improvement is rare. The only available therapy is supportive care, and the time to death after developing symptoms of radiation-induced dementia ranges from 1 month to 2 years (Keime-Guibert et al. 1998). The use of concurrent chemotherapy increases the incidence of radiation-induced dementia (Frytak et al. 1989).

Typically, however, neurocognitive deficits in adults are subtle, and outcomes are generally favorable with modern fractionation schemes (Brown et al. 2003). Armstrong et al. reported on a series of young patients with supratentorial, favorable-histology brain tumors who received partial brain RT with doses ranging from 46 to 63 Gy (Armstrong et al. 1995). Serial neurocognitive testing (at baseline and at regular intervals up to 3 years after completing RT) was performed; the RT patients were also compared with a group of age-matched controls. Patients experienced "subtle early-delayed memory changes [that were] followed by a rebound of ability" by 1 year after completing RT. Disease control (Regine et al. 2001) and pre-treatment cognitive function (Brown et al. 2001) also appear to be important predictors of post-RT cognitive status. Temporal lobe radionecrosis has also been correlated with neurocognitive deficits (Cheung et al. 2000).

Of particular interest is a study published by Klein et al. (2002) in which the authors attempted to differentiate effects of tumor, radiotherapy, anticonvulsants, and surgical intervention in a group of 195 patients with low-grade glioma, 104 of whom had undergone radiotherapy. The group was compared to 100 patients with low-grade hematologic malignancies non-Hodgkin lymphoma and chronic

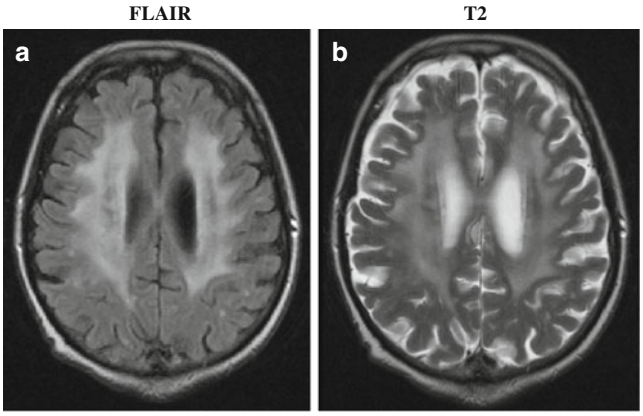


Fig. 7 Radiation-Induced Diffuse White Matter Abnormality: a 73 year-old man presented with a single brain metastasis from colon cancer. He received 37.5 Gy in 2.5 Gy fractions of whole brain radiation followed by radiosurgery boost. He recurred with multiple new enhancing lesions (all subcentimeter) suspicious for metastasis. He received 21.6 Gy in 1.8 Gy fractions of repeat whole brain radiation. Six months later, his MRI revealed diffuse white matter changes on both FLAIR (**a**) and T2 (**b**) sequences

lymphocytic leukemia (NHL/CLL) as well as 195 healthy controls. The use of anticonvulsants also had a significant negative impact on cognitive function. Glioma patients as a group had poorer cognitive functioning than both the NHL/CLL patients and the healthy controls. The use of radiation was correlated with cognitive deficits when irradiated glioma patients were compared with glioma patients who did not receive radiation. This effect was strongly dose- and fraction size-dependent. Patients who received >2 Gy/day of radiation accounted for nearly all cases of cognitive disability in this series. The authors concluded that tumor effects were responsible for the majority of cognitive deficits in low-grade glioma patients, although the delivery of radiation doses >2 Gy/day also had a significant impact on cognitive function (Klein et al. 2002).

4.1.3 Neurocognitive Decline in Patients with CNS Metastasis

Historically, brain radiation has been frequently cited as the major cause of neurocognitive decline in patients treated for metastases. One of the most misinterpreted studies on this subject is the Memorial Sloan-Kettering experience from DeAngelis et al. who reported an 11 % risk of radiation-induced dementia in patients undergoing WBRT for brain metastasis (DeAngelis et al. 1989a). Of the 47 patients who survived 1 year after WBRT, 5 patients (11 %) developed severe dementia. When these 5 patients are examined, all were treated in a fashion that would significantly increase the risk of late radiation toxicity (i.e., large daily fractions and concurrent radiosensitizer). Three patients received 5 and 6 Gy daily fractions, while a fourth patient received 6 Gy fractions with concurrent adriamycin. Only one patient received what is considered a standard radiation fractionation scheme (i.e., 30 Gy in 10 fractions), but this patient received a concurrent radiosensitizer (lonidamine). No patient who received the standard 30 Gy in 10 fractions WBRT alone experienced dementia. Even though the study included 232 patients in the initial analysis, it only examined the 47 patients who survived at least 1 year. The principles of conditional probability dictate that the 11 % risk is accurate only if a patient survives 1 year, which is significantly longer than most reported series. Therefore, a radiation-induced dementia risk of $\approx$2 % (5/232) might be a better estimate of the true probability ab initio for patients with brain metastasis treated with the various radiation doses and drugs used in that study.

Recent studies that have used sophisticated neurocognitive testing are clearly demonstrating that the brain tumor itself (presence, recurrence, and progression) has the greatest effect on neurocognitive decline. In the large phase III motexafin gadolinium study, the neurocognitive battery examined memory recall, memory recognition, delayed recall, verbal fluency, pegboard hand coordination, and executive function (Meyers et al. 2004). This study demonstrated that 21–65.1 % of patients had impaired functioning at baseline before treatment with WBRT (30 Gy in 10 daily fractions). Furthermore, patients who progressed in the brain after treatment experienced significantly worse scores in all of these individual tests.

Patients frequently present to the radiation oncologist already started on prophylactic anticonvulsants. This represents one of the most preventable causes of neurocognitive decline in brain tumor patients. Anticonvulsants are clearly known to adversely affect quality of life and neurocognition. In a study of 156 patients with low-grade glioma (85 % experiencing a seizure), Klein and colleagues correlated seizure-burden with quality of life and neurocognitive function (Klein et al. 2003). This study convincingly demonstrates the significant correlation between the increase in the number of anticonvulsants (even with lack of seizures) and the decrease in quality of life and neurocognitive function. Based on four negative randomized trials, the American Academy of Neurology recommends that prophylactic anticonvulsants not be initiated in newly diagnosed brain tumor patients who have not experienced a seizure (Glantz et al. 2000).

4.1.4 Radiation Necrosis

As described above, CNS radionecrosis is a focal, well-circumscribed lesion that develops in regions of the brain near the primary tumor that have received high doses of radiation. Necrosis is typically associated with focal neurologic deficits that correspond to the lesion's location. Distinguishing these lesions from tumor recurrence can be problematic, but specialized imaging techniques may aid in diagnosis (Fig. 8). The lesion is frequently associated with significant cerebral

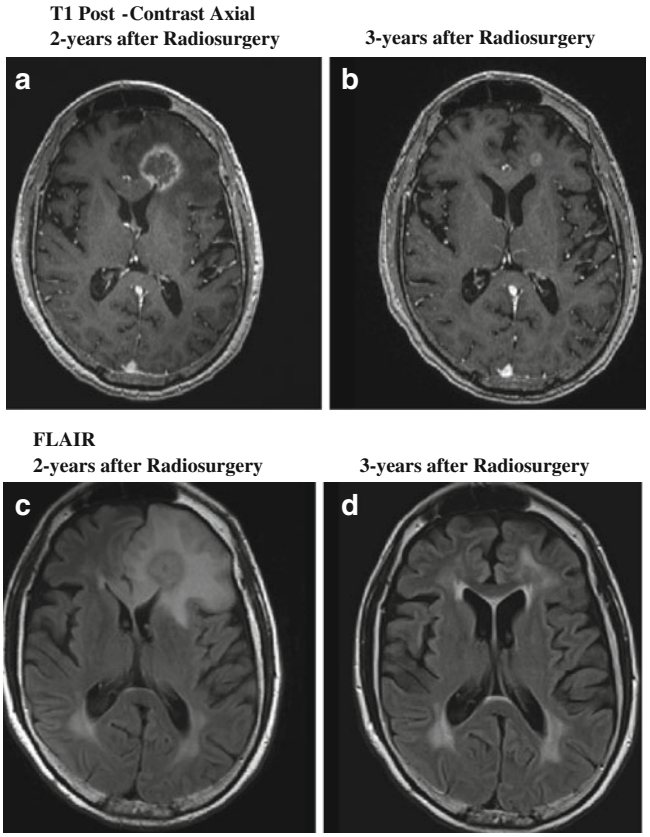


Fig. 8 Resolving Radiation Necrosis: the above images illustrate a case of proven radiation necrosis. The patient was a 62 years old female with 1.5 cm metastatic solitary brain metastasis from non-small cell lung cancer. She received 37.5 Gy in 2.5 Gy fractions of whole brain radiation, followed by radiosurgery boost to 24 Gy. Two years after radiosurgery boost, she developed radiation necrosis. Patient was almost asymptomatic; therefore, she was managed conservatively with no medical intervention. Over a course of 12 months, MRI slowly normalized. Images in the *first row* show T1 post-contrast axial images of a heterogeneously enhancing lesion with mass effect with subsequent resolution. (**a** 2-year, **b** 3-year) *Lower* images demonstrate FLAIR abnormalities indicating significant edema (**c** 2-year, **d** 3-year)

edema, which precedes the development of radiation necrosis (Delattre et al. 1988). Edema and accompanying breakdown of the BBB increase parenchymal susceptibility to radiation necrosis by facilitating a cascade of local inflammatory mediators. This can be effectively inhibited with steroid therapy. Early (i.e., when focal edema is present but the area treated has not yet frankly necrosed) treatment with dexamethasone appears to improve outcomes significantly (Lee et al. 2002). If steroid therapy is delayed until the development of a cystic lesion, improvement of symptoms with medications alone is unlikely, and surgical excision of the mass may be indicated (Gutin 1991).

Necrosis develops months to years after RT (Sloan and Arnold 2003). Total dose and fraction size clearly predict for the development of radionecrosis (DeAngelis et al. 1989b; Sheline et al. 1980). Data from a large series (n = 1,032) of patients treated with RT for nasopharyngeal cancer show an increased risk of necrosis with fraction sizes ≥2 Gy/day (median total dose 62.5 Gy), twice-daily RT, shorter treatment times, and an increased value of the product of total dose and fraction size (Lee et al. 2002). The recent QUANTEC analysis summarized the incidence of necrosis following fractionated partial brain irradiation for patients receiving variable doses per fraction (Fig. 9) (Lawrence et al. 2010).

Among patients undergoing stereotactic radiosurgery [mean dose of 28.6 Gy (range 18.2–53.3)], increased tumor volume, treated volume, V10 (volume of tissue receiving >10 Gy), low conformality index, and repeated treatments to the same lesion have been found to be correlated with an increased incidence of radiation necrosis (Chin et al. 2001; Valéry et al. 2003). The summary data from QUANTEC is reproduced in Fig. 10. Note the steep increase in incidence of necrosis with dose.

4.2 Detection and Diagnosis: Imaging characteristics of radiation-induced CNS lesions

Radiologic findings consistent with demyelination, white matter necrosis, and parenchymal volume loss mirror the pathologic changes induced by brain and spinal cord radiation. Magnetic resonance imaging (MRI) is a sensitive imaging modality for white matter lesions (Tsuruda et al. 1987). Figure 7 depicts the typical MRI appearance of radiation-induced white matter changes. Both the incidence and severity of white matter lesions in the brain are directly related to increasing RT dose and worsen with time. Data from RTOG 83-02, which was a prospective dose-escalation study in malignant gliomas (see Table 4), shows a clear dose-response relationship for radiation necrosis (Corn et al. 1994) A more recent publication has reported on a group of 24 patients who underwent serial MRI following whole brain radiation (Fujii et al. 2006). Low-grade white matter changes were noted as early as 2 months after WBRT, with a median time to onset of 5.5 months, and continued to evolve for as long as 2 years. No patient developed grade 3 or greater changes before 6 months post-RT, and the median time to onset of these more severe changes was 12.5 months. Radiation myelopathy has a variable appearance on MRI, and may appear as cord edema, increased T2 white matter signal, and gadolinium-enhancing T1 white matter lesions. Changes may progress to cord atrophy or radiation necrosis (Maranzano et al. 2001; Alfonso et al. 1997).

Focal areas of radiation necrosis are often indistinguishable from tumor recurrence, even with high-resolution contrast enhanced MRI (Wen et al. 2010). A typical lesion of radiation necrosis is shown in Fig. 8. T1-weighted

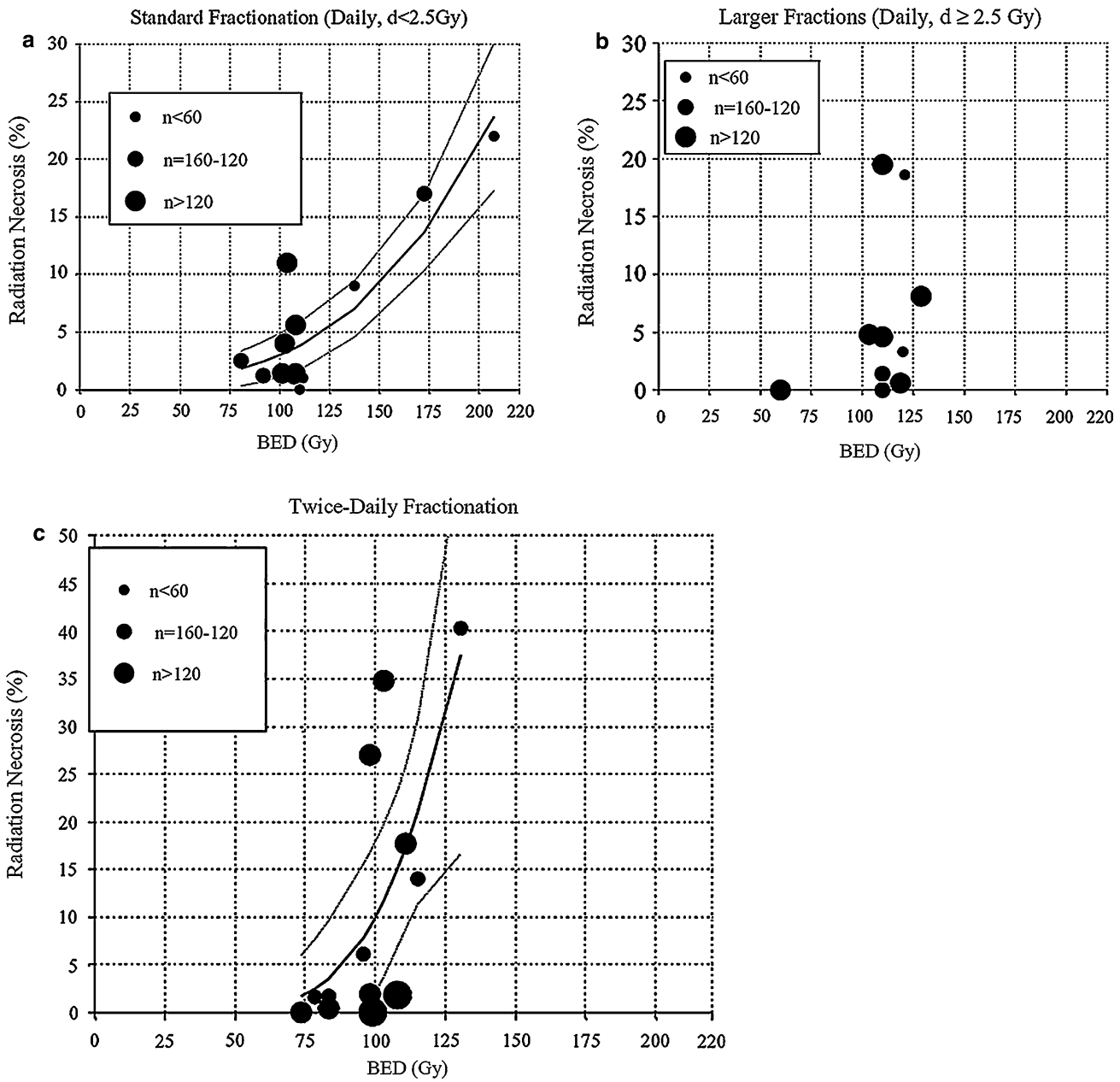


Fig. 9 Relationship between biologically effective dose (BED) and radiation necrosis after fractionated radiotherapy. Fit was done using nonlinear least-squares algorithm using Matlab software (The MathWorks, Natick, A). Nonlinear function chosen was probit model (similar functional form to Lyman model). Dotted lines represent 95 % confidence levels; each dot represents data from specific study, n = patient numbers as shown. **a** Fraction size <2.5 Gy, **b** fraction size ≥2.5 Gy (data too scattered to allow plotting of ''best-fit'' line), and **c** twice-daily radiotherapy (with permissions from Lawrence et al. 2010)

sequences show a ring-enhancing lesion with a necrotic center. On FLAIR (or T2-weighted) sequences, significant surrounding cerebral edema can be seen. Spontaneous regression of this lesion after 1 year of observation was noted (Brandsma et al. 2008). New imaging modalities, such as FDG–PET and magnetic resonance spectroscopy, may be helpful in the evaluation of radiation necrosis. The use of FDG–PET scanning (which utilizes a radiolabeled glucose molecule) for the evaluation of intracranial radiation necrosis is complicated by the brain's high intrinsic rate of glucose metabolism. Radiolabeled amino acids and radiolabeled thymidine are more specific markers for metabolic activity within the brain and have the potential to differentiate areas of active tumor from areas of radiation necrosis (Herholz et al. 2007). Magnetic resonance spectroscopy is able to differentiate between the molecular resonance frequencies of different constituents of the CNS, although its spatial resolution is poor. CNS lesions

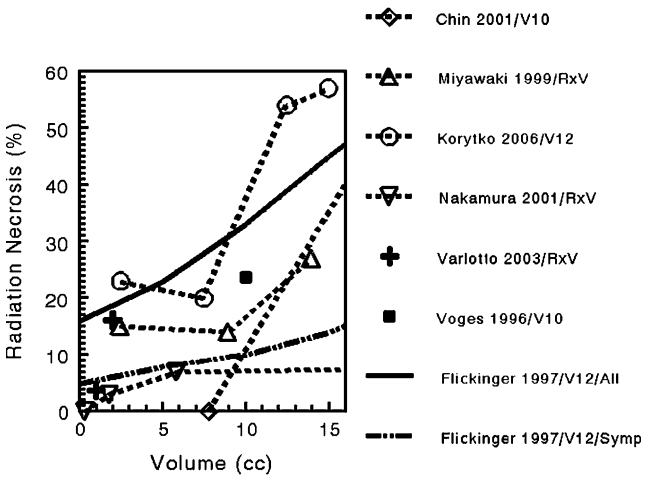


Fig. 10 Relationship between volume receiving high-dose irradiation and incidence of radiation necrosis in single-fraction stereotactic radiosurgery. Studies differed in their completeness of follow-up, definition of volume, and definition of radiation necrosis. Volume plotted as a point, representing mid-point of volume range. V10 = volume receiving 10 Gy, V12 = volume receiving 12 Gy, RxV = treatment volume. Flickinger data is shown for patients with either radiologic or symptomatic evidence of necrosis (marked as "All"), or only those with symptomatic necrosis (Symp). The other authors' data refers to symptomatic necrosis (with permissions from Lawrence et al. 2010)

have distinctive magnetic resonance "fingerprints" based on their relative concentrations of choline (associated with the cell wall), creatine (normalization element), N-acetyl aspartate (NAA associated with mature neurons), lactate, and lipid (both associated with necrotic tissue). Specifically, radiation necrosis is characterized by: low choline signal relative to both NAA and creatinine, high NAA signal relative to creatinine and choline, and high lactate/lipid signal relative to choline (Rock et al. 2002). The addition of diffusion sequences to MRS may further aid in differentiating areas of tumor from areas of necrosis (Rock et al. 2004).

MRI is the ideal modality to detect the gradual whitening of the cerebral cortex indicating progressive leukoencephalopathy. Radionecrosis is best visualized with a contrast enhanced MRI, although CT may image the necrotic area in some cases. To establish a distinction between tumor necrosis and radiation induced necrosis. MRS may be useful in some cases.

5 Radiation Tolerance: Current Recommendations for Normal Tissue Dose Limits in the Nervous System

In 1991, Emami et al. published an exhaustive summary of data then available regarding radiation toxicity in normal tissue (Emami et al. 1991). Clinical outcomes, quoted as 5 and 50 % risk of complication within 5 years (TD5/5 and TD 50/5) were correlated with volume of normal tissue radiated. At the time, three-dimensional treatment planning was not widely used, and radiation dose estimates for normal tissue were inaccurate. These data have since been updated in a second review published in 2007 (Milano et al. 2007).

Rubin's original estimate for fractionated partial brain RT (5 % risk at 5 years for one-third brain, 60 Gy) appears to be somewhat conservative. The QUANTEC review concluded that the 5 % risk at 5 years of the partial brain for normally fractionated RT is 72 Gy (range, 60–84). For standard fractionation, a 5 and 10 % risk of symptomatic radiation necrosis is predicted to occur at a BED of 120 Gy (range, 100–140) and 150 Gy (range, 140–170), respectively [corresponding to 72 Gy (range, 60–84) and 90 Gy (range, 84–102) in 2 Gy fractions]. The brain is especially sensitive to fraction sizes >2 Gy (Mayo et al. 2010). Thus, partial-brain fractionated RT to 54–60 Gy in 1.8–2 Gy daily fractions, a very common regiment for many brain lesions, is also well tolerated, with a low incidence of late neurocognitive effects or radio-necrosis. When choosing a fractionation scheme for whole brain radiation, the patient's life expectancy must be considered carefully. Late radiation side effects are clearly correlated with daily fraction sizes that exceed 3 Gy and total dose, but this toxicity is less important in patients with a limited life expectancy, who will benefit from a shorter RT schedule (e.g., due to convenience) and the higher probability of tumor control afforded by a treatment scheme such as 30 Gy in 10 fractions. For patients with a longer (>6 months) life expectancy, more prolonged treatment schemes (40 Gy in 2 Gy/day fractions or 37.5 Gy in 2.5 Gy/day) are typically recommended, although confirmatory evidence is modest. Table 5 summarizes widely applied dose limitations for brain, spinal cord, and other critical structures in the CNS for conventional fractionation.

For radiosurgery, the risk of complications increases with the size of the target volume. Toxicity increases rapidly once the volume of the brain exposed to >12 Gy is >5–10 cm^3. Eloquent areas of the brain (brain stem, corpus callosum) require more stringent limits (Mayo et al. 2010). For lesions involving the brainstem parenchyma, dose for single fraction radiosurgery is often limited to 15 Gy or lower. Nevertheless, small portions of the brainstem can tolerate higher doses as there is a strong volume effect. For example, stereotactic radiosurgery doses of 15–18 Gy (10–20 % line of prescribed 75–90 % to Dmax) are routinely administered to small areas of the brainstem surface for the treatment of trigeminal neuralgia.

6 Chemotherapy

There is strong evidence that chemotherapy contributes significantly to neurocognitive outcomes in cancer patients (Brezden et al. 2000; Tchen et al. 2003). Double-blinded

Table 4 Incidence of White Matter (WM) Abnormalities in RTOG 83-02

Dose group	Grade ≥2 WM changes (%)	Grade ≥3 WM changes (%)	Radiation necrosis (Grade 6) (%)
Low (48–54.4 Gy in 1.6 Gy bid)	26.6	8.3	1.6
Intermediate (64.8–72 Gy in 1.2 Gy bid)	27.6	20.0	4.6
High (76.8–81.4 Gy 72 Gy in 1.2 Gy bid)	40.4	36.5	19.2

randomized trials of healthy volunteers have demonstrated that corticosteroids can have significant impact on recall testing, attention, EEG testing, and hippocampal volume and activity (Newcomer et al. 1994; Schmidt et al. 1999; Brown et al. 2004). Studies of healthy volunteers have further demonstrated that medications commonly used in cancer patients, such as benzodiazepines and opioids, can cause profound neurocognitive deficits (Zacny and Gutierrez 2003).

A number of chemotherapeutic agents have been historically associated with acute and late toxicities (Table 6) (Anderson et al. 1997; Watterson et al. 1994; Madhu et al. 1993). Entities such as acute and chronic encephalopathy, necrotizing leukoencephalopathy, acute cerebellar syndromes, and peripheral neuropathies, reflect both drug and radiation toxicities. This is of particular concern in children (Allen and Siffert 1996; Prassopoulos et al. 1997).

7 Special Topics

7.1 Cranial Nerves

Optic Nerves

Radiation-induced pathology of the optic nerve is associated with two discrete clinical syndromes. Anterior ischemic optic neuropathy is believed to be secondary to vascular injury of the distal portion of the optic nerve. Patients present with gradual, painless visual loss, with median time to onset 2–4 years after completing RT. Funduscopic examination reveals edema of the optic disk which progresses to atrophy over the course of months to years. Retrobulbar optic neuropathy results from damage to proximal segments of the optic nerve. Visual field deficits and rapidly progressive vision loss, sometimes associated with ocular, periorbital, or retrobulbar pain, are characteristic of retrobulbar optic neuropathy, and disk abnormalities are infrequently observed. Both forms of optic neuropathy are refractory to treatment with steroids and hyperbaric oxygen. Both types of injury are correlated with increasing patient age, total RT doses >59 Gy, and daily fraction size >2 Gy (Parsons et al. 1994).

The QUANTEC review concludes, "The Emami estimate of 5 % probability of blindness within 5 years of treatment for a dose of 50 Gy appears inaccurate. From the present data review, 50 Gy is closer to a "near zero" incidence. The incidence of RION was unusual for a Dmax <55 Gy, particularly for fraction sizes <2 Gy. The risk increases (3–7 %) in the region of 55–60 Gy and becomes more substantial (>7–20 %) for doses >60 Gy when fractionations of 1.8–2.0 Gy are used. The patients with RION treated in the 55–60 Gy range were typically treated to doses in the very high end of that range (i.e., 59 Gy). For particles, most investigators found that the incidence of RION was low for a Dmax < 54 CGE. One exception to this range was for pituitary tumors, in which investigators used a constrained Dmax of <46 Gy for 1.8 Gy/fraction. For single-fraction SRS, the studies have indicated the incidence of RION is rare for a Dmax < 8 Gy, increases in the range of 8–12 Gy, and becomes >10 % in the range of 12–15 Gy."

The recent QUANTEC review generated a nice dose–response curve for optic nerve injury following conventional fractionation (Fig. 11) (Mayo et al. 2010). The tolerance (<1 % risk) of the optic nerve at single fraction radiosurgery doses appears to be 8–10 Gy provided that the patient does not have a history of external radiation (Tishler et al. 1993; Stafford et al. 2003).

7.1.1 Other Cranial Nerves

The olfactory optic nerves are similar to CNS brain tissue in radiation sensitivity. The data presented above regarding the tolerance of the optic nerve cannot be extrapolated to the remainder of the cranial nerves. The majority of cranial nerves are similar to peripheral nerves as to their radiosensitivity. Cranial nerves within the cavernous sinus appear to be radioresistant and have been reported to tolerate single-fraction doses of up to 40 Gy (Tishler et al. 1993). The trigeminal nerve at the root entry zone is routinely irradiated to 90 Gy (Dmax) for trigeminal neuralgia and cumulative doses of 160 Gy or higher have been reported with minimal risk for subsequent sensory abnormalities (Pollock 2005). The vestibulocochlear nerve (CN VIII) appears to be somewhat less radioresistant, with hearing loss reported at doses above 54 Gy in conventional fractionation (Johannesen et al. 2002). This may be related to radiation-induced bone sclerosis within the middle ear.

Table 5 Commonly clinically applied normal tissue 'dose limits' for the CNS associated generally with a low risk of injury

Structure	Total dose (Gy)/Dose per fraction (Gy)
Spinal cord	45–50/1.8–2.0; 45/1.2 BID
Partial brain	60/1.8–2.0
Whole brain	30/3; 37.5/2.5; 40/2
Retina	45/1.8
Optic nerve/Chiasm	54/1.8; 8–10 single fraction
CN VIII	54/1.8
Other cranial nerves	60/2
Peripheral nerve plexus	60/2

7.2 Fetal Effects

Exposure of the fetal nervous system to ionizing radiation between the gestational ages of 8 and 25 weeks is associated with microcephaly and mental retardation. This was most clearly demonstrated in the Japanese populations exposed to radiation from the atomic bombs of Hiroshima and Nagasaki. The highest risk period for the development of radiation-associated mental retardation appears to be between the gestational ages of 8 and 16 weeks, which coincides with neuronal proliferation, differentiation, and migration into the developing cerebral cortex. Although the dosimetry associated with the atomic bomb exposures is somewhat uncertain, the incidence of mental retardation appears to be linearly associated with dose, with a possible threshold dose of 0.12–0.2 Gy. An exposure of 1 Gy at the most sensitive gestational age of 8–15 weeks is associated with an estimated 43 % risk of mental retardation. Radiation exposure between 16 and 25 weeks is associated with increased risk of mental retardation as well, but the incidence is lower than at the 8–16 week period. Less pronounced cognitive impairment (measured in the atomic-bomb survivors by IQ testing and school performance) is also evident among individuals exposed to lower doses of radiation between 8 and 26 weeks gestational age, with a linear relationship between decreased IQ/school performance and increased radiation doses. No effect on IQ nor school performance was observed among children who were exposed to radiation before 8 weeks nor after 26 weeks (Hall 2006c; National Academy of Sciences/National Research Council 1990).

7.3 Effects in Childhood

Neurocognitive and neuropsychologic consequences of brain radiation in children may occur in up to 50 % of children who undergo brain radiation (Walter et al. 1999; Packer et al. 1987). The clinical manifestations are variable, ranging from overt mental retardation among children receiving high doses of radiation at a young age to subtler cognitive and behavioral deficits. In infants and toddlers, mental retardation, growth delay, and leukoencephalopathy are sufficiently profound that cranial radiotherapy is preferentially delayed until after age 3, except in extreme circumstances (Duffner et al. 1993). Serial IQ testing is commonly used to quantify the extent of neurocognitive impairment among children who have received brain radiation. Declines in IQ have been observed in multiple trials to be age- and dose-dependent (Silber et al. 1992; Merchant et al. 2005; Mulhern et al. 1998). Among survivors of childhood cancer who received radiation, deficits in attention and concentration appear to be particularly significant contributors to cognitive decline (Langer et al. 2002; Briere 2008). It is important to note, however, that many children with brain tumors have cognitive deficits at baseline (i.e., before radiation therapy begins), likely secondary to tumor effect as well as pre-radiotherapy interventions such as surgery (Merchant et al. 2002; Sonderkaer et al. 2003). It is unlikely that cranial radiotherapy will be completely eliminated as part of the treatment paradigm for pediatric malignancies such as medulloblastoma, high-risk

Table 6 Antineopastic drugs associated with cerebral encephalopathy

Antimetabolites
High-dose methotrexate
5-Fluorouracil (with allopuronol)
Cytosine arabinoside (ara-C)
Fludarabine
PALA (*N*-[phosphonacetyl]-L-aspartate)
Alkylating agents
Cisplatin
Lfosfamide
BCNU (carmustine)
Spiromustine
Plant alkyloids
Vincristine (associated with inappropriate antidiuretic hormone secretion)
High-dose regimens used in bone marrow transplantation
Nitrogen mustard
Etoposide
Procarbazine
Miscellaneous
Mitotane
Misonidazole
L-asparaginase
Hexamethylmelamine
Interleukin-2

From Kagan (1993), with permission

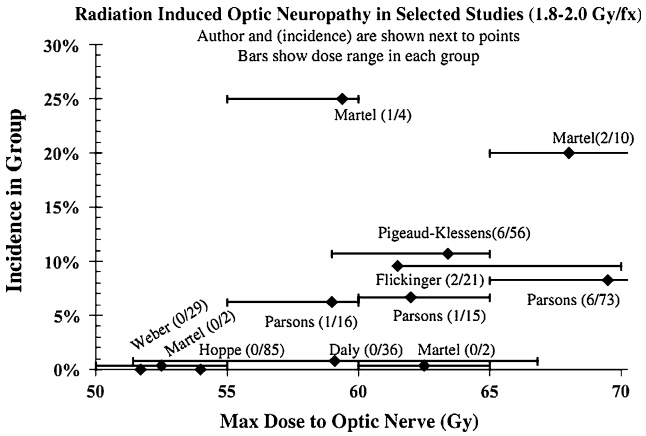


Fig. 11 Comparison of incidence of radiation-induced optic neuropathy (RION) versus maximum dose (Dmax) to optic nerves (from Mayo et al. 2010). Selected studies generally used fraction sizes with range of 1.8–2.0 Gy, assessed the dose to the nerve directly from their best estimate of dose distribution in the structure (i.e., not as a partial volume average), did not include pituitary lesions (lower tolerance), and selected patient age <70 years (if segregated). *Bars* illustrate range of doses for groups characterized by incidence values. Points offset from 0 to ≤1 % were shifted to clearly show range bars. For points displayed at 0 %, available range information was outside 50–70 Gy. Threshold for RION appears to be 55–60 Gy. However, range bars illustrate treatment in 60–65 Gy range for some studies without RION. Data estimated from tables, figures, and text reported in the studies, because exact incidence data were not always provided (with permission from Mayo et al. 2010)

acute lymphoblastic leukemia (ALL), and ependymoma. Continuing clinical investigation is focusing on minimizing the cognitive impact of cranial RT in children by attempting to lower total RT dose and volume as well as by utilizing technologies such as proton-beam RT (Merchant et al. 2009).

8 Management of Nervous System Toxicity

Corticosteroids are the mainstay of treatment for many radiation-induced CNS toxicities, including radiation necrosis, cranial nerve palsy, and peripheral neuropathy. Treatment with corticosteroids often affords significant symptomatic benefit. It may also alter the pathophysiology of radionecrosis by reducing local edema and interrupting local inflammatory cascades. However, the side effects of steroids are manifold, including worsening diabetic hyperglycemia, immunosuppression, loss of muscle mass, osteoporosis, peripheral edema, weight gain, skin changes, and psychosis. Therefore, if steroid therapy is initiated, it should only be continued if effective, and efforts should be made to taper steroids quickly as symptoms begin to resolve.

The benefit of hyperbaric oxygen (HBO) therapy for radiation-induced CNS toxicity has been investigated in a number of small trials (Hulshof et al. 2002; Ohguri et al. 2007; Chuba et al. 1997). No consistent benefit has been reported and no large randomized trial has been conducted. At this point, there is insufficient evidence to recommend for or against HBO in patients with CNS toxicity secondary to radiotherapy. Pentoxifylline, which may also improve tissue oxygenation and down-regulate inflammatory cytokines, has also been suggested as a treatment for radionecrosis and RT-induced cranial and peripheral nerve injury. However, no well-designed, prospective trials have been performed to demonstrate its efficacy. While there is increased tissue oxygen delivery and down-regulation of inflammatory cytokines with pentoxifylline, there is also evidence that tumor oxygenation and increased tumor growth can occur (Vernimmen et al. 1994; Grzela et al. 2003). Similarly, HBO increases tumor oxygenation which most likely explains the multiple reports of explosive tumor recurrences and accelerated disease progression following HBO therapy (Wang 1999; Bradfield 1996). While erythropoietin has neuroprotective effects after injury, this has not been studied in radiation patients; moreover, there have been multiple randomized trials recently reported that demonstrate its negative effect on overall survival in cancer patients (van der Kooij et al. 2008; Leyland-Jones et al. 2005; Smith et al. 2008). Therefore, these agents should be routinely avoided in patients with active tumor or in those who are still in the window in which the risk of disease recurrence is high.

A variety of psychoactive drugs have been utilized to treat post-RT cognitive dysfunction. Methylphenidate, a stimulant used to treat attention deficit disorder, may improve psychomotor slowing and arousal in patients with lassitude or lethargy following radiation (Meyers et al. 1998). Donepezil is an acetylcholinesterase inhibitor used to improve cognitive function in patients with dementia. Donepezil significantly improved mood, cognitive function, and health-related quality of life in a phase II trial of irradiated brain tumor patients (Shaw et al. 2006). A recently opened Phase III trial (RTOG 0614) is investigating another anti-dementia agent, memantine, in patients undergoing whole brain radiation for brain metastases. Memantine is an N-methyl-D-aspartate receptor antagonist which slows the progression of and improves symptoms related to vascular dementia. Because vascular injury plays a key role in the pathogenesis of radiation injury to the brain, memantine is an attractive therapeutic agent. Bevacizumab, as described above, has the potential to modulate post-RT vascular pathology as well and is under active investigation.

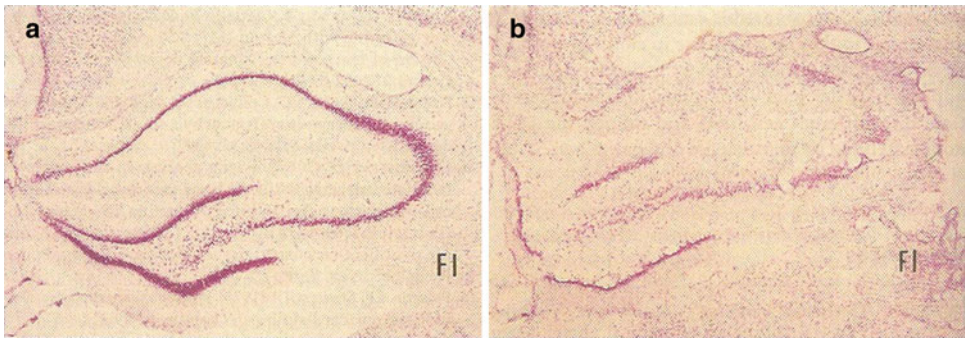


Fig. 12 Coronal (30 μm) section through the anterior hippocampus, stained with cresyl violet. In comparison to normal controls (**a**), the 30 Gy irradiated animals (**b**) showed marked disruption of the cytoarchitecture of the hippocampal formation, large holes, and almost complete degeneration of the fimbria *(FI)* (with permission from CURED LENT II 2008)

9 Future Research: Stem Cell Transplant

The transfusion of pluripotent stem cells to regenerate parenchymal and endothelial cells is no longer the impossible dream. The new exciting advances in the bioengineering of adult skin cells by insertion of three genes into histocompatible stem cells opens the door for an improved therapeutic ratio, that is, the stabilization and reversal of the radiation Biocontinuum (Gutin 1991).

An apocryphal study utilized rat embryonic grafts, implanted as a core of tissue in irradiated adult rat brain; appeared to reverse most the morphologic and functional aspects of neuronal damage (Fig. 12a, b) (Pearlman et al. 1990).

10 Review of Literature/Historical Highlights

1937 O'Connell and Brunschwig: After a thorough analysis of the literature and cases, concluded that the brain and its blood vessels are injured. Suggested that 15,000 R not be exceeded and that the optimal dose is 4,500 R.

1943 Smithers, Clarkson and Strong: Reported a case of Brown-Sequard syndrome one year and three months after irradiation of the esophagus (5,800 R in 39 days).

1948 Pennybacker and Russell: Presented a clinical and pathologic review of five cases of brain necrosis following therapy for brain tumor (except one case of rodent ulcer). The damage was due to thrombosis of small vessels.

1951 and onward: Lars Leksell pioneers the concept of stereotactic radiosurgery.

1954 Arnold, Bailey and Laughlin: Conducted an experimental study of a wide range of single doses to the brain and primates, concluding that the brain is more radioresponsive than generally conceded.

1954 Arnold, Bailey and Harvey: In experimental studies, suggested that the brain stem and hypothalamus are more sensitive to irradiation than the cerebrum.

1958 Berg and Lindgren: Conducted an excellent experimental study of time-dose relationship and morphology of delayed radiation lesions of the brain in rabbits.

1963 Berg and Lindgren: Presented data relating tolerance of the brain to field size, using an experimental situation in which select fields were used.

1964 Haley and Snider: Conducted a multidisciplinary symposium on the response of the nervous system to ionizing irradiation with emphasis on cytologic, histologic, anatomic, functional, biochemical and behavioral aspects.

1965 Vaeth: Offered a time-dose plot for radiation myelitis.

1966 Bouchard: Presented the most recently published treatise on the radiation therapy of brain tumors and the tolerance of the brain to irradiation.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

1988: Kjellberg and Abe suggest a series of 'iso effect' curves for various doses/volumes for single fraction radiosurgery, based on combined animal and human data (Kjellberg and Abe 1988). The 1 % iso-effect line is latter suggested by Marks and Spenser (based on a literature review) to closer to a 3–8 % risk, (Marks and Spencer 1991) and by Flickinger, Schell, Larson (based on clinical data) to be closer to a 3 % risk (Flickinger et al. 1990).

1990: Pearlman, Rubin, White, et al. Fetal hypothalamic transplants into irradiated brains of rats: restore the histopathology to normal (Pearlman et al. 1990).

1991: Gutin, Leibel and Sheline publish "Radiation Injury to the Nervous System".

1993 Tishler, Loeffler, Lunsford, et al. (Tishler et al. 1993) demonstrate a steep dose response for optic nerve injury following radiosurgery.

1993 Flickinger, Lunsford, Kondziolka, et al. illustrate the higher rate of imaging-defined brain injury (vs. symptom-defined injury) following radiosurgery, and the importance of 'location' within the brain in estimating the risk of injury with radiosurgery (Flickinger et al. 1992).

1996 and onward: Shaw and other investigators at the RTOG define volume dependent tolerance doses for brain radiosurgery (Shaw et al. 1996).

2001: Ang et al. report marked recovery of "tolerance" in primate spinal cord. (Ang et al. 2001).

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Spinal Cord and Peripheral Nervous System

John P. Kirkpatrick

Contents

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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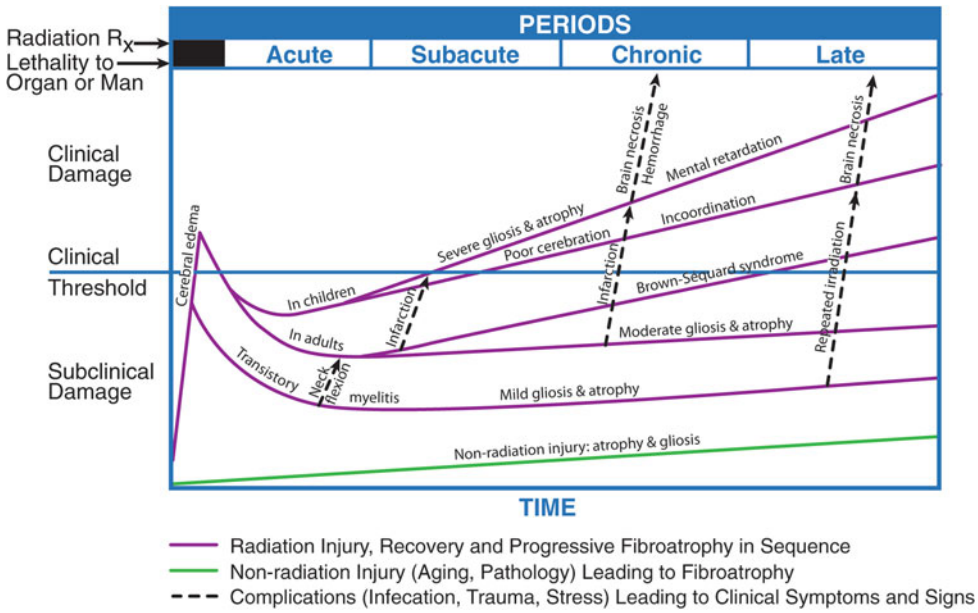


Fig. 1 Biocontinuum of radiation induced acute, subacute, chronic, and late effects of the CNS (with permission from Rubin and Casarett 1968)

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 ≤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). Bicontinuum 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 house 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 lumber 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.

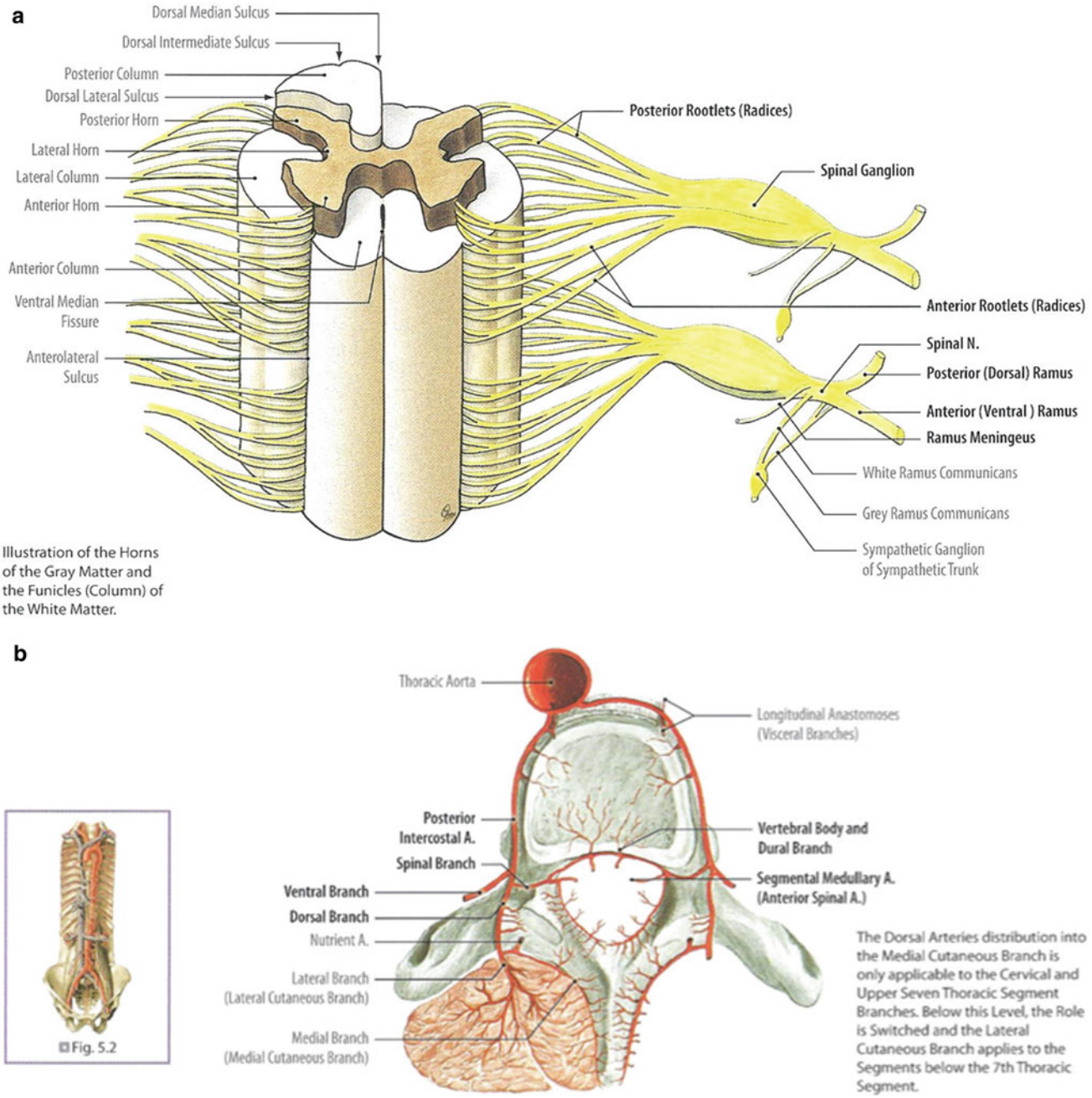


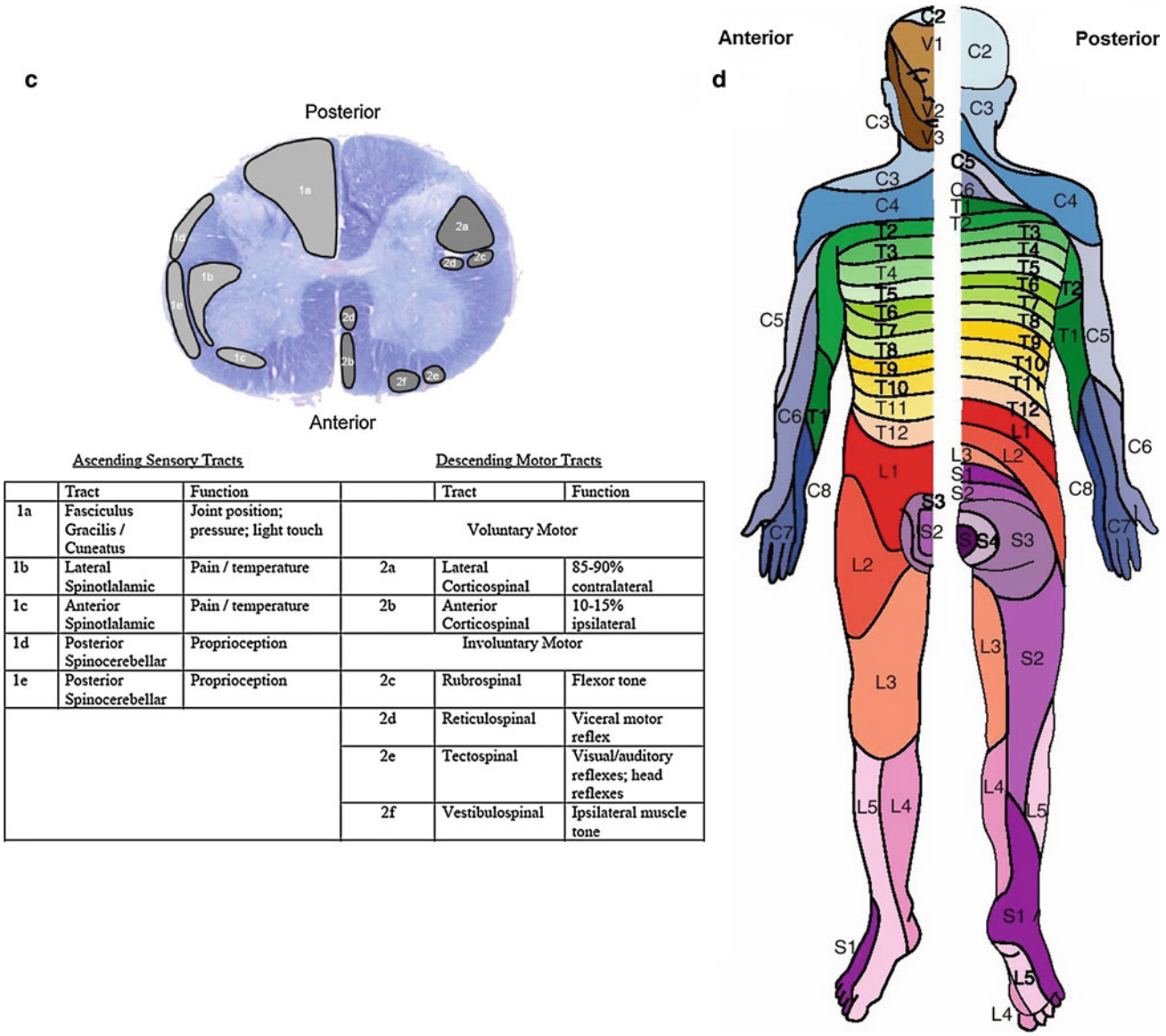
Fig. 2 **a** Spinal nerves are formed from the motor and sensory fibers coming from the spinal cord. **b** The vascular supply of the spinal cord is shown. **c** Axial image of the spinal cord with different functions linked to different regions is shown. From Nelson et al. with permission. **d** Dermatomes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



Ascending Sensory Tracts

	Tract	Function
1a	Fasciculus Gracilis / Cuneatus	Joint position; pressure; light touch
1b	Lateral Spinotlalamic	Pain / temperature
1c	Anterior Spinotlalamic	Pain / temperature
1d	Posterior Spinocerebellar	Proprioception
1e	Posterior Spinocerebellar	Proprioception

Descending Motor Tracts

	Tract	Function
Voluntary Motor		
2a	Lateral Corticospinal	85-90% contralateral
2b	Anterior Corticospinal	10-15% ipsilateral
Involuntary Motor		
2c	Rubrospinal	Flexor tone
2d	Reticulospinal	Viceral motor reflex
2e	Tectospinal	Visual/auditory reflexes; head reflexes
2f	Vestibulospinal	Ipsilateral muscle tone

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:		
Internal Sphincter M.		▶ Contraction
Genitals:	Female	▶ Contracts the uterine musculature
	Male	▶ Contracts the smooth musculature of the seminal vesicle, the prostate, and the ductus deferens
Spleen:		▶ Contracts the smooth muscles In the capsule of the spleen
Adrenal Gland:		▶ Secretes adrenalin and noradrenalin

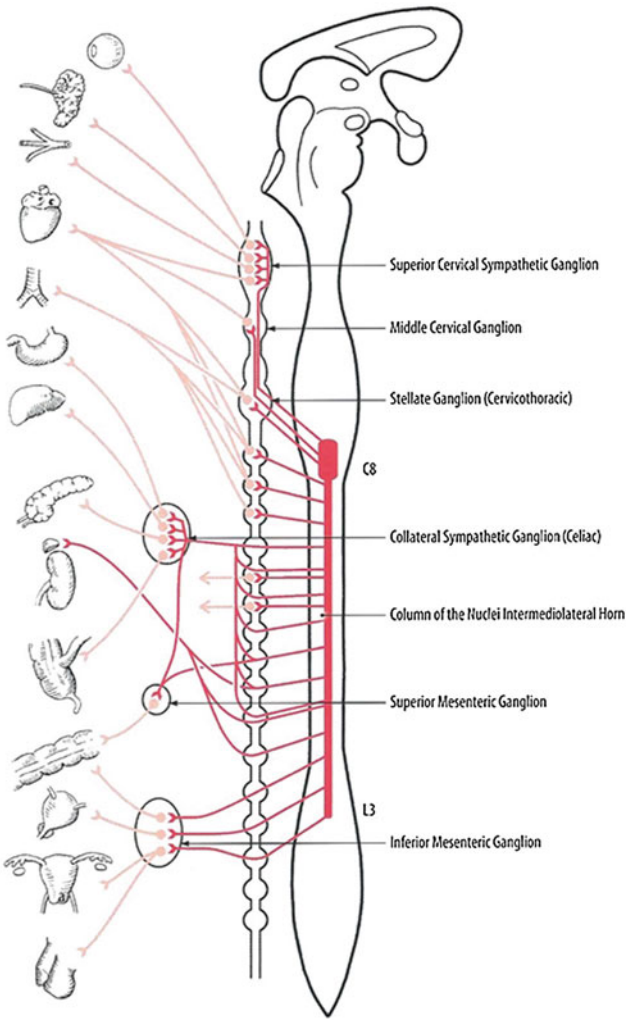


Fig. 2 (continued)

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

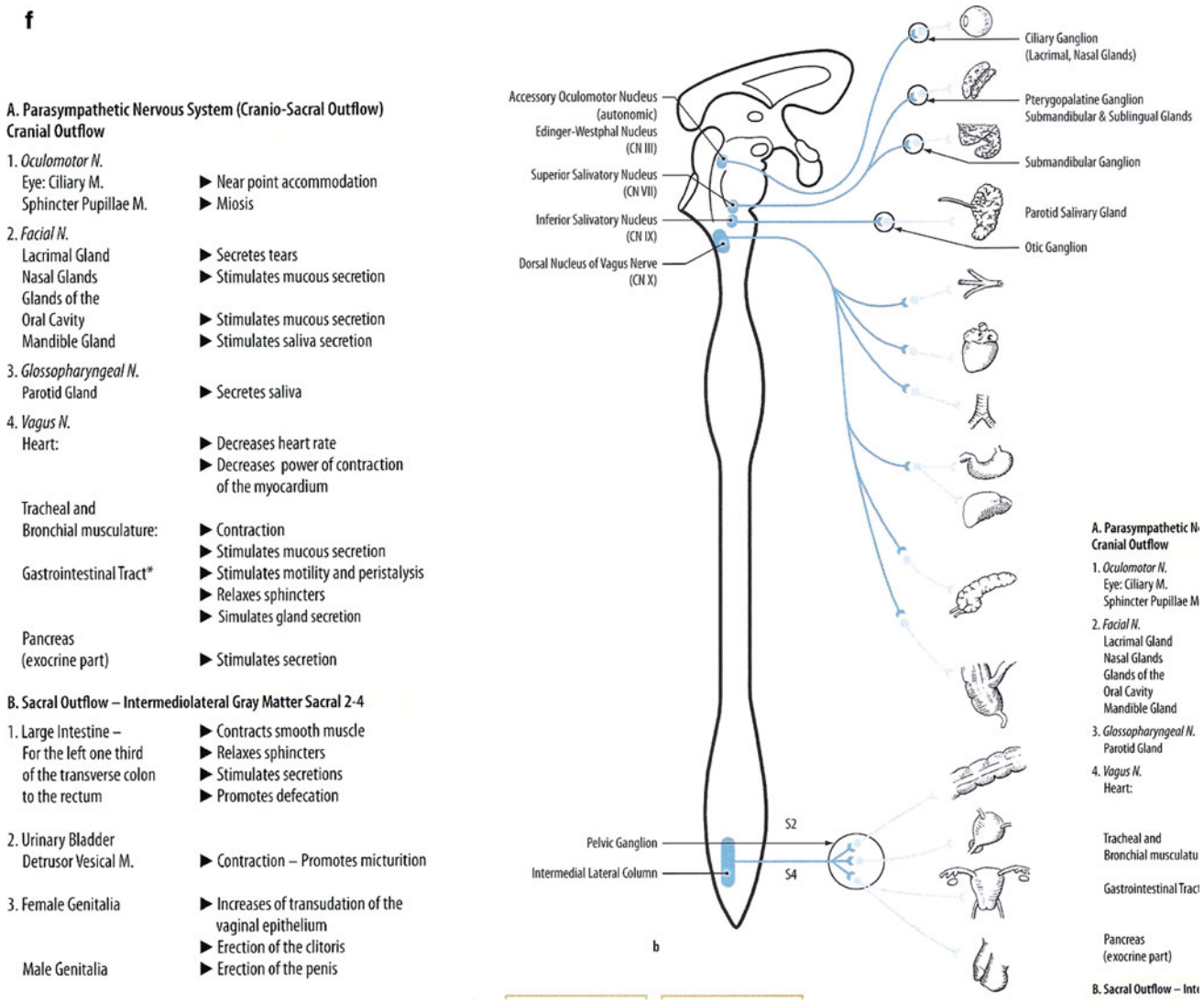


Fig. 2 (continued)

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.

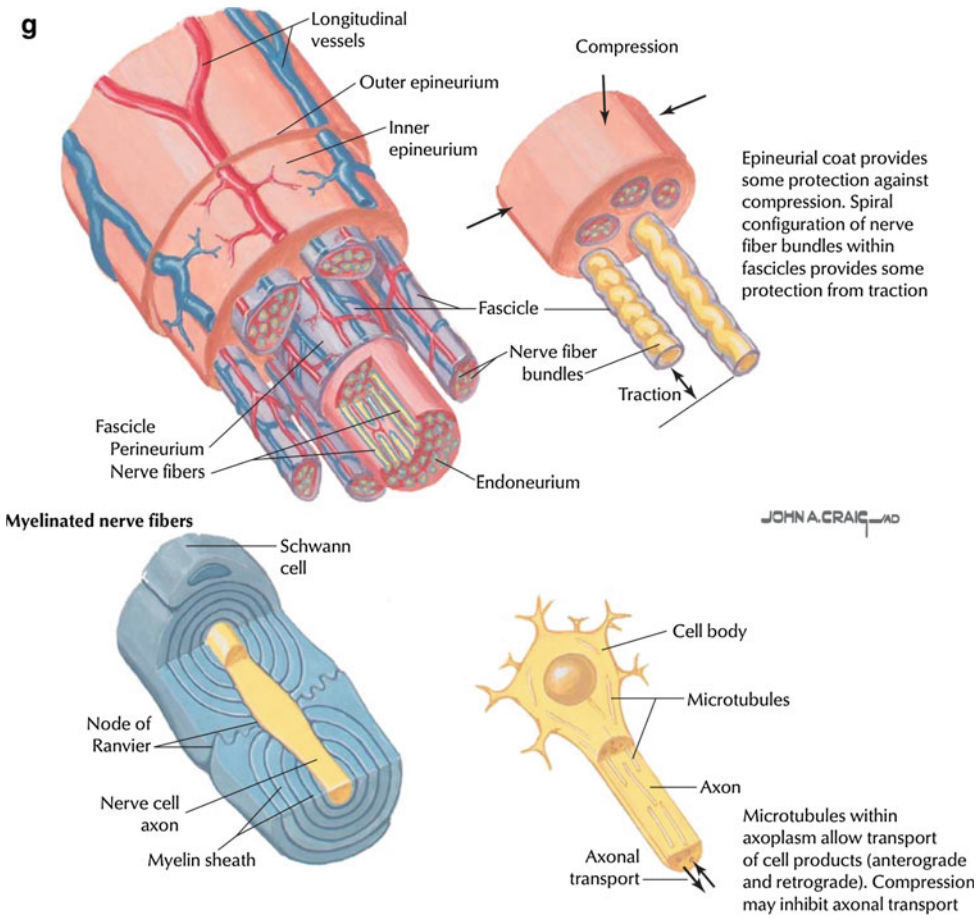


Fig. 2 (continued)

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. Cerebeller 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.

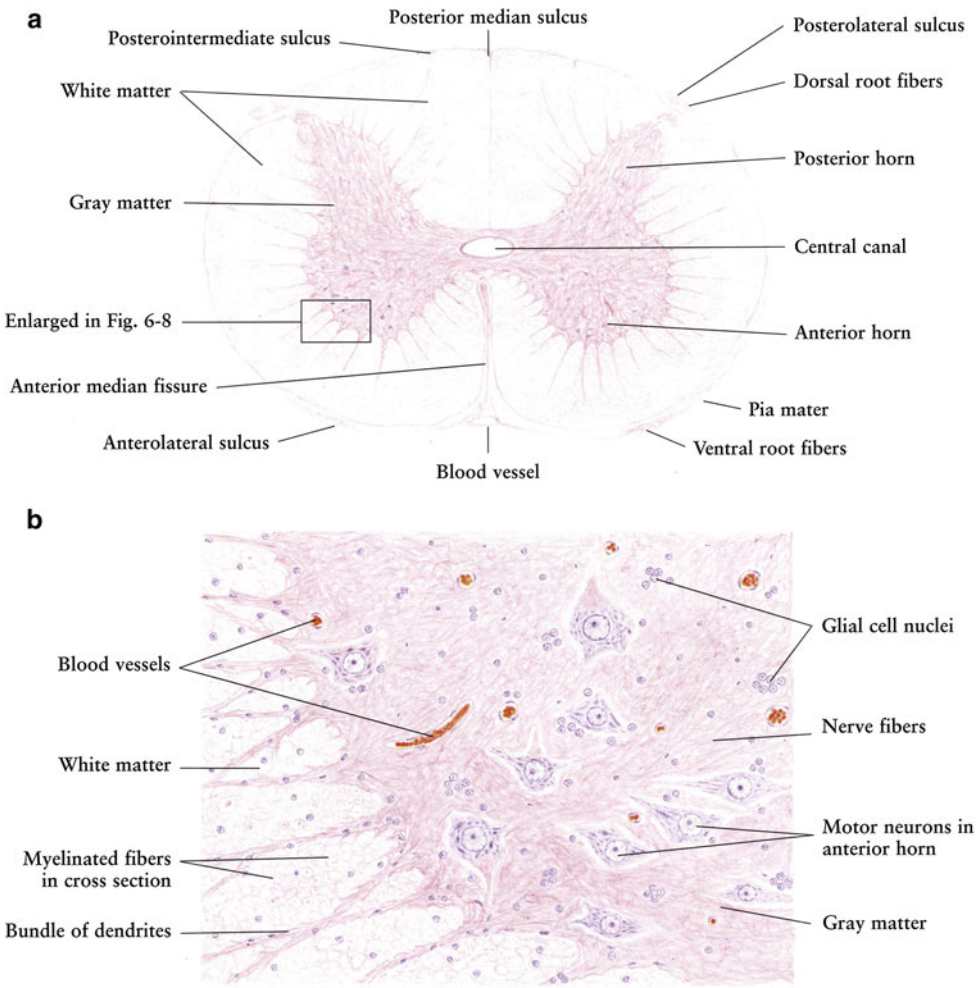


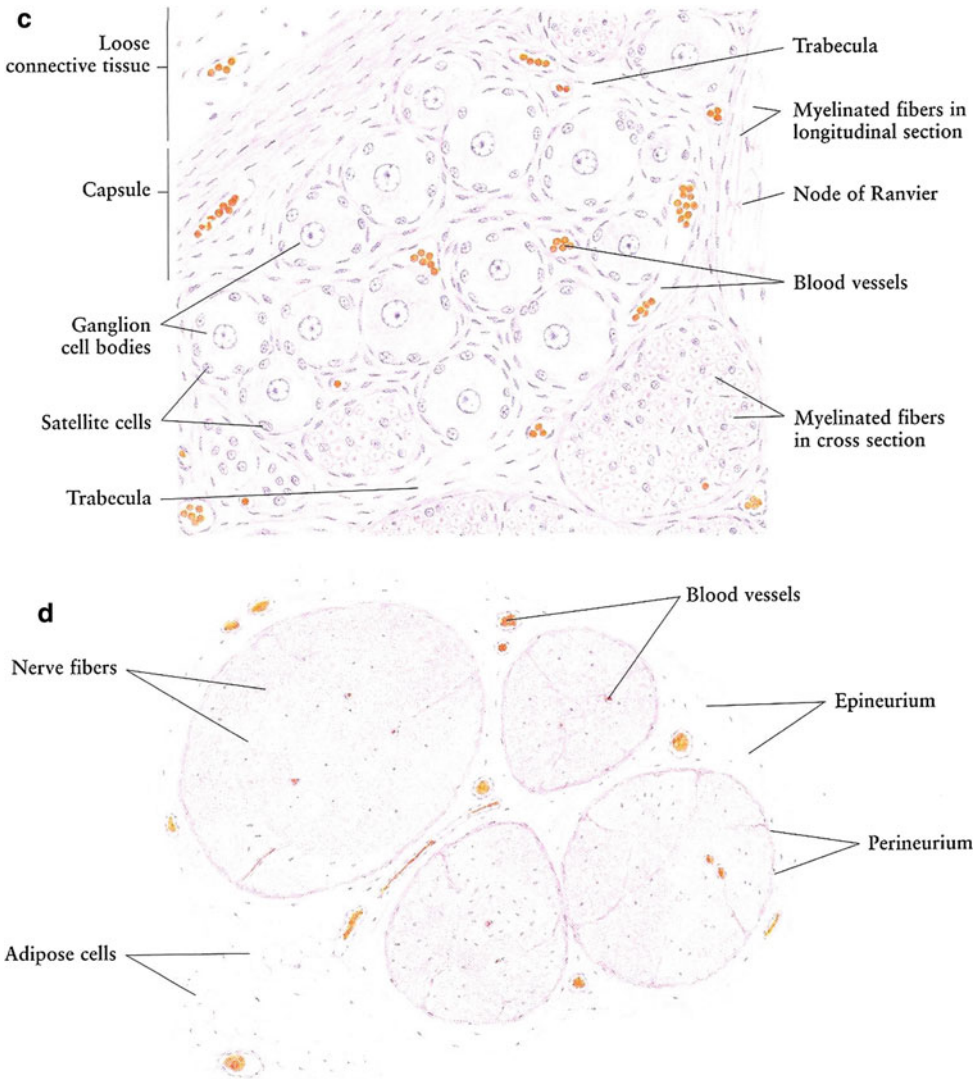
Fig. 3 Histology: **a** spinal cord segments, **b** spinal horn neurons (with permissions from Zhang 1999), **c, d** spinal ganglion

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

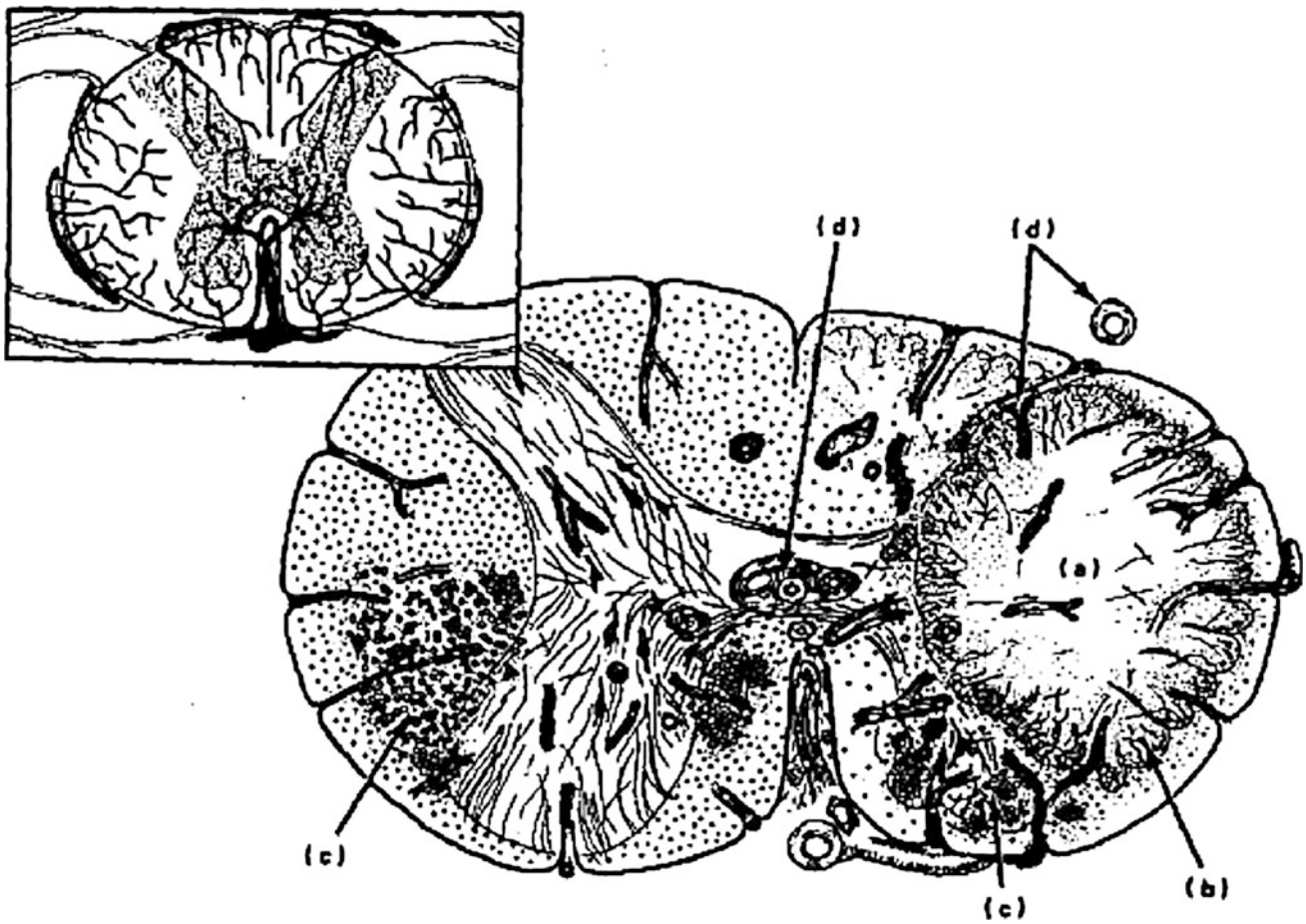


Fig. 4 **a** Delayed radiation myelopathy: The inset demonstrates the principal arterial distribution with the anterior spinal artery and two posterior spinal arteries giving off circumferential and penetrating branches. The irradiated cord may at any one time present a diversity of effects in various 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. MicrogliaJmacrophages
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. Vasculitus	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 ^{18}FDG 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_5 of 50 Gy has been suggested. However, this TD_5 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
Subjective				
Parethesias (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
Objective				
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 continuos care
Management				
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 ≈ 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 α/β 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 χ^2 statistic of 2.1 for 5 degrees of freedom, providing a reasonable fit of the model as shown in Fig. 6a.

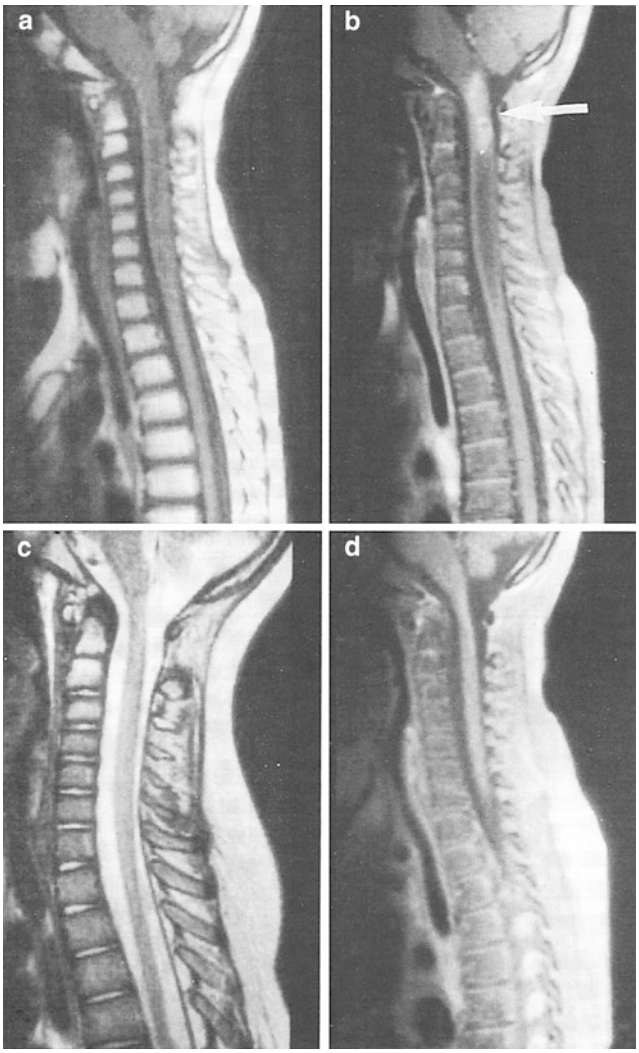


Fig. 5 Postradiation changes in the spinal cord: chemoradiation myelitis in 8-year-old girl with history of chemotherapy and radiation for acute lymphocytic leukemia (ALL). One year after the therapy, she developed limb weakness and urinary retention. **a** Sagittal T1-weighted magnetic resonance (MR) 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-wieghted 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 α/β. 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[a]	2-Gy dose equivalent[b]
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

[a] Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in Schultheiss (2008)
[b] 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[a]	2-Gy dose equivalent[b]
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

[a] Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in Scultheiss 2008
[b] 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_{50} is relatively high (e.g., >80 Gy for a 2 mm length of cord irradiated). The ED_{50} 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

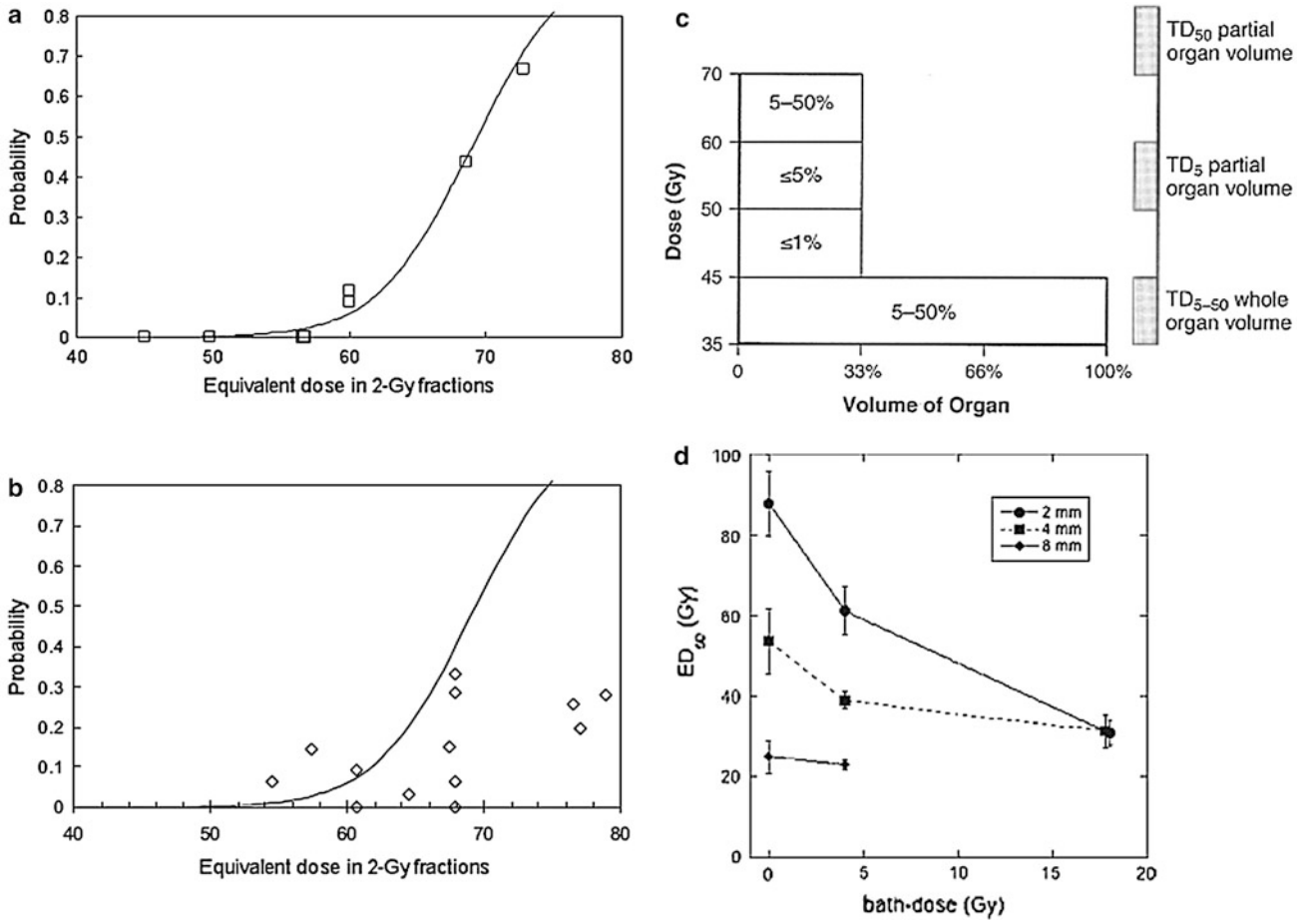


Fig. 6 **a** The dose–response function for the myelopathy of the cervical spinal cord and associated data points are from Table 3 (Reprinted with the permission of *International Journal of Radiation Oncology Biology Physics*). **b** The dose–response function for myelopathy of the *cervical* cord (*solid 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_{5-50} for whole organ irradiation. The left axis relates dose to risk for volumes irradiated. (Modified with permissions from Rubin et al. 1997). **d** ED50 for rats irradiated with protons to 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 $\approx$ $43Gy_2$). 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

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

From Kagan (1993), with permission

(BED $\approx$ 81Gy$_2$). 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$_2$) 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 sequentially. 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

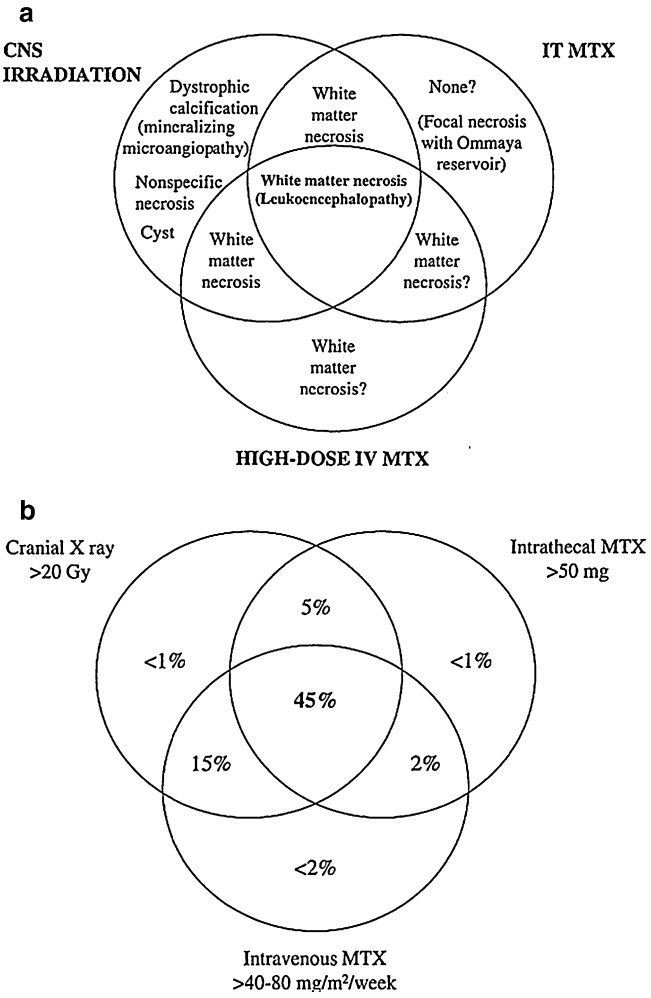


Fig. 7 Encephalopathies are induced by both irradiation and chemotherapy and can be acute and chronic. **a** A Venn diagram illustrates the pathophysiology of delayed neurotoxic sequelae seen months to years later associated with CNS irradiation, intrathecal methotrexate, and high-dose intravenous methotrexate, alone or in combination. **b** 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. (From Evans et al. 1981, with permission)

such treatments without further careful study. The effect of concurrent chemotherapy is essentially unknown in that situation. In using any mathematical model for evaluation of treatment plans it is prudent to see if its predictions are in qualitative agreement with clinical observations of complications for patients treated in one's own center, using specific protocols.

Published reports of spinal cord myelopathy associated with SBRT to the spine are summarized in Table 6. These studies include de novo irradiation alone, re-irradiation alone, and combined de novo and re-irradiation (mixed series).

As Sahgal et al. (2007a, b) emphasize in their comprehensive review of spinal radiosurgery, there is a broad variation in the metrics used to assess the dose to the spinal cord, making interpretation of the above results difficult. For example, some authors use the dose to an absolute volume (Sahgal et al. 2007a, b) while many others use the dose to a relative volume (e.g., Ryu et al. 2007, Nelson et al. 2009) or do not precisely define the dose metric (e.g., Benzil et al. 2004). Moreover, many of these cases involve stereotactic radiosurgery to cord previously treated to its full circumference with conventional external beam radiotherapy (EBRT). Nonetheless, radiation induced-myelopathy has not been reported when the maximum dose to 90 % (D10), 99 % (D1) or 100 % (maximum point dose) of the spinal cord over the level of treatment is less than 10, 12, or 13.8 Gy, respectively (Ryu et al. 2007). Note that the time frame for follow-up is short and the number of patients at risk is small.

8.1.2 Accelerated Hyperfractionated Schedules

Accelerated hyperfractionated schedules have been utilized to treat lung cancer and head and neck cancers. The interval between fractions were often less than 6 h and did not allow for full recovery and repair of spinal cord, leading to a surprisingly high incidence of spinal cord injury (Dische et al. 1988).

8.1.3 Matching Adjacent Fields (GAP): Double Overdose

There are numerous indications for a 'perfect' match of adjacent/abutting radiation fields that potentially overlap over the spinal cord. When abutting fields are treated concurrently (as in the examples of head and neck cancer and medulloblastoma below), and there is unintended overlap, both the total dose and the dose per fraction are higher than intended; sometimes referred to as "double trouble").

- *Hodgkin's Lymphoma* was commonly treated with total nodal irradiation TNI to include major lymph node bearing regions above and below the diaphragm, often to doses of ≈40 Gy. When the TNI became more widely utilized, and when a "GAP" between fields was omitted (e.g. between the mantle and the para-aortic field), some Hodgkin's survivors developed cord injury.
- *Nasopharyngeal and oropharyngeal* cancers used to be often treated with parallel opposed lateral fields. To encompass the regional cervical nodes at risk, a split anterior field was utilized to treat the lower neck cervical and supraclavicular nodes. Proper placement of cervical spinal cord shields and field matches are essential to avoid overlapping fields.
- *Medulloblastomas* of the cerebellum are treated with opposed lateral brain fields matched to a series of posterior spine fields (that indeed are matched to each other as well. Precision in matching fields, and use of various 'gap feathering' methods are used to avoid myelopathy.

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_3)	Proportion of patients previously irradiated to involved segment of spine
Gibbs et al. (2009)	6/1075	12.5–25	5–25	D_{max}: 3–28	Range: 24–121 Gy_3	>55 %
		25	**12.5**	**D_{max}: 26.2**	**D_{max}: 141**	
		20	**12.5**	**D_{max}: 29.9**	**D_{max}: 81**	
		21	**10.5**	**D_{max}: 19.2**	**D_{max}: 46**	
		24	**8**	**D_{max}: 13.9**	**D_{max}: 129**	
		20	**10**	**D_{max}: 10**	**D_{max}: 33**	
		20	**20**	**D_{max}: 8.5**	**D_{max}: 43**	
Ryu et al. (2007)	1/86[a]	<10–18	<10–18	Mean + s.d. D_{max}: 12.2 ± 2.5 D1: 10.7 ± 2.3 D10: 8.6 ± 2.1 Maximum D_{max}: 19.2 D1: 15.8 D10: 13	Mean ± s.d. D_{max}: 62 ± 4.6 D1: 49 ± 4.1 D10: 33 ± 3.6 Maximum D_{max}: 142 D1: 99 D10: 69	0 %
		18[b]	18	Mean ± s.d. D_{max}: 13.8 ± 2.2 D1: 12.1 ± 1.9 D10: 9.8 ± 1.5	Mean ± s.d. D_{max}: 77 ± 3.8 D1: 61 ± 3.1 D10: 42 ± 2.3	
		16	**16**	**D_{max}: 14.8 D1: 13.0 D10: 9.6**	**D_{max}: 88 D1: 69 D10: 40**	
Gwak et al. (2005)	2/9	21–44	3–5	Median D_{max}: 32.9 D25: 11.0 Range D_{max}: 11–37 D25: 1.2–24	Median D_{max}: 106 D25: 21 Range D_{max}: 19–172 D25: 1–88	33 %
		30	**10**	**D_{max}: 35.2 D25: 15.5**	**D_{max}:172 D25: 42**	
		33	**11**	**D_{max}: 32.9 D25: 24.0**	**153 88**	
Benzil et al. (2004)	3/31	Median: 10	Median: 5	Median: 6.0	12	Unknown
		100	**50**			
		12	**12**			
		20	**5**			
Sahgal et al. (2007a, b)	0/38	24	8	Median $D_{0.1cc}$: 10.5 D_{1cc}: 7.4	Median $D_{0.1cc}$: 23 D_{1cc}: 14	62 %
Sahgal et al. (2007a, b)	0/16	21	7	Median D_{max}:20.9 $D_{0.1cc}$: 16.6 D_{1cc}: 13.8 Range D_{max}: 4.3–23 $D_{0.1cc}$: 3.4–22 D_{1cc}: 2.8–19	Median $D_{0.1cc}$: 61 D_{1cc}: 22 Range $D_{0.1cc}$: 7–76 D_{1cc}: 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 %
Gertzsen et al. (2005)	0/50	19	19	Mean D_{max}: 10 Range D_{max}: 6.5–13	Mean D_{max}: 21 Range Dmax: 11–32	96 %
Nelson et al. (2009)	0/32	Median: 18	Median: 7	Mean ± s.d. D_{max}: 14.4 ± 2.3 D1: 13.1 ± 2.2 D10: 11.5 ± 2.1 Maximum D_{max}: 19.2 D1: 17.4 D10: 15.2	Mean ± s.d. D_{max}: 46.0 ± 13.2 D1: 39.0 ± 10.8 D10: 31.2 ± 8.1 Maximum D_{max}: 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**

[a] Patients surviving at least 1 year

[b] Results for subset of 39 lesions treated at Henry Ford Hospital with a single 18 Gy fraction

[c] 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_3 versus < 50Gy_3 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_{2Gy} is less than 135.5 Gy_2 with no course exceeding 98 Gy_2 and that the interval between courses of radiotherapy is greater than 6 months.

The data are sparse for myelopathy when spinal radiosurgery 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_3), as this dose yields a risk of transverse myelitis <0.2 % (Schultheiss 2008).
2. Calculate the time-discounted prior BED (BED_{prior}) to the cord by assuming an α/β 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_{prior} would be 43 Gy_3, 67 % of 64.2 Gy_3
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_3–BED_{prior}. In the above example, the cord tolerance would be 40 Gy_3, 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 α/β 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 ≤100 Gy_2 (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_3) Median (Range)	BED, re-irradiation (Gy_3) Median (Range)	Interval between courses (months) Median (Range)	Total BED (Gy_3) 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[a]	60 All 60	37 73[b] (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)
Stereotactic Body Radiotherapy								
Gwak et al. (2005) 1/3 1 2 Case with myelopathy No myelopathy	1/3 1 2	24	(60–81) 81 60, 81	(64–154) 154 64, 90	(18–120) 18 54, 120	(145–235) 235 145, 150	(87–141) 141 87, 90	(98–179) 179 98,114

[a] Overall survival
[b] 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_2)	Incidence of radiation-induced brachial plexopathy
Stoll and Andrews (1966) 84	33	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[a] 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)[b]	152	63 %
Bajrovic et al. (2004)	140	Breast	52 Gy (20 × 2.6 Gy)	119.6	14 %
START A (2008a) 1487	749[c]	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) 1110	1105[d]	Breast	50 Gy (25 × 2 Gy) 40 Gy (15 × 2.67 Gy)	100 93.3	0 % 0 %

[a] Out of a total of 1,117 patients, 330 received chemotherapy
[b] Two of 3 fields were treated each session, with the brachial plexus receiving 1.8, 3.4, or 5.2 Gy
[c] A total of 122 patients in the 50 Gy group and 196 patients in the hypofractionated group received radiation therapy to regional lymphatics
[d] 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 re-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
Brachial Plexus		
Musculocutaneous n.	C5–C7	Coracobrachialis, brachialis, and biceps brachii/lateral forearm
Axillary n.	C5, C6	*Anterior branch*: deltoid and portion of overlying skin *Posterior branch*: 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 lexor 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
Lumbosacral Plexus		
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	*Genital Branch*: Cremaster muscle/skin of scrotum/labia majora *Femoral Branch*: 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	*Tibial n.*: Posterior compartment/posterolateral leg and foot (medial sural cutaneous n. *Common fibular n.*: 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_{50} 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_{50} 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_{50} 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 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_{50} 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_{50} to 15 Gy and shortened the latency period for the onset of neurologic deficits.

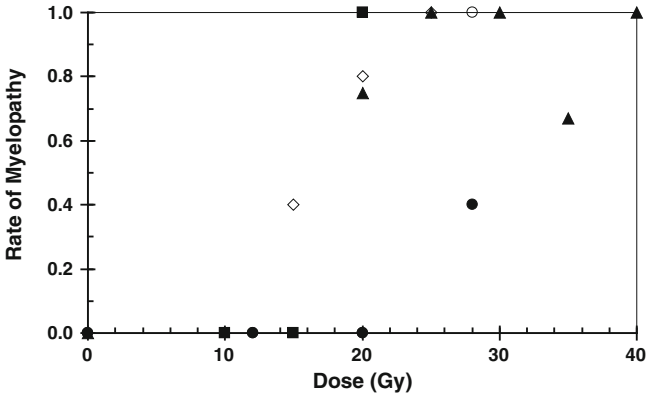


Fig. 8 Crude rate of myelopathy as a function of IORT dose in canine models. *Closed symbols* represent observed neurologic deficits (Kinsella 1985▲; Kinsella 1991 ■; Vujaskovic 1994 ●) and the *open symbols* EMG abnormalities (LeCouteur 1989 ◇; Vujaskovic 1994 ○)

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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Neuroendocrine Complications of Radiation and Cancer Therapy

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Contents

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Abstract

- Increased recognition is necessary for the neuroendocrine sequelae of cancer therapy, the contribution of radiation therapy (RT), and an emphasis on early detection and follow-up because of the potential impact on quality of life.
- Circulating serum growth hormone (GH) stimulates the production of insulin-like growth factor I (IGF-I) in all tissues. IGF-I mediates GH effects on growth, bone mineralization, and body composition (decreased fat deposition, increased muscle mass).
- GH deficiency is commonly believed to be the first hypothalamic–pituitary deficiency to emerge after injury to the hypothalamic–pituitary axis (HPA), followed by deficiencies of gonadotropin, ACTH, and thyroid-stimulating hormone (TSH) due to the radiation dose sensitivities; however, these deficiencies can occur in any order.
- The 5- and 10-year estimates of endocrinopathy in patients treated for base of skull tumors with proton therapy were as follows: 72 and 84 % for hyperprolactinemia, 30 and 63 % for hypothyroidism, 29 and 36 % for hypogonadism, and 19 and 28 % for hypoadrenalism.
- Rates of hypothyroidism for adults and children treated for Hodgkin's lymphoma can be as high as 65 % after radiation doses exceeding 40 Gy to the thyroid gland; lower doses are associated with a lower likelihood of injury.
- Primary ovarian failure is characterized by amenorrhoea, hypoestrogenism, and hypergonadotropism.

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- Altered GH secretion is an important and well-documented cause of poor growth in childhood cancer survivors, particularly in young children after surgery in the suprasellar region, cranial irradiation (>18 Gy), or total body irradiation (>12 Gy).
- The symptoms of central adrenal insufficiency can be subtle and include poor weight gain, anorexia, easy fatigability, and poor stamina.
- Hypothalamic damage from a tumor or cancer treatment can also result in hypothalamic obesity—unrelenting weight gain that does not respond to caloric restriction or exercise. Peak GH levels after RT decline as an exponential function of time based on mean dose of the hypothalamus.
- Routine yearly measurements of TSH and free T4 should be done in all patients who have received cranial irradiation, because the symptoms of central hypothyroidism are often subtle, and TSH secretory dysregulation after irradiation may precede other endocrine disorders.
- Any patient identified with GHD should be evaluated for possible ACTH deficiency and for central hypothyroidism.
- GnRH agonists are the most effective treatments for precocious puberty, rapid tempo puberty, or normally timed puberty that is inappropriate for height.
- Standard treatment for TSH deficiency or for primary hypothyroidism is levothyroxine replacement therapy.
- Hydrocortisone is the preferred agent for glucocorticoid replacement in children, because it is least likely to impair growth.

Abbreviations

ACTH	Adrenocorticotropin
BMD	Bone mineral density
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GH	Growth hormone
GHRH	Growth-hormone-releasing hormone
HPA	Hypothalamic-pituitary axis
IGF-I	Insulin-like growth factor I
LH	Luteinizing hormone
OGTT	Oral glucose tolerance testing
PRL	Prolactin
QOL	Quality of life
RT	Radiation therapy
SD	Standard deviation
TRT	Testosterone replacement therapy
TSH	Thyroid-stimulating hormone
TRH	Thyrotropin (or Thyroid-stimulating hormone)-releasing hormone

1 Introduction

Neuroendocrinopathy after therapeutic irradiation represents a treatable late effect of successful cancer therapy and highlights the importance of careful follow-up for adults and children. The endocrine effects of irradiation have been extensively studied and demonstrate the systemic manifestations of late effects after localized or large volume cranial irradiation, the differential sensitivity of functional subunits of the hypothalamus and other critical endocrine organs to radiation dose, the low-dose radiation effects in normal tissues, and the benefit of newer radiation methods and modalities.

There is significant morbidity and mortality linked to the late effects of cancer therapy. Despite our understanding of the endocrine effects of cancer therapy, this information is often not considered when models of treatment outcomes and therapy effects are developed. It is possible that the contribution of endocrine deficits to morbidity and mortality is not fully appreciated. Endocrine deficiencies affect patients who do not have CNS tumors (Agha et al. 2006) as well as those whose treatment volume encompasses the hypothalamic–pituitary axis (HPA). Rare late effects of treatment most often attributed to the volume of irradiation might be linked to the indirect effects of damage to the HPA or other organs of the endocrine system. A striking example is the link between anticancer therapy for patients with pituitary tumors and craniopharyngioma. These patients are at increased risk for mortality mainly due to radiation-associated vascular disease rather than endocrinologic abnormalities (Sherlock et al. 2010). There needs to be increased recognition of neuroendocrine sequelae of cancer therapy, the contribution of radiation therapy (RT), and an emphasis on early detection and follow-up because of the potential impact on quality of life (QOL) (Stava et al. 2007). Long-term survivors are at increased risk for broad ranging side effects including metabolic syndrome, growth hormone deficiency, and cardiovascular disease (Gurney et al. 2006). The field of endocrinology primarily encompasses noncologic diseases, yet is uniquely capable of intervention to treat the late effects of cancer therapy. Endocrinologists should be consulted early in the management of patients at high risk for preexisting endocrine deficiencies and those likely to develop these common complications.

Therapeutic external irradiation to the central nervous system, head, nasopharynx, or face that includes the HPA is known to result in a variety of neuroendocrine disturbances. Although deficiency of one or more anterior pituitary hormones may ensue following radiation to the HPA, increased secretion of prolactin, and premature activation of the hypothalamic–pituitary gonadal system can also occur after

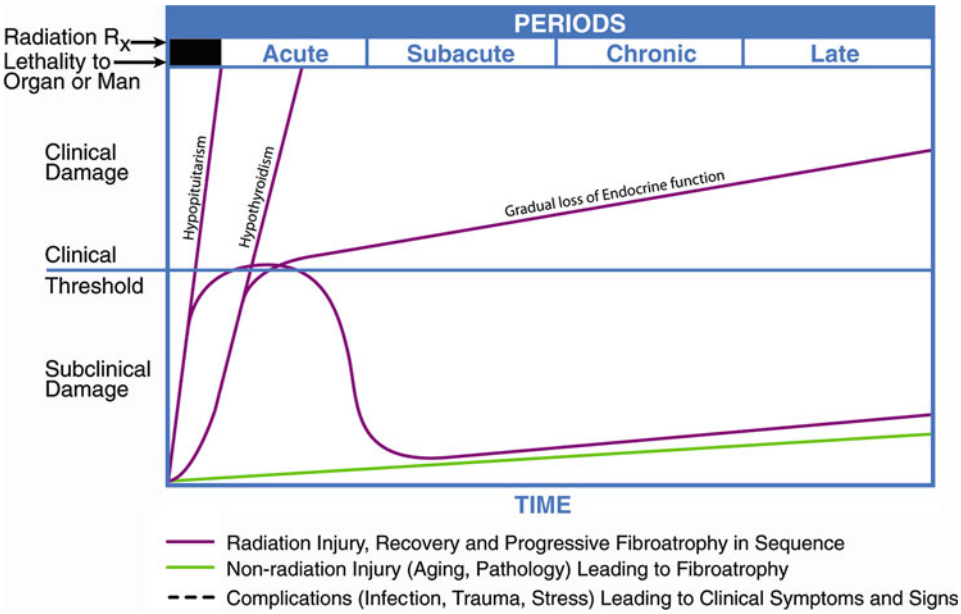

Fig. 1 Biocontinuum of adverse and late effects of the neuroendocrine system (with permission from Rubin and Casarett 1968)

treatment with radiation. In the following discussion, we have outlined the basic pathophysiology of the HPA and given a broad overview of the clinical manifestations of radiation-induced neuroendocrine dysfunction. Based on review of the current literature, we have attempted to provide dose tolerance information for each endocrine disturbance. The latter are derived from data obtained from both children and adults following irradiation of the HPA. To minimize the potential confounding effects of the primary disease and any associated surgical intervention on neuroendocrine function, we have emphasized studies in which the original lesion itself did not directly involve the HPA.

The biocontinuum of adverse and late effects are illustrated in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The HPA is a highly complex system that allows neurological and chemical signals from the brain to be translated into endocrine responses. The hypothalamus is connected to various regions of the brain via reciprocal neuronal circuits. As a result of these afferent and efferent nerve pathways, the hypothalamus serves as a vital link between distant and diverse regions of the brain. The hypothalamus is also the site of production of several peptide hormones and biogenic amines that are the predominate regulators of the anterior pituitary hormones (Fig. 2). The vascular blood supply is unique in that the superior hypophysial artery immediately joins a complex venous plexus network which further branch into a venous capillary arborization that envelopes the pituitary gland (Fig. 2). These hypothalamic factors reach the anterior pituitary gland by way of a portal venous plexus that is composed of the primary and secondary capillary plexus. The hypothalamic regulatory factors generally stimulate the secretion of anterior pituitary hormones, but mixed stimulatory and inhibitory, as well as predominant inhibitory control, also occur. A brief summary of the regulation and mechanism(s) of action of the anterior pituitary hormones follows.

2.2 Histology

The **pituitary gland** is a small complex endocrine organ about 10 mm in length, 13 mm in width, 5 mm in height, and 0.5 g in weight. It is located in a bony fossa of the sphenoid bone, the *sella turcica*, and is covered by a dense connective tissue, **capsule**, derived from the dura mater.

Histologically, the hypophysis consists of two different tissues: adenohypophysis and neurohypophysis. The adenohypophysis (glandular portion) develops from the ectoderm at the roof of the oral cavity of the embryo. These cells migrate dorsally and form Rathke's pouch and produce a variety of hormones described below. The neurohypophysis (nervous portion) is derived from an outgrowth of the floor of the diencephalon (forebrain).

The **term anterior lobe** (Fig. 3a) refers to the pars distalis and the pars tuberalis, and the posterior lobe refers to the pars nervosa and the pars intermedia. Figure 3a is a sagittal section of the human hypophysis, clearly showing the different parts of the organ.

The pituitary is made up of different types of glandular cells (Fig. 3b).

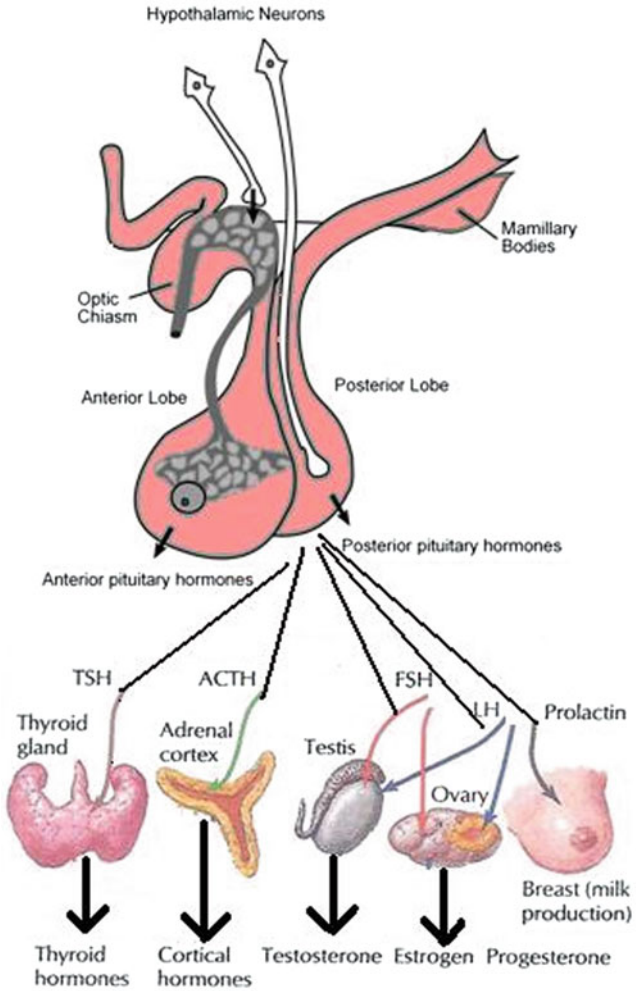

Fig. 2 Diagrammatic representation of the gross anatomy of the hypothalamic–pituitary axis and schematic representation of the anatomy of the hypothalamus and the pituitary gland, and its associated hormonal functions

The chromophils may be subdivided into two categories, acidophils and basophils.

- The acidophils, accounting for 35 % of the glandular cells in the pars distalis, are large and round or ovoid in shape. Their cytoplasm is packed with small pink or red specific granules and the secretory granules. The acidophils are composed of two cell types: somatotrophs and mammotrophs, which can be distinguished by specific immunohistochemical techniques. The somatotrophs produce growth hormone, which stimulates general body growth, particularly the growth of the epiphyses of long bones. The mammotrophs synthesize prolactin which promotes the secretion of milk during lactation.
- The basophils, representing about 15 % of the cell population of the adenohypophysis, are slightly larger in size than the acidophils. Their cytoplasm is crowded with small bluish secretory granules. Three kinds of basophils may be classified: the corticotrophs, involved in the formation of adrenocorticotropic hormone (ACTH), which promotes secretion of glucocorticoids in the cortex of the adrenal gland; the thyrotrophs, responsible for the secretion of thyrotropic hormone (thyroid-stimulating hormone, TSH), stimulating the synthesis, storage, and liberation of thyroid hormone; and the gonadotrophs, which secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Zhang 1999).

3 Physiology and Biology

3.1 Normal Hypothalamic–Pituitary Axis

The HPA is the primary interface between the nervous system and the endocrine system. The actions and interactions of the endocrine and nervous systems constitute the major regulatory mechanisms for virtually all physiologic activities. The hypothalamus has extensive neural communications with other brain regions and regulates brain functions including temperature, appetite, thirst, sexual behavior, and fear. The hypothalamus contains two types of neurosecretory cells (Fig. 2): (1) neurohypophysial neurons, which transverse the hypothalamic–pituitary stalk and release vasopressin and oxytocin from their nerve endings in the posterior pituitary, and (2) hypophysiotropic neurons, which release hormones into the portal hypophysial vessels to regulate the secretion of tropic hormones from the anterior pituitary. The six anterior pituitary hormones and their major hypothalamic regulatory factors are listed in Table 1.

3.1.1 Growth Hormone

Growth hormone (GH) is a 191-amino acid polypeptide hormone synthesized and secreted by the somatotrophs in the anterior pituitary gland in response to hypothalamic releasing hormones, primarily GH-releasing hormone (GHRH) and somatostatin. GHRH secretion is usually steady, whereas somatostatin secretion is interrupted intermittently. Somatostatin contributes to the synthesis of GH in the pituitary, but paradoxically inhibits GH release (Rose 1994). When somatostatin concentrations decrease, the tonic concentration of GHRH causes the release of GH into the systemic circulation. Ghrelin, released from the stomach during fasting, contributes to release of GH and pulses during the night (Wagner et al. 2009). Factors such as neuropeptide Y, leptin, and galanin may also regulate GH secretion. In healthy children and adults, GH secretion is pulsatile, particularly during sleep, with 2–6 pulses per night (Rose and Municchi 1999). In adolescents, additional pulses occur during the day, and the pulses have higher peaks than those seen in children and adults.

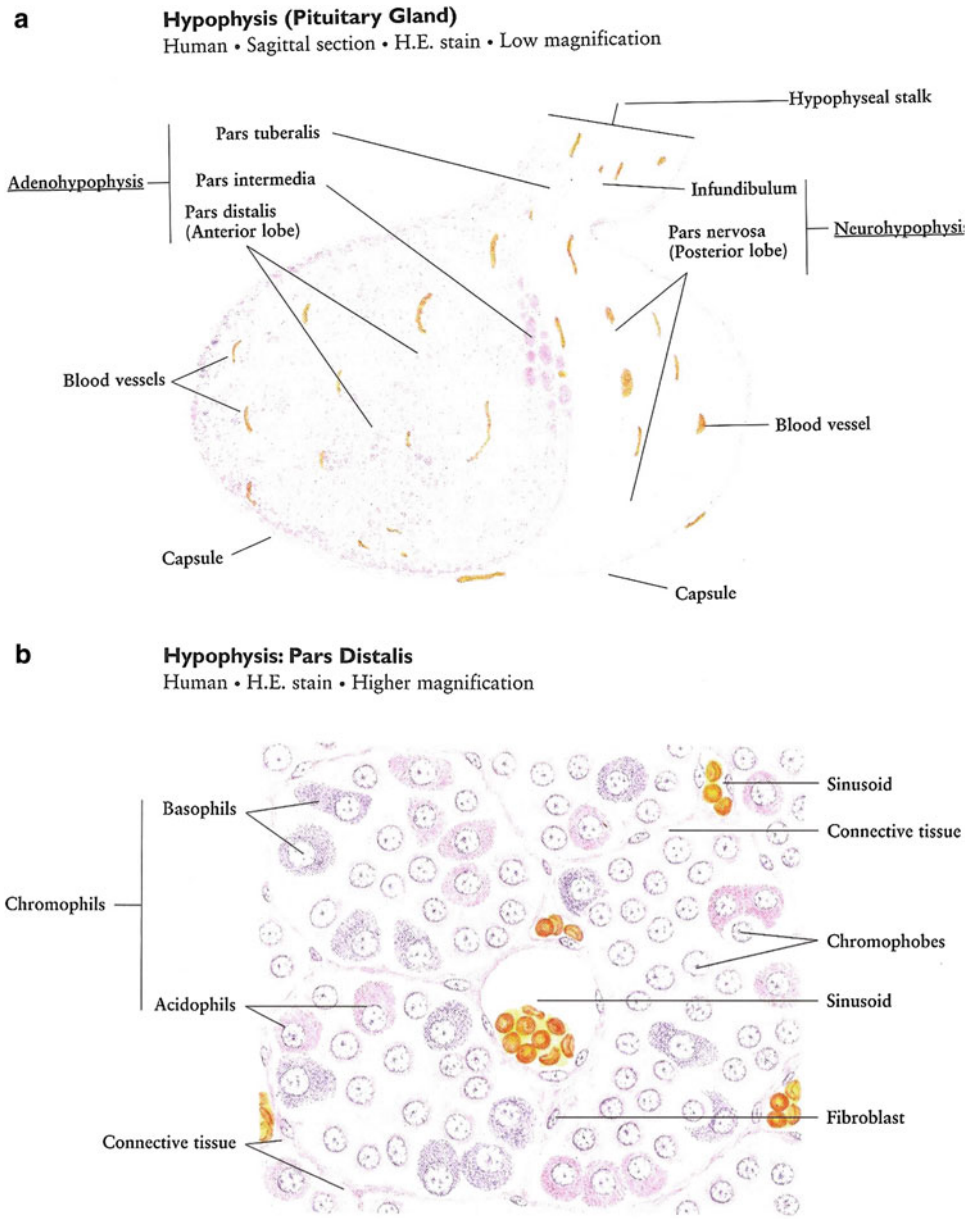

Fig. 3 Histologic examples from the **a** Anterior Lobe, **b** Glandular cells (with permission from Zhang 1999)

Circulating serum GH stimulates the production of insulin-like growth factor I (IGF-I) in all tissues. IGF-I mediates GH effects on growth, bone mineralization, and body composition (decreased fat deposition, increased muscle mass) (Vance and Mauras 1999). IGF-I is bound to IGF-binding proteins such as IGFBP3 and is transported in the blood. IGF-I and IGFBP3 concentrations are stable during the day and each reflects the integrated concentration of secreted GH.

3.1.2 Thyroid-Stimulating Hormone

Thyrotropin, also known as TSH, is a glycoprotein synthesized in the anterior pituitary. The secretion of TSH is stimulated by thyrotropin (or TSH)-releasing hormone (TRH) and inhibited by somatostatin and dopamine secreted from the hypothalamus. In persons older than 12 months of age, TSH concentration is low in the afternoon, rises dramatically (*surges*) after 1900 hours, and reaches highest concentrations between 2200 and 0400 hours (Rose and Nisula 1989). At least one-third of the trophic influence of TSH on the thyroid gland occurs at night. TRH is necessary for TSH synthesis, post-translational glycosylation, and secretion of a fully bioactive TSH molecule from the pituitary (Rose 2000). Altered TSH glycosylation, resulting in altered bioactivity, is seen in mixed hypothyroidism (central hypothyroidism with mild TSH elevation [5–15 mU/L]) (Lee et al. 1995; Rose 2001).

TSH stimulates the thyroid gland to produce thyroxine (T4) and triiodothyronine (T3). T4 and T3 circulate in the bloodstream bound to thyroxine-binding globulin and

Table 1 Anterior pituitary hormones and hypothalamic regulatory factors

Pituitary hormone	Hypothalamic factor
Growth hormone (GH)	GH-releasing hormone (GHRH)(+) Somatostatin (−)
Prolactin (PRL)	Dopamine (−)
Luteinizing Hormone (LH) and follicle-stimulating hormone (FSH)	Gonadotropin-releasing hormone (GnRH)(+)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH)(+)
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH)(+)

(+) Stimulatory, (−) Inhibitory

albumin; only small amounts are free or unbound. Free T4 undergoes intracellular deiodination to form free T3, which interacts with DNA in the cell nucleus to influence cellular mRNA and protein synthesis. Free T4 provides negative feedback at the hypothalamus and pituitary to modulate the secretion of TRH and TSH.

3.1.3 Adrenocorticotropin

Adrenocorticotropin (ACTH) is a 39-amino acid peptide hormone processed in the corticotrophs from a large precursor molecule, proopiomelanocortin. In healthy individuals, hypothalamic corticotrophin-releasing hormone and vasopressin released in two or three synchronous pulses per hour synergistically stimulate secretion of ACTH from the pituitary (Chrousos 1995). ACTH secretion is pulsatile and varies throughout the day; it peaks before the person awakens in the morning, increases with stress, and is inhibited by glucocorticoids. Because cortisol secretion is regulated by ACTH, the diurnal pattern of cortisol secretion has characteristics similar to secretion of ACTH. In addition to the negative feedback of glucocorticoids, ACTH inhibits its own secretion (short loop feedback).

3.1.4 Gonadotropins

LH and FSH are glycoproteins both stored in the same cells in the anterior pituitary. Their overall patterns of secretion vary according to the age and gender of the person. The pituitary gland produces and secretes LH and FSH in a pulsatile manner in response to a concordant episodic release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. The hypothalamic stimulus is actively inhibited between 6 months of age and the usual age of onset of puberty. This inhibition can be disturbed by tumor, surgery, or irradiation, thereby resulting in precocious puberty in children. LH stimulates testosterone production in the Leydig cells of the testes; normal spermatogenesis requires both LH and FSH. FSH stimulates follicle development in the ovary and the production of estrogen, and LH stimulates the production of progesterone from the ovarian corpus lutea after ovulation. The LH surge near the end of the follicular phase of the menstrual cycle is necessary to stimulate ovulation. Development of the ovarian follicles is largely under FSH control, and the secretion of estrogen from the follicle is dependent on both FSH and LH.

3.1.5 Prolactin

Prolactin (PRL) is a 198-amino acid polypeptide hormone synthesized and secreted from the lactotrophs of the anterior pituitary. A precursor molecule is also secreted and can constitute as much as 10–20 % of the PRL immunoreactivity in the plasma of healthy persons. The hypothalamic control of PRL secretion (primarily through dopamine release) is different than that of the other pituitary hormones in that the hypothalamus inhibits the secretion of PRL rather than stimulating it. Thus, an elevated PRL level can be a useful marker of hypothalamic disorders that leave the pituitary intact.

4 Pathophysiology

4.1 Injury of the Hypothalamic–Pituitary Axis

The HPA is vulnerable to damage by certain tumors, surgical trauma, irradiation, and chemotherapy (Constine et al. 1993; Shalet 1993). Patients with tumors in the area of the HPA (e.g., craniopharyngioma or hypothalamic and chiasmatic tumor) are at particular risk for neuroendocrinopathy (Fouladi et al. 2003; Merchant et al. 2002a, b, c, d). Many HPA injuries are attributable to damage caused by RT (see Sect. 4.2). However, the incidence of pre-RT neuroendocrinopathies in pediatric patients with brain tumors is high. Of 68 pediatric patients in one study (Merchant et al. 2002a, b, c, d), 45 (66 %) showed evidence of neuroendocrinopathy before RT, including 15 of 32 patients with tumors in the posterior fossa not adjacent to the HPA. Seventeen of the 45 patients (38 %) had abnormality in GH, 19 (43 %) in TSH, 10 (22 %) in ACTH, and 6 (13 %) in gonadotropin. In addition, patients who receive chemotherapy alone (with no history of RT or CNS tumor) may also be at risk for neuroendocrinopathy (Rose et al. 2004). Thirty-one patients were evaluated for altered growth and development in one study; of those referred patients, 48 % had GH deficiency, 52 % had central hypothyroidism, and 32 % had pubertal abnormalities (Rose et al. 2004).

GH deficiency has been commonly believed to be the first hypothalamic-pituitary deficiency to emerge after injury to the HPA, followed by deficiencies of gonadotropin, ACTH, and TSH (Shalet 1993; Spoudeas 2002); however, these deficiencies can occur in any order (Lam et al. 1991; Constine

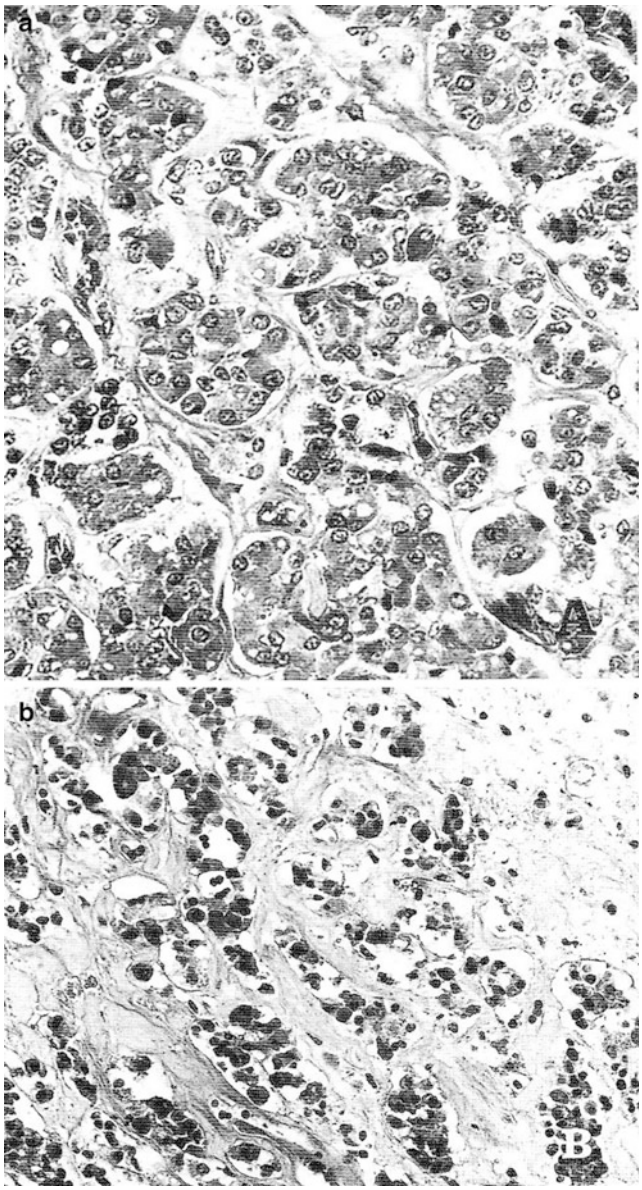

Fig. 4 Comparison of the normal epithelial cells of the anterior lobe (**a**) and the post-irradiation atrophied cells of the anterior lobe (**b**). The photomicrographs are at the same magnification. Note the severe atrophy of the epithelial cells with bands of interstitial fibrosis that also resulted from the radiation injury (with permissions from Fajardo 2001)

et al. 1993; Rose et al. 1999a, b; Merchant et al. 2002a, b, c, d; Spoudeas et al. 2003a, b). Although the most common neuroendocrinologic abnormality in survivors of childhood cancer is GH deficiency, hypothyroidism is at least as prevalent when sensitive testing methods are used (Rose et al. 1999a, b). The next most common alterations are in pubertal timing (early, rapid, precocious, delayed, or absent). ACTH deficiency, though less common than the other disorders, has more serious consequences if it is not detected. Osteopenia may result from hypothalamic–pituitary deficiency, particularly GH deficiency, hypothyroidism, and hypogonadism.

Table 2 Type and frequency of hormonal dysfunction(s) in 32 patients receiving either cranial or cranial-spinal radiation

	Cranial group	Cranial-spinal group	All
Abnormality	n = 23	n = 9	n = 32
Thyroid	17 (74 %)	5 (56 %)	22 (69 %)
Gonad[a]	11 (65 %)	3 (50 %)	14 (61 %)
Prolactin	12 (52 %)	4 (44 %)	16 (50 %)
Adrenal[b]	12 (55 %)	1 (11 %)	13 (42 %)
Number of abnormalities[a, b]			
0	1 (4 %)	2 (22 %)	3 (9 %)
1	5 (22 %)	4 (44 %)	9 (28 %)
2	7 (30 %)	1 (11 %)	8 (25 %)
3	7 (30 %)	1 (11 %)	8 (25 %)
4	3 (13 %)	1 (11 %)	4 (13 %)

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[a] Prepubertal and puberal patients ($n = 9$) excluded from gonadal category (six from cranial group, three from cranial-spinal group)

[b] One patient not tested (cranial group) three excluded from adrenal category

Hypothalamic injury resulting from tumor, surgery, or irradiation can result in unrelenting weight gain, termed hypothalamic obesity. Examples of histologic effects of RT are shown in Fig. 4.

4.2 Contribution of Radiation to Hypothalamic–Pituitary Axis Injury

RT is a significant contributor to neuroendocrine complications commonly observed after treatment for CNS tumors and tumors of the head and neck when the hypothalamus is subtended by the irradiated volume. Constine et al. reported on the radiation dose associations and frequency of HPA injury (other than GH) that occurred after treatment of CNS tumors, and demonstrated that the hypothalamus was the most sensitive component of the axis (Table 2; Constine et al. 1993). Historically, other common causes of endocrine deficiencies included CNS preventative therapy for ALL, and total body irradiation as part of preparation for bone marrow transplantation. Similar complications are observed when the HPA is incidentally irradiated in the treatment of nasopharyngeal cancer, retinoblastoma, Hodgkin lymphoma with involvement of Waldeyer's ring, and pediatric sarcomas of the head and neck (e.g., parameningeal and orbital rhabdomyosarcoma). Patients with orbital rhabdomyosarcoma are known to have excellent long-term survival; however, they are at increased risk for GH deficiency and other endocrine effects after irradiation (Forstner et al. 2006).

The timing of most hormone deficiencies after RT has been well documented (Rose 2008). Partial damage may

occur in some patients such that they respond normally to provocative tests but at much lower levels than they might have otherwise. Partial deficiencies probably have the greatest impact on children who are in their growth phase (Darzy 2009) or those with adrenal insufficiency who experience stress from intercurrent illness. The incidence and time to onset of neuroendocrine sequelae after RT are difficult to predict because of other contributors to HPA dysfunction that may coincide temporally with the administration of RT. A notable example is hydrocephalus which can cause mass effect in the region of the anterior third ventricle and generalized diminished blood flow to sensitive regions of the brain. In one study, 59 children with infratentorial ependymoma underwent provocative testing for GH, thyroid hormone, and ACTH secretion abnormality prior to RT (Lee et al. 2002). Abnormal testing was observed in 27 patients (46 %) with 30 % of the 59 manifesting an abnormality in GH secretion. Serial measurements of ventricular size from the time of diagnosis to 1 year after RT were recorded and modeled to show that ventricular size at the time of diagnosis could be used to predict pre-irradiation endocrinopathy; in addition, change in ventricular size over time could predict GH deficiency prior to irradiation. This study was remarkable because it demonstrated a relatively high rate of pre-irradiation endocrinopathy in a well-defined group and confirmed another important tumor-related cause of endocrinopathy.

Clinical data describing neuroendocrine effects of RT have been derived using generalized estimates of radiation dose under conditions where the dose to the HPA was relatively homogeneous and discrete. Examples include patients treated with single dose or fractionated TBI (8–14 Gy), cranial irradiation for ALL (18 and 24 Gy), or who have tumors of the sellar or parasellar region in which the HPA was uniformly included in the volume of prescribed dose (>50 Gy) (Fig. 5). For other diseases, the HPA may have been located within the irradiated volume for part or all of the treatment or in the gradient of dose (dose fall off) experiencing only a fraction of the daily dose administered. These circumstances make it difficult to assign a dose to the HPA and to determine the risk for late effects. These difficulties are present when the patient is seen by the endocrinologist years after treatment when retrospective dose calculations may be difficult to perform. Newer radiation techniques employ 3-dimensional imaging (CT and MR) in the planning process. The HPA and other normal tissues can be contoured on CT or MR data and the dose calculated and reported more accurately. Correlated with objective measures of endocrine effects, this information will become increasingly valuable in predicting the incidence of specific endocrine effects. Already this type of data has been modeled to predict peak GH secretion after RT (Merchant 2006) and may in the future be used to optimize RT for children.

In pediatric radiation oncology, reducing side effects of treatment is an important goal. Reducing side effects can be primarily achieved by limiting CNS irradiation only to those patients for whom the indications are clear and the benefits outweigh the risks. CNS irradiation has been effectively eliminated from the treatment of the majority of children with ALL and a significant proportion of children with low-grade glioma who may be cured with surgery. For the remainder, CNS irradiation will remain a mainstay in the treatment of most children with brain tumors. Incidental irradiation of the CNS will continue to be observed in children with ocular tumors or tumors of the head and neck destined to receive RT. Increased awareness of the importance of the hypothalamus as the effector organ in radiation-related neuroendocrine sequelae, and the use of 3-dimensional imaging in planning treatment of these tumors may lead to a reduction in late effects. Reducing the risk of complications can also be achieved by delaying the administration of RT (Shalet 1993; Spoudeas 2002; Lustig et al. 2003a, b), reducing the total dose, and by reducing the volume of irradiation. Dose reductions have been achieved for many tumors including retinoblastoma, pediatric soft-tissue sarcomas of the head and neck, and certain CNS tumors including CNS germinoma. Volume reduction has been an important area of research in the treatment of medulloblastoma, ependymoma, low-grade astrocytoma, craniopharyngioma, and CNS germinoma (Merchant et al. 2001, 2004). The risk of treating smaller volumes must be carefully balanced with objective gains documenting reductions in side effects in prospective clinical trials. To this end, the inclusion of endocrinology and its quantitative and relatively objective measures is essential. The risk of endocrine-related complications should be carefully considered in planning RT but should not be used as a reason to avoid curative therapy. Careful follow-up and evaluation will lead to early intervention and means to mitigate the consequences of irradiation.

The incidence of endocrine deficiencies and their time to onset has been well documented in children with brain tumors and patients with base of skull tumors who appear to be at risk because of the location of their tumor relative to the HPA axis, or because the radiation volume includes this structure. Thus, endocrine deficiencies are common prior to irradiation and uniformly present after irradiation in all patients with craniopharyngioma (Merchant 2006; Di Battista et al. 2006). Similarly, the incidence of hormone deficiencies is highest for children with medulloblastoma after craniospinal irradiation (Heikens et al. 1998; Laughton et al. 2008), followed by children with low-grade glioma of the diencephalon and optic pathways (Merchant et al. 2009), and less common in children with ependymoma of the posterior fossa (Spoudeas et al. 2003a, b). Complicating this picture is the occurrence of endocrine deficiencies due to incidental or scattered irradiation of non-CNS hormone-secreting tissues

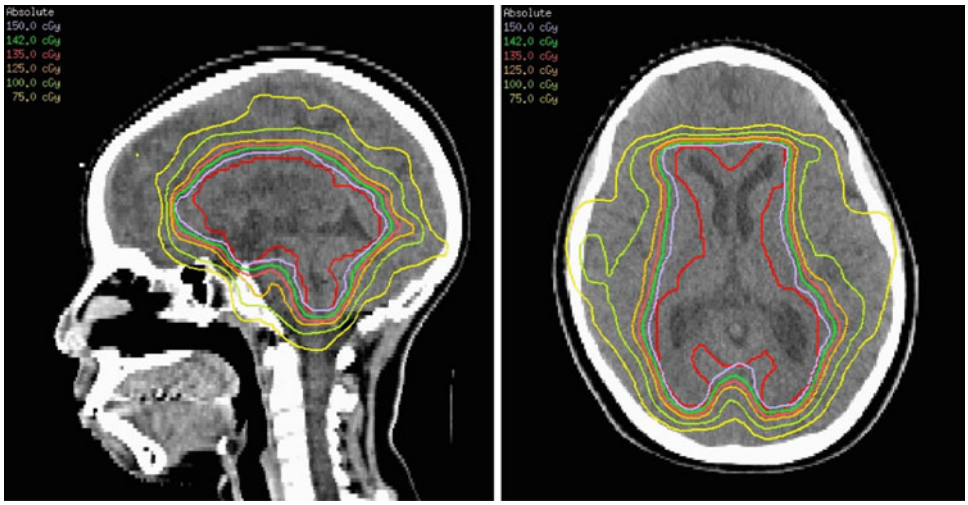

Fig. 5 Example of uniform irradiation of the HPA–whole ventricle irradiation for CNS germinoma, sagittal and axial images with overlying *isodose lines*

(Rohrer et al. 2009). For example, scattered radiation to the testes, even very low doses, results in endocrine effects for patients treated with pelvic RT (Yau et al. 2009). Nevertheless, those patients who most often develop endocrine deficiencies are those with tumors adjacent to the hypothalamus regardless of treatment modality (e.g. radiation delivery system). The 5- and 10-year estimates of endocrinopathy in patients treated for base of skull tumors with proton therapy were as follows: 72 and 84 % for hyperprolactinemia, 30 and 63 % for hypothyroidism, 29 and 36 % for hypogonadism, and 19 and 28 % for hypoadrenalism (Pai 2010). The risk of endocrinopathy was greatest among patients when the hypothalamic dose exceeded 50 Gy. These data support the work by Merchant et al. (2009) who showed that for children with low-grade glioma treated with ≥40 Gy, the 10-year cumulative incidence of hormone replacement therapy and treatment of precocious puberty were: GH 54.7 %, thyroid hormone 69.1 %, glucocorticoid 20.0 %, desmopressin 6.2 %, sex hormone 16.4 %, and GnRH agonist therapy 35.3 %. Laughton et al. (2008) showed that the incidence at 4 years of GH deficiency (93 ± 4 %), TSH deficiency (23 ± 8 %), ACTH deficiency (38 ± 6 %), and primary hypothyroidism (65 ± 7 %) was highest in patients whose hypothalamus dose exceeded 42 Gy.

4.3 Contribution of Chemotherapy to Hypothalamic–Pituitary Axis Injury

There is little doubt that chemotherapy contributes to endocrine deficiencies in long-term survivors; however, there is limited evidence because few long-term survivors in historical series reporting late effects have been cured without the use of RT. Relative exceptions include patients with leukemia, lymphoma, and extra-CNS germ cell tumors for whom chemotherapy alone was prescribed or non-TBI based conditioning regimens for stem cell transplant.

Older chemotherapy regimens used to treat HD were known to result in endocrine effects including decreased height and changes in body mass or bone mineral density (van Beek et al. 2009). Hormone deficiencies are among the leading side effects in survivors of stem cell transplantation (Leung et al. 2007). While the attribution is often given to RT, patients treated with intensive chemotherapy should be monitored for GHD (Haddy et al. 2006). Hypogonadism seems to be most common (Harris et al. 2001a, b). Alterations of gonadotropin levels and Leydig cell insufficiency persist in more than half of young patients cured from testicular cancer by cisplatin-based combination chemotherapy.

5 Clinical Syndromes

5.1 Clinical Syndromes

The LENT-SOMA provides a system for categorizing and grading the toxicity associated with hypothalamic–pituitary damage for the various hormonal axes with the exception of GH (Table 3).

5.1.1 GH Deficiency

Growth hormone deficiency is the first and most common side effect of cranial irradiation in brain tumor survivors. The risk increases with radiation dose and time after treatment. GHD is the earliest hormone deficiency and sensitive to low doses. Other hormone deficiencies require higher doses and their time to onset is much longer than for GHD (Darzy 2009). The prevalence in pooled analysis was found to be approximately 35.6 % (Mulder et al. 2009).

Altered GH secretion is an important and well-documented cause of poor growth in childhood cancer survivors, particularly in young children after surgery in the suprasellar region, cranial irradiation (≥18 Gy), or total body irradiation (≥12 Gy). Hypothalamic function is affected

Table 3 LENT-SOMA toxicity scoring for the hypothalamic-pituitary-thyroid axis

	Grade 1	Grade 2	Grade 3	Grade 4	Scoring
A. *For the hypothalamic-pituitary (thyroid axis)*					
Subjective					
Metabolic	Occasional chilliness[a]	Intermittent chilliness	Needs supplement heat		*Instructions*
Gastrointestinal	Occasional constipation[a]	Intermittent constipation	Persistent constipation		Score the 13 SOM parameters with 1–4
Weight	≥5 % gain[a]	<10 % gain	≥10 % gain		
Skin texture		Intermittent sensation of dryness	Persistent sensation of dryness		
Energy level	Occasional fatigue[a]	Intermittent fatigue	Persistent fatigue		
Objectives					
Facies		Barely noticeable puffiness and thickened lips	Obvious puffiness and thickened lips		Score = 0 if there are no toxicities
Speech quality		Barely noticeable hoarseness and slowed speech	Obvious hoarseness and slowed speech		
Skin temperature		Cool	Cold		Total the score and divide by 13
Hair texture		Difficult to comb	Brittle, splitting, hair loss		
Nodules				Palpable	
Heart rate			Slowed		
Management					
All SOM symptoms		Thyroid replacement therapy			LENT Score:
Nodules			Surgery/radionuclide therapy		
Analytic					
Basal T4	Normal limits	0–50 % decrease	>50 % decrease		Y/N Date:
Basal TSH[b]	Increased				Y/N Date:
Basal TSH[a]	Decreased				
Stimulated TSH[b]	Assessment of thyroid responsiveness				Y/N Date:
Stimulated TSH[a]	Assessment of pituitary responsiveness and hypothalamic/pituitary-thyroid axis integrity				
B. *For the hypothalamic–pituitary–adrenal axis*					
Subjective					
Activity level	Occasional fatigue	Intermittent fatigue and drowsiness	Drowsiness and weakness	Paralysis/coma	*Instructions*

(continued)

Table 3 (continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Scoring
Appetite	Occasional anorexia	Anorexia/nausea	Persistent vomiting	Refractory vomiting	Score the 8 SOM parameters with 1–4
Skin color	Darkened scars	Darkened mucosa, palmar crease	Darkened skin		
Objective					
Strength			Muscle weakness	Paralysis	Score = 0 if there are no toxicities
Cardiovascular		BP 20 % below baseline	BP 20–50 % below baseline	BP > 50 % below baseline	
Metabolic	Occasional salt craving and muscle cramping	Intermittent salt craving and muscle cramping, light headedness	Persistent salt craving and muscle cramping, dizziness, syncope	Refractory muscle cramping, coma	Total the scores and divide by 8
Skin color	Darkened scars	Darkened mucosa, palmar creases	Darkened skin		
Management					
Hypoadrenalism	Hydrocortisone replacement				LENT Score:
Analytic					
Corticotrophin-stimulation test	Assessment of adrenal responsiveness and hypothalamic/pituitary-adrenal axis integrity				Y/N Date:
Corticotrophin-releasing hormone stimulation test	Assessment of adrenal responsiveness and hypothalamic/pituitary-adrenal axis integrity				Y/N Date:

C. *For the male hypothalamic/pituitary (gonadal)*					
Subjective					
Libido	Occasionally suppressed	Intermittently suppressed	Persistently suppressed	Refractory and excruciating	*Instructions* Score the 4 SOM parameters with 1–4
Objective					
Fertility				Impotent	Score = 0 if there are no toxicities
Libido	Occasional loss	Intermittent loss	Persistent loss		Total the score and divide by 4
Management					
Libido		Hormone replacement			LENT Score:
Analytic					
FSH/LH	Normal limits or borderline decreased	Decreased			Y/N Date:
Testosterone	Normal limits or borderline decrease	Decreased			Y/N Date:
Stimulated FSH/LH	Assessment of testes responsiveness and hypothalamic/pituitary-testes axis integrity				Y/N Date: Y/N Date:

(continued)

Table 3 (continued)

Grade 1		Grade 2	Grade 3	Grade 4	Scoring
D. *For the female hypothalamic/pituitary (gonadal)*					
Subjective					
Hot flashes	Occasional	Intermittent	Persistent		*Instructions*
Dysmenorrhea	Occasional	Intermittent	Persistent		Score the 10 SOM parameters with 1–4
Menstruation		Oligomenorrhea	Amenorrhea		
Libido	Occasionally suppressed	Intermittent suppressed	Persistent suppressed		
Objectives					
Ovulation			Anovulation in premenopausal women		Score = 0 if there are no toxicities
Involuntary infertility				Infertile	Total the score and divide by 10
Osteoporosis			Radiographic	Fracture	
Management					
Dysmenorrhea, hot flashes		Persistent hormone replacement			LENT Score:
Menstruation		Hormone replacement			
Osteoporosis		Hormone replacement, Calcium supplements			
Analytic					
FSH/LH/Estradiol	Assessment of hypothalamic/pituitary-gonadal axis integrity				Y/N Date:
Bone densitometry	Quantify bone density				Y/N Date:
Stimulated FSH/LH	Assessment of pituitary responsiveness				Y/N Date:

[a] Hypothalamic/pituitary-thyroid axis
[b] Primary thyroid

more than is pituitary function (Shalet 1993). In most patients with GHD, the deficiency occurs in the levels of hypothalamic GHRH and somatostatin, with a resulting loss of the circadian pulsatile pattern of GH secretion. The radiation effect on GH secretion is dependent on fraction size and total hypothalamic dose-volume (Merchant et al. 2002a, b, c, d). A large fraction size of radiation administered over a short period of time is more likely to cause GHD than is the same total dose administered in smaller fractions over a longer period of time. In one prospective study, all of the 21 children treated with a total dose of more than 45 Gy for optic pathway tumor experienced GHD and significant slowing of growth rate within 2 years after irradiation (Brauner et al. 1990). At doses of cranial irradiation higher than 30 Gy (e.g., for suprasellar or posterior fossa tumor), the risk for GHD may be more than 80 % by 10 years after RT (Shalet et al. 1976a, b). Cranial irradiation doses in excess of 24 Gy results in GH deficiency in as many as two-thirds of patients (Shalet 1993; Sklar 1997). In many younger children, GHD results from lower doses (>18 Gy). Doses of only 12–14 Gy of total body irradiation combined with chemotherapy and bone marrow transplantation also pose a significant risk for GHD (Leung et al. 2000a, b, 2002; Sklar 1997).

The growth rate is typically slow in children who are undergoing treatment for cancer and usually improves or shows catch up after completion of cancer therapy. Children whose growth rate does not improve or whose growth rate is less than the mean for age and sex should be evaluated for growth failure. Causes of slow growth other than GHD include hypothyroidism, radiation damage in growth centers of the long bones or the spine, chronic unresolved illness, poor nutrition, and depression. In individuals who have attained adult height, GHD is usually asymptomatic (Vance and Mauras 1999), but may be associated with easy fatigability, decreased muscle with increased fat mass, and increased risk for cardiovascular disease (Cummings and Merriam 2003; Gilchrist et al. 2002).

Patients with GHD, both children and adults, are at increased risk for additional endocrine deficiencies. Roughly 35 % of patients presenting with isolated GHD will eventually develop other endocrine deficiencies (Klose et al. 2009). Patients treated with cranial irradiation are at increased risk for a broad spectrum of metabolic changes including obesity, dyslipidemia, hypertension, and hyperuricemia. GH may be used to ameliorate metabolic problems (Pietilä et al. 2009). GH replacement in patients treated with TBI may have a positive impact (Bakker et al. 2007).

5.1.2 TSH Deficiency

Central hypothyroidism refers to thyroid hormone deficiency caused by a disorder of the pituitary, hypothalamus, or hypothalamic-pituitary portal circulation. In contrast, primary hypothyroidism refers to under-function of the thyroid gland itself. Primary hypothyroidism is the most common form of hypothyroidism in the general population and may occur in cancer survivors related to family history and additional contribution from the cancer therapy. The thyroid gland may have been injured through irradiation or autoimmune activity, but the central axis is intact. Central hypothyroidism in many survivors of childhood cancer is characterized by blunted or absent nocturnal TSH surge, suggesting the loss of normal circadian variation in TRH release (Pitukcheewanont and Rose 1997). Using sensitive testing of TRH and nocturnal TSH surge, Rose et al. (1999a, b) showed that central hypothyroidism, defined by a blunted TSH surge, low and delayed TSH peak or delayed TSH decline after TRH administration, is more common than previously suspected. Central hypothyroidism was found in as many as 65 % of the survivors of brain or nasopharyngeal tumors, 35 % of bone marrow transplant recipients, and 10–15 % of leukemia survivors (Rose 2000, 2001) (Table 3A).

In cancer survivors, mixed hypothyroidism reflects separate injuries to the thyroid gland and the hypothalamus (e.g., radiation injury to both structures). TSH values may be elevated and, in addition, the secretory dynamics of TSH are abnormal with a blunted or absent TSH surge or a delayed peak response (i.e., >45 min) to TRH (Rose et al. 1990, 1999a, b). This is in contrast to primary hypothyroidism in which the TSH surge and timing of response to TRH are normal. In a study of 208 childhood cancer survivors referred for evaluation of possible hypothyroidism or hypopituitarism, mixed hypothyroidism was present in 15 (7 %) (Rose et al. 1999a, b). All of the patients with mixed hypothyroidism had free T4 concentrations in the low-normal range; four had no elevation of basal TSH but elevated peak TSH, and seven had basal elevated TSH, but peak response to TRH in the normal range. Both the TRH test and the TSH surge test were required to make the diagnosis (Rose et al. 1999a, b). Among patients who received total body irradiation (fractionated total doses of 12–14.4 Gy) or craniospinal irradiation (fractionated total cranial doses higher than 30 Gy), 15 % had mixed hypothyroidism.

Secretory dysregulation of TSH after irradiation may precede other endocrine disorders. For example, 1 year after receiving cranial irradiation for nasopharyngeal carcinoma, 90 % of patients in one study had a delayed TSH peak response to TRH, which is suggestive of central hypothyroidism (Lam et al. 1991). Five years later, 64 % of this cohort had GH deficiency, 31 % had gonadotropin deficiency, and 27 % had ACTH deficiency. In another study, seven children with brain tumors who were studied prospectively after cranial irradiation (>30 Gy) had a blunted TSH surge before the onset of reduced GH concentrations (Spoudeas 1996). In

another cohort of patients with central hypothyroidism, 34 % had dysregulation of TSH secretion before the development of GH deficiency (Rose et al. 1999a, b).

Central hypothyroidism is difficult to diagnose because of its subtle clinical and laboratory presentation. It is particularly difficult to recognize in patients whose growth is complete, because slowed growth rate can no longer be used as a sign. Symptoms of central hypothyroidism (e.g., asthenia, edema, drowsiness, adynamia, and skin dryness) may have a gradual onset and go unrecognized until thyroid replacement therapy is initiated and the patient feels better (Ferretti et al. 1999). In addition to delayed puberty and slow growth, hypothyroidism may cause fatigue, dry skin, constipation, increased sleep requirement, and cold intolerance. Radiation dose to the hypothalamus in excess of 42 Gy was associated with an increase in the risk of developing TSH deficiency, 44 ± 19 % (dose > 42 Gy) and 11 ± 8 % (dose < 42 Gy) (Laughton et al. 2008).

5.1.3 ACTH Deficiency

ACTH deficiency is less common than other neuroendocrine deficits but should be suspected in patients who have a history of brain tumor (regardless of therapy modality), cranial irradiation, GH deficiency, or central hypothyroidism (Constine et al. 1993; Rose et al. 2005). Though uncommon, ACTH deficiency can occur in patients who have received intracranial radiation that did not exceed 24 Gy and has been reported to occur in less than 3 % of patients after chemotherapy alone (Rose et al. 2005) (Table 3B).

The symptoms of central adrenal insufficiency can be subtle and include poor weight gain, anorexia, easy fatigability, and poor stamina. In patients who have ACTH deficiency, as opposed to primary adrenal insufficiency, symptoms of salt craving, electrolyte imbalance, vitiligo, and hyperpigmentation usually are not observed. More overt manifestations of complete ACTH deficiency include weight loss and shakiness that is relieved by eating (hypoglycemia). Signs of adrenal crisis at times of medical stress include weakness, abdominal pain, hypotension, and shock.

Patients with partial ACTH deficiency may have only subtle symptoms unless they become ill. Illness can disrupt these patients' usual homeostasis and cause a more severe, prolonged, or complicated course than expected. As in complete ACTH deficiency, incomplete or unrecognized ACTH deficiency can be life-threatening during concurrent illness.

5.1.4 LH/FSH Deficiency

High doses of cranial radiation (≥30 Gy) are more likely to cause hypothalamic GnRH deficiency and, therefore, gonadotropin deficiency (or in some patients precocious onset puberty through loss of inhibition that later progresses to gonadotropin deficiency through loss of GnRH secretory cells). Lower doses of cranial radiation (18–24 Gy) are more likely to cause damage to gamma-aminobutyric acid secreting neurons alone (leading to disinhibition and premature activation of GnRH neurons) and therefore, rapid tempo of puberty or precocious puberty (Roth et al. 2001; Oberfield et al. 1996; Ogilvy-Stuart et al. 1994). In girls, the first signs of puberty are growth spurt and breast development (palpable breast buds or thelarche), followed by pubic hair growth and, after about 2 years, by menarche. In boys, the first sign of puberty is testicular enlargement (testes length > 2.5 cm), followed by penile and pubic hair growth and growth spurt. In most studies of normal children, pubertal milestones are attained at ages that are normally distributed, with a standard deviation (SD) of approximately 1 year (Tanner and Davies 1985). Children entering puberty more than 2 SDs earlier or later than average should be considered for endocrine evaluation. The average age that girls experience thelarche is 10 years, and that of menarche is 12.8 years; the average age when boys experience onset of testicular growth is 11 years (Table 3C, D).

Patients with gonadotropin deficiency may have delayed, interrupted, or absent puberty. Staging of puberty is usually performed by the criteria of Tanner (Tanner and Davies 1985). In survivors of childhood cancer, we initiate evaluation for delayed puberty in girls with no onset of breast development by 12 years of age or no menarche by 14 years of age; and in boys with no sign of testicular growth by 13 years of age. Boys treated with agents that cause infertility may have normal pubertal hormones but reduced testicular volume because of damage to the seminiferous tubules and reduced sperm production. Hypogonadism may result from undiagnosed primary hypothyroidism and may be reversible with thyroid hormone replacement.

5.1.4.1 Precocious or Rapid Tempo of Puberty

Precocious puberty is defined as the onset of secondary sexual development before age 8 years in girls and before age 9 years in boys (Boepple and Crowley 1996). Despite controversy that puberty prior to these ages may occur in normal children (Herman-Giddens et al. 1997), younger occurrence than age 8 or 9 years may be the only clue to the presence of pathology and should not be ignored (Midyett et al. 2003). Pubic hair, acne, and body odor are not usually part of the presentation of precocious puberty in children younger than 4 years. Precocious puberty occurs in childhood cancer survivors who have lost inhibition of hypothalamic GnRH release as a result of tumor presence, raised intracranial pressure, cranial surgery, or low dose cranial irradiation (18–24 Gy) (Burstein 1994; Ogilvy-Stuart et al. 1994). Female sex and younger age at the time of cancer treatment are risk factors for precocious puberty: precocious puberty occurs at a lower HPA dose in girls compared to

boys. In some children who have received cranial irradiation, puberty may start at a normal age and advance rapidly. Thus, tempo of progression as well as timing of onset must be monitored. Rapid puberty is also caused by loss of inhibition of hypothalamic GnRH secretion. Short adult height is the outcome of early onset and/or rapid tempo puberty. Early bony maturation may cause the child to lose 1 to 3 years of growth.

5.1.5 Hyperprolactinemia

Hyperprolactinemia has been described in patients who have received doses of radiation larger than 50 Gy to the hypothalamus, or surgery disrupting the integrity of the pituitary stalk. Hyperprolactinemia may result in delayed puberty. In adult women, hyperprolactinemia may cause galactorrhea, menstrual irregularities, loss of libido, hot flashes, infertility, and osteopenia; in adult men, impotence and loss of libido. Primary hypothyroidism may lead to hyperprolactinemia as a result of hyperplasia of thyrotrophs and lactotrophs, presumably due to TRH hypersecretion. The PRL response to TRH is usually exaggerated in these patients.

5.2 Detection

Signs and symptoms prompting immediate evaluation

Survivors of childhood cancer with any of the following 10 symptoms should be referred for the evaluation of neuroendocrinopathy: (1) slow growth rate or failure to show catch up growth; (2) failure to thrive; (3) obesity; (4) persistent fatigue or anorexia; (5) polydipsia and polyuria; (6) severely dry skin, or thin and brittle hair; (7) altered timing of onset of puberty (e.g., signs of puberty before age 9 years or in patients with short height, failure to enter puberty by age 12 years in girls and by age 13 years in boys); (8) abnormal tempo of puberty (e.g., rapid or interrupted progression of puberty); (9) galactorrhea; and (10) abnormal menstruation or sexual function.

Surveillance of asymptomatic patients

Asymptomatic patients who are at risk for neuroendocrinopathy (Table 4) should undergo the following routine yearly surveillance:

- Accurate measurements of height, or arm span (an alternative estimate of height) if the patient received total body or spinal irradiation or has scoliosis or kyphosis (factors that lead to reduced spinal bone growth or measurement)
- Accurate measurement of weight and assessment of body mass index
- Assessment of nutritional status, adequacy of dietary calcium and vitamin D intake
- Ascertainment of Tanner stage, testicular volume (as measured by Prader orchidometry), and interpretation of whether the pubertal status and tempo of progression are appropriate for age and height
- Measurement of the serum concentrations of free T4 and TSH.

5.2.1 GH Deficiency

GH deficiency should be considered in children who have a slow growth rate and a medical history that indicates that they are at risk for GHD (Growth Hormone Research Society 2000; Wilson et al. 2003). Bone age, as determined by radiographic analysis of the left hand and wrist, should be determined, and IGF-I and IGFBP3 should be measured in children who are growing too slowly. The combination of previous cranial or total body irradiation, slow growth rate, normal weight gain, no intercurrent illness, delayed bone maturation, and low plasma levels of IGF-I and IGFBP3 (i.e., concentrations lower than 1 SD of the mean for the child's age group) are highly suggestive of GHD. The diagnosis should be confirmed by GH stimulation testing (Rose et al. 1988). Evaluation of the nocturnal profile of GH secretion is rarely necessary to make the diagnosis, but the study may be abnormal in symptomatic children after cranial irradiation that have normal stimulated GH results (Blatt et al. 1984) (Table 4).

Recognition of GHD in adults is more difficult, because slow growth rate is not available as a marker. Recognition depends on clinical suspicion related to medical history. Diagnosis of GHD in adults requires evidence of other hypothalamic–pituitary hormone deficiencies and a low peak response to GH stimulation tests (Biller et al. 2002).

IGF-I receptor inhibition has been developed as a targeted therapy for a variety of adult and pediatric malignancies because IGF-I signaling has been shown to be involved in tumor cell growth and survival (LeRoith and Helman 2004). As IGF-IR blockade may lead to an increase in the production of IGF-I through normal feedback mechanisms, the effects of a paradoxical increase in circulating levels of IGF-I should be monitored.

The impact of GH deficiency in children with brain tumors

Neurons in the hypothalamus that produce GHRH are sensitive to the effects of tumor and treatment including surgery, radiation, and chemotherapy. GHD is a common side effect of CNS-directed therapy in oncology. The extent and impact of GHD before and after RT is largely unknown and should be viewed as an important research focus. Estimating the extent of this underreported problem may prompt research to identify means for intervention and improvement in screening guidelines for those at risk. We recently showed the extent and impact of GHD in GH replacement therapy on three distinct groups of children with localized brain tumors, ependymoma, and low-grade glioma and craniopharyngioma (Merchant et al. 2011).

Table 4 Evaluation of patients at risk for late effects: neuroendocrine (with permission from Halperin et al. 2010)

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
GH deficiency		>18 Gy to HP axis	Tumor in region of HP axis	Falling off of growth curve Inadequate growth velocity Inadequate pubertal growth spurt	Annual stadiometer height (q6 months at age 9–12 years) Growth curve Bone age at 9 years, then yearly until puberty is reached Insulin stimulation test and pulsatile GH analysis	GH therapy Delay puberty with GnRH agonist
Adrenocorticotropic hormone deficiency		>40 Gy to HP axis	Tumor in region of HP axis	Muscular weakness, anorexia, nausea, weight loss, dehydration hypotension, abdominal pain, increased pigmentation (skin, buccal mucosa)	Cortisol (a.m.) for baseline, PRN Insulin-hypoglycemia; metyrapone stimulation tests	Hydrocortisone
Thyrotropin-releasing hormone deficiency		>40 Gy to HP axis	Tumor in region of HP axis	Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy, poor linear growth, menstrual irregularities, pubertal delay bradycardia, hypotension	Free T4, T3, TSH baseline, q1 year	Hormone replacement with thyroxine Anticipatory guidance regarding symptoms of hypothyroidism
Precocious puberty (especially girls)		>20 Gy to HP axis	Tumor in region of HP axis	Early growth spurt False catch-up Premature sexual maturation Female: breast development and public hair before 8 years and menses before 9 years Male: testicular and penile growth and pubic hair before 9.5 years	Height, growth curve q year Bone age q2 years until mature LH, FSH, estradiol or testosterone Pelvic ultrasound, GnRH stimulation testing	GnRH agonist
Male gonadotropin deficiency		>40 Gy to hypothalamic region	Tumor in region of hypothalamus	Delayed, arrested, or absent pubertal development: lack of diminished pubic and axillary hair, penile and testicular enlargement, voice change, body odor, acne	LH, testosterone q1–2 years GnRH testing	Testosterone replacement

The low-grade glioma cohort included 78 patients with a median age of 8.7 years treated between 1997 and 2006. Using standard provocative testing, pre-irradiation GHD was identified in 50 % (18/36) of children at a level less than 10 ng/ml. Based on a level of 7 ng/ml, 25 % of the children 9/36 were identified as having GHD prior to

radiation. The accessed 5 year incidence of hormone replacement therapy in patients with low-grade glioma was 57 % for thyroid hormone, 44 % for GHRH, 43 % for GNRH agonist, and 22 % for cortisol replacement. The median follow-up on these data was 54 months (Fig. 6a) (Merchant et al. 2009).

A similar assessment was performed in 88 children with ependymoma. GHD was evaluated before and after RT and the incidence of hormone replacement therapy. Considering patients treated between 1997 and 2006 with a median age of 2.8 years, pre-irradiation GHD was identified in 28 % (24/87) using a cut-off level of 10 ng/ml. The pre-irradiation incidence of GHD was 14 % (12/87) using a cut-off level of 7 ng/ml. The 5-year incidence of hormone replacement therapy was 26 % for thyroid hormone, 18 % for GH, and 6 % for control (Fig. 6b).

Patients with craniopharyngioma were markedly different. They had the highest incidence of pre- and post-irradiation GHD and hormone replacement therapy. Among 27 patients with craniopharyngioma treated between 1998 and 2003, with a median age of 7.9 years, pre-irradiation GHD was identified in 81 % (22/27) using a cut-off of 10 ng/ml. The incidence was 53 % (19/36) using a level of 3 ng/ml (severe GHD). The baseline, 6, 12, and 24 months incidence of hormone replacement therapies were 0, 0, 46 and 71 % for GH; 43, 46, 54, and 57 % for desmopressin; 75, 79, 89, and 93 % for thyroid hormone; and 71, 75, 75, and 75 % for adrenal hormone replacement.

GH secretion has shown the highest level of sensitivity to the effects of RT on hypothalamus. Peak GH levels after RT decline as an exponential function of time based on mean dose of the hypothalamus. These data are consistent among patients with ependymoma, low-grade glioma/optic pathway glioma, and craniopharyngioma. The marked difference is that children with craniopharyngioma often have a very high rate of pre-irradiation endocrinopathy and a fall to near undetectable GH levels only 12 months after RT. Likewise, patients with low-grade glioma or optic pathway glioma tend to have a high incidence of pre-irradiation endocrinopathy and GHD. Their mean GH level prior to RT, excluding patients who have definite pre-irradiation deficits, tends to be higher than in those CNS patients with craniopharyngioma, yet lower than the ependymoma group. However, patients with ependymoma are more susceptible to the effects of hydrocephalus. Patients with optic pathway tumors and craniopharyngioma (suprasellar location) tend to have a higher incidence of pre-irradiation endocrinopathy based on tumor and surgical factors.

We have shown in children with ependymoma that pre-irradiation GHD affects baseline and longitudinal change in cognitive function. The baseline effects are most prominent for IQ, memory, and measures of academic achievement including mathematics scores (Fig. 6c). The effect of pre-irradiation GHD on longitudinal clinical changes after RT is most notable for reading scores (as a part of academic achievement testing). Similar findings have been noted evaluating cognition after RT in patients with optic pathway glioma. GHD is shown to impact reading scores over time (Fig. 6d). Though the changes over time were statistically significant compared to no change, they were not statistically different in the group that did not have GHD. The impact was most notable for reading scores in IQ. Finally, among children with craniopharyngioma, pre-irradiation GHD impacted both baseline and longitudinal change in IQ and reading scores (Fig. 6e). The assessment of pre- and post- irradiation GH secretion abnormalities in children with brain tumors can be divided into whether patients had hydrocephalus, HPA tumor invasion, or extension to adjacent regions. Treatment-related GHD most often resulted from surgical intervention with direct damage to the hypothalamus, but also the insidious effects of RT and or chemotherapy.

Pre-irradiation GHD can predict post-irradiation effects on cognition, along with endocrine effects and other somatic effects not discussed here. Post-irradiation GHD is known to correlate with hypothalamic dose. Post-irradiation GHD can predict functional outcomes. Patients at risk for GHD include those with brain tumors, head and neck tumors (including nasopharyngeal cancer), and retinoblastoma. Brain tumor patients included those with medulloblastoma, ependymoma, craniopharyngioma, and low-grade glioma (most often central or optic pathway tumors). GH testing regimen included stimulation using arginine and carbidopa-levodopa. This testing was performed in our prospective institutional series at baseline, 6 and 12 months after RT. In previous studies, we also tested at 36 and 60 months. The value of testing after 3 years was limited, since within 3 years the majority of children who will require GH replacement therapy were receiving that treatment thus skewing the data for the 60 month evaluation. Requirements include the test agents and IV placement, thus, requiring a dedicated nursing support team. Having detailed hypothalamic dosimetry from conformal treatment techniques adds to the value of this testing.

5.2.2 TSH Deficiency

We suggest that routine yearly measurements of TSH and free T4 be done in all patients who have received cranial irradiation, because the symptoms of central hypothyroidism are often subtle, and TSH secretory dysregulation after irradiation may precede other endocrine disorders (Lam et al. 1991; Rose et al. 1999a, b). The diagnosis of hypothyroidism may be delayed in as many as one-third of patients, if TSH secretion is not tested until GH deficiency becomes apparent. Such a delay may be acceptable in a minimally symptomatic adults. In children, however, the

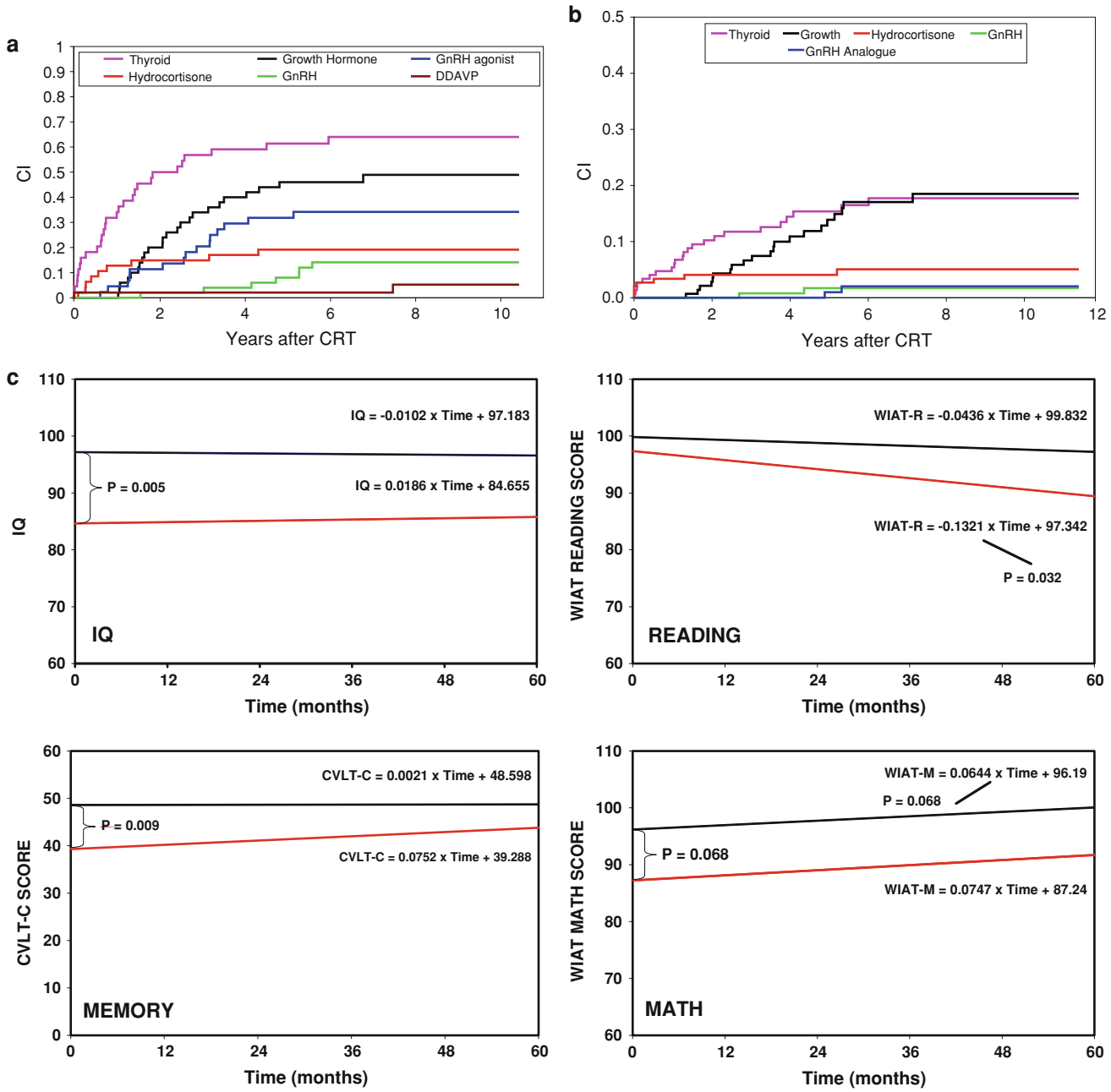

Fig. 6 **a** Incidence of hormone replacement therapy following RT for an optic pathway glioma. **b** Incidence of hormone replacement therapy following RT for a posterior fossa ependymoma. **c** The impact of growth hormone deficiency on IQ, memory and measures of academic achievement including mathematics scores, both at baseline (far *left-hand side* of the graphs) and over time in patients with ependymoma. *Red lines* are patients *with* growth hormone deficiency pre-therapy, compared to those without (*black line*). **d** The impact of growth hormone deficiency on IQ and reading scores both at baseline (far *left-hand side* of the graphs) and over time in patients with optic pathway glioma. *Red lines* are patients with growth hormone deficiency pre-therapy, compared to those without (*black line*). **e** The impact of growth hormone deficiency on IQ and reading scores both at baseline (far *left-hand side* of the graphs) and over time in patients with craniopharyngioma. *Red lines* are patients with growth hormone deficiency pre-therapy, compared to those without (*black line*). *GHD* growth hormone deficiency

potential functional implications of hypothyroidism and lost growth opportunity require early intervention (Rose 1995). Early diagnosis of mild hypothyroidism permits early intervention to improve growth velocity and QOL (Table 3A).

Free T4 and serum TSH are the best screening tests for thyroid status. Free T4 below the normal range without TSH elevation is strongly suggestive of central hypothyroidism. However, many patients with central hypothyroidism have free T4 concentrations in the lowest third of the normal

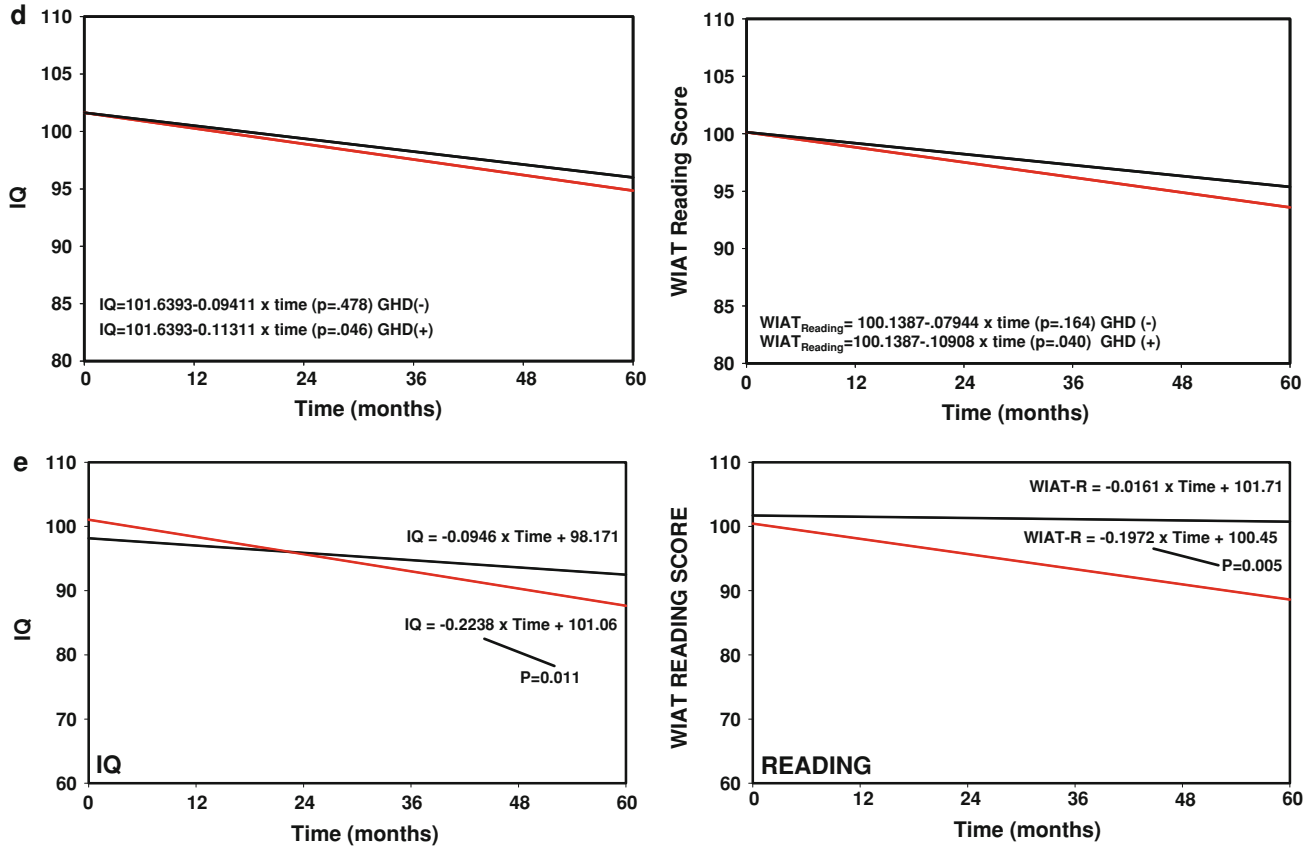

Fig. 6 (continued)

range (Rose 1995, 1996; Rose et al. 1999a, b). The first laboratory evidence of central hypothyroidism may be a small decline in free T4. In a person not on pharmacologic steroids, obtaining a TSH at 8 a.m. and one at 4 p.m. can be informative: an 8 a.m./4 p.m. TSH ratio $\leq$1.3 confirms central hypothyroidism (Rose 2010). If further testing confirms central hypothyroidism, treatment should be initiated even though free T4 is still within the normal range because it is likely to be below the individual's optimal set-point. Both the TRH test and the TSH surge test were performed in our patients when the free T4 was in the lowest third of the normal range and TSH was not elevated. The TRH test confirmed 60 % of cases of central hypothyroidism after cranial irradiation. Measurement of the nocturnal TSH surge confirmed 71 % of cases. Measurement of both the TSH surge and the response to TRH were considered optimal in order to identify all cases (Rose et al. 1999a, b); unfortunately TRH is no longer available in the United States as a test agent.

5.2.3 ACTH Deficiency

For patients at risk for ACTH deficiency (e.g., those who received $\geq$30 Gy irradiation to HPA), surveillance should include the yearly measurement of plasma cortisol concentration at 0800 hours. If cortisol level is below 18 μg/dL (497 nmol/L) at 0800 hours, then further evaluation should be directed by an endocrinologist. The optimal evaluation for ACTH deficiency is controversial (Rose et al. 1999a, b, Kazlauskaite et al. 2008). Measurement of the basal plasma ACTH concentration usually can distinguish primary adrenal disease from central adrenal insufficiency if the ACTH assay is reliable, and there is no urgency in establishing the cause of adrenal insufficiency. Patients with primary adrenal insufficiency have a high concentration of plasma ACTH at 0800 hours; ACTH levels can be as high or higher than 4000 pg/mL (880 pmol/L). In contrast, plasma ACTH concentrations are low or low-normal in patients with secondary or tertiary adrenal insufficiency. The normal value at 0800 hours is usually 20–80 pg/mL (4.5–18 pmol/L) (Table 3B).

The approach is somewhat different in patients who present in hypotensive crisis. These patients may have adrenal insufficiency or another cause of hypotension. Furthermore, adrenal insufficiency, if present, may have been caused by infection, hemorrhagic diathesis, or metastatic disease that requires prompt diagnosis and treatment. In these patients, measurement of basal serum cortisol followed by the low-dose ACTH stimulation test (see below)

provides the most rapid and reliable diagnosis. A basal plasma ACTH measurement can be ordered at the same time, but diagnosis and treatment must proceed immediately without waiting for the ACTH and cortisol results.

The gold standard for diagnosis of ACTH deficiency is failure of serum cortisol to rise above 20 μg/dL (552 nmol/L) in response to insulin-induced or spontaneous hypoglycemia (Kazlauskaite et al. 2008). Another method of diagnosis involves the administration of metyrapone to block the adrenal conversion of 11-deoxycortisol to cortisol. This method stimulates the production of ACTH and a secondary increase of 11-deoxycortisol. Failure of the concentration of 11-deoxycortisol to rise above 7 μg/dL (200 nmol/L) in the presence of a low serum cortisol (below 5 μg/dL [138 nmol/L]) signifies ACTH deficiency (Clayton 1996; Shankar et al. 1997).

An attempt to simplify the evaluation of the hypothalamic-pituitary-adrenal axis led to development of the 1-h ACTH test (or high-dose ACTH test), which consists of the administration of ACTH (250 μg/m^2) by intravenous infusion over 1 min (Rose et al. 1999a, b). Serum cortisol is measured 1 h later and is normally greater than 20 μg/dL (552 nmol/L). Patients with complete ACTH deficiency (in whom the adrenal glands have not been exposed to ACTH for 4–10 weeks) fail to respond with a 1-h serum cortisol concentration more than 20 μg/dL (552 nmol/L) (Soule et al. 1996). In contrast, patients with partial ACTH deficiency or recent onset of complete ACTH deficiency may have a normal serum cortisol response to this dose of ACTH, and ACTH deficiency may not be detected by this test.

The low-dose ACTH test is the most sensitive test for partial ACTH deficiency. A meta-analysis performed by Kazlauskaite et al. (2008) suggested that the low-dose ACTH test (1 mcg/m^2, up to 1 mcg) is more sensitive for the diagnosis of partial ACTH deficiency than the 250 mcg ACTH test. In this test, a more physiologic dose of ACTH (1 μg/m^2) is administered by intravenous infusion over 1 min, and blood for a serum cortisol assay is drawn 20 min after the infusion. Peak serum cortisol higher than 20 μg/dL (552 nmol/L) is considered normal, and peak serum cortisol lower than 18 μg/dL (497 nmol/L) is considered low. Patients with cortisol peaks between these values have indeterminate results; these patients should be treated with glucocorticoids when they are ill and will require further evaluation (Soule et al. 1996). Further evaluation can include a second low-dose ACTH test or metyrapone administration 2 months to 1 year later.

The low-dose and high-dose ACTH stimulation tests have supplanted insulin-induced hypoglycemia and metyrapone in clinical practice. The results are similar to those obtained with insulin-induced hypoglycemia; in addition, ACTH tests can be performed without a physician being present and are less expensive.

5.2.4 LH/FSH (Gonadotropin) Deficiency

During the range of ages in which puberty is normally expected to occur, breast development, pubic hair growth and distribution, and vaginal estrogenization should be monitored every 6 months in those girls at risk of having LH/FSH deficiency. Similarly, testes size, pubic hair growth and distribution, and phallus length should be monitored every 6 months in boys. Testicular size in some boys may be small for their virilization because of radiation or chemotherapy-induced damage to the seminiferous tubules (Table 3C, D).

Measurement of bone age, serum LH, FSH, and sex steroid (testosterone or estradiol) should be performed in children with delayed or interrupted progression of puberty. Evaluation by an endocrinologist should be prompted by the absence of progression of puberty by 1 year after completion of cancer therapy in girls >13 years of age, or in boys >14 years of age. Stimulation testing with synthetic GnRH provides more information than does a single, randomly drawn level of LH and FSH. An alternative to a GnRH stimulation test may be a serum sample for LH, FSH, and testosterone or estradiol drawn between 4 and 8 a.m., at the time shortly after nighttime pulses of LH have been occurring.

5.2.4.1 Precocious Puberty

Precocious puberty is diagnosed if the onset of secondary sexual development is before age 8 years in girls and before age 9 years in boys. A radiograph of the left hand and wrist may show a bone age that is advanced compared to chronologic age. However, bone age may be consistent with chronologic age or even delayed in a child who has concurrent GH deficiency or hypothyroidism, and who has not undergone a growth spurt. Because concurrent GH deficiency may not be discovered until after successful treatment of precocious puberty, we routinely perform provocative GH testing in patients with precocious puberty who have a history of cancer.

5.2.5 Hyperprolactinemia

Hyperprolactinemia is diagnosed when the serum level of PRL is elevated. The PRL level should be periodically measured in patients with symptoms outlined above (Sect. 3.6) and in those who received more than 50 Gy of irradiation to the hypothalamus. The definitive PRL level should not be drawn in the hour or two after breast examination or nipple stimulation.

6 Radiation Tolerance

6.1 GH Deficiency

GHD is the most common and frequently the only anterior pituitary deficit to develop after cranial irradiation. It has

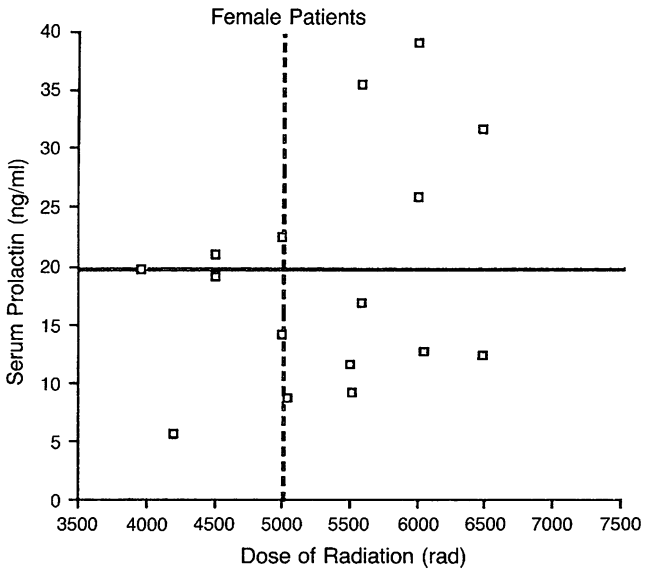

Fig. 7 Relationship between the serum prolactin concentration to the estimated dose of radiation to the HPA in females with brain tumors. Note increased levels of prolactin with higher RT doses (reprinted by permission of The New England Journal of Medicine, Massachusetts Medical Society, Constine et al. 1993)

been noted following conventional fractionated radiation with doses ≥18 Gy to the HPA and following total doses as low as 9–10 Gy when given in a single dose (e.g., total body irradiation for BMT). Current data suggest that nearly all children treated with doses in excess of 35 Gy will develop GHD, which generally occurs within the first 5 years after treatment. In children, a spectrum of GH neurosecretory dysfunction exists that appears to be dose dependent. When the HPA dose is >30 Gy, reduced GH following both pharmacological testing as well as physiological studies is noted. Following 20–40 Gy, spontaneous GH secretion remains low, while the GH response to provocative agents is often normal. The threshold dose for GHD appears to be higher in adults, and for any given dose of irradiation the incidence of GHD is lower in adults than in children (Constine et al. 1993) (Figure 7).

6.2 TSH Deficiency

The data, again, are limited and the threshold dose required to induce TSH deficiency is not known. At doses to the HPA under 40 Gy, TSH deficiency is very unusual. In two pediatric series following HPA irradiation of 40–50 Gy, the incidence of TSH deficiency was 3–6 % after a mean follow-up of 9–10 years. The incidence of TSH deficiency increases substantially, when the HPA dose exceeds 50 Gy. Although some studies have suggested that TSH is the anterior pituitary hormone least likely to be affected by irradiation, Constine et al. noted a 65 % incidence of TSH deficiency in their patients treated with a mean dose of 57 Gy (Constine et al. 1993).

6.3 ACTH Deficiency

The data concerning the relationship between HPA irradiation and the evolution of ACTH insufficiency are quite limited. Moreover, interpretation of the data are complicated by the fact that different investigators use different methods of assessment and the incidence of adrenal insufficiency tends to vary, depending on the testing procedure employed. Clinically apparent ACTH deficiency is distinctly uncommon in patients receiving HPA irradiation <50 Gy. Following doses >50 Gy, the reported incidence of ACTH deficiency varies from 18 to 35 % during follow-up periods ranging from 5 to >15 years. Limited data suggest that the incidence of ACTH deficiency may be higher in older patients compared to children and adolescents.

6.4 Gonadotropin Deficiency

Detailed information on the threshold dose for LH/FSH deficiency are lacking. Nonetheless, it appears to be quite rare following HPA doses <40 Gy. There is a progressive increase in incidence as the dose to the HPA exceeds 50 Gy. At the higher dose range, gonadotropin deficiency has been noted in 20–50 % of patients followed long term, making it the second most common pituitary abnormality in many series.

6.4.1 Early Sexual Maturation

This phenomenon, originally described in patients treated with relatively high-dose cranial irradiation (24–45 Gy), is probably most often noted following 18–24 Gy as is given for CNS prophylaxis for leukemia. It is likely that at doses greater than 50 Gy, the prevalence of early puberty decreases as the incidence of gonadotropin deficiency increases.

6.5 Prolactin (Hyperprolactinemia)

Elevated plasma concentrations of prolactin are seen infrequently in patients treated with HPA irradiation under 40–45 Gy. Mild increases in prolactin are particularly commonly observed after cranial radiotherapy with doses greater than 50 Gy, especially among women (Fig. 7) (Constine et al. 1993). The overall incidence of hyperprolactinemia has varied from 20 to 50 %.

7 Chemotherapy

At the present time, there is very little data to support the contention that chemotherapeutic agents, either singly or in combination, have the capacity to permanently impair anterior pituitary function. Although certain drugs (e.g., cyclophosphamide, vinca alkaloids, cisplatin) have been associated with transient episodes of inappropriate vasopressin secretion, chronic abnormalities of posterior pituitary function have not been reported following treatment with radiation or chemotherapy. For example, Fig. 8 illustrates data reporting the impact of chemotherapy with or without RT on height in survivors of acute lymphoblastic leukemia, suggesting that RT has a far greater impact on growth than does chemotherapy.

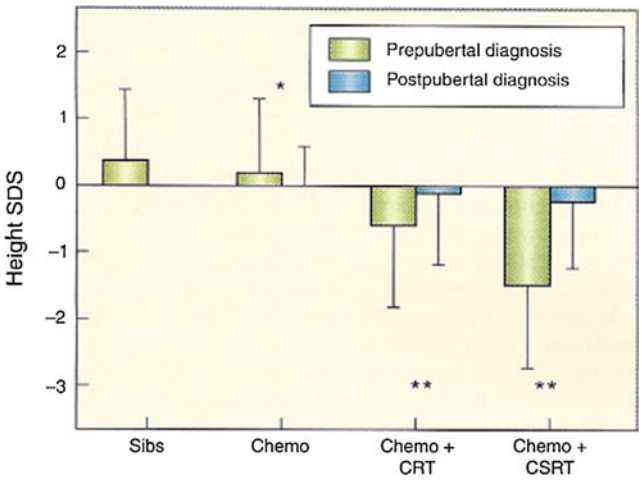

Fig. 8 Height standard deviation scores (SDS) for ALL survivors treated pre- or post-pubertally with chemotherapy alone, cranial or craniospinal RT (with permission from Chow et al. 2007)

8 Special Topics

8.1 Diabetes Insipidus

Urine specific gravity of patients with diabetes insipidus is usually lower than 1.010 (<300 mOsm/L), unless the patient is severely dehydrated. In most of these patients, serum osmolarity is slightly increased, and the plasma concentration of antidiuretic hormone is inappropriately low for the osmolarity. However, patients with an intact thirst mechanism may be able to drink sufficiently to avoid laboratory abnormality. Symptoms of polydipsia, polyuria, and nocturia or enuresis may be the only evidence of diabetes insipidus. In partial diabetes insipidus, a water deprivation test may be needed to establish the diagnosis and to rule out other causes of polyuria.

Diabetes insipidus may be caused by histiocytosis, germinomas, surgical trauma, or CNS-involved leukemia. Patients with diabetes insipidus usually present with obvious symptoms of excessive thirst and urination with nocturia or enuresis. However, the diabetes insipidus may not be recognized until they have dehydration during an intercurrent illness. The urine remains clear in color throughout the day. In patients with CNS-involved leukemia, severe hypernatremic dehydration can occur if the CNS lesion also affects the centers for thirst regulation.

8.2 Osteopenia

Osteopenia in cancer survivors may be unrecognized in the absence of fractures unless evaluation is performed. Serum osteocalcin and urine pyridinoline crosslinks or N-telopeptide do not identify whether there is low bone mineral. Identification requires performance of a dual-energy X-ray absorptiometry (DXA) which offers precise estimates of bone mineral density (mg/cm^2) at multiple sites for the least amount of radiation exposure, or a quantitative computerized tomography (QCT) which measures true volumetric density (mg/cm^3) of trabecular or cortical bone at any skeletal site of choice. T-scores may be calculated in reference to normal young adults (age of peak bone mass, 20–35 years) and Z-scores in reference to age-matched normal individuals of the same gender, respectively. Results of DXA must be adjusted for patient height and age. T-scores should not be used in pediatric age patients.

Osteopenia may result from HPA abnormality (GH deficiency, hypothyroidism, hypogonadism, or hyperprolactinemia) in association with direct effects of glucocorticoid therapy, methotrexate inactivity, and dietary changes. Osteopenia may present with fractures or may be asymptomatic. Among 141 survivors of childhood leukemia in one study, 30 (21 %) had abnormally low bone mineral density (BMD > 1.64 SD below the mean of normal population). Risk factors for bone mineral decrement included male gender, Caucasian race, and cranial irradiation. BMD was inversely correlated with the cumulative dose of cranial irradiation or antimetabolites (Kaste et al. 2001).

There is increasing evidence that bone health is impaired in patients treated with combined modality therapy that does not necessarily include glucocorticoid therapy. Patients with Hodgkin lymphoma, for example, comprise a group of patients at risk for bone mineral deficits, among whom male patients were identified as those at increased risk (Kaste et al. 2009). Similar findings were noted for male patients with brain tumors (Morris et al. 2008). Osteonecrosis has been recognized as a late complication of therapy in adult

survivors of pediatric cancer (Kadan-Lottick et al. 2008). Osteonecrosis has also been shown to be an early complication of antiangiogenic therapy suggesting that endocrine-related effects may be part of the toxicity profile of newer treatments (Aragon-Ching et al. 2009).

8.3 Hypothalamic Obesity

Clinical symptoms are the basis for diagnosis of hypothalamic obesity. These include rapid weight gain, voracious appetite, and aggressive food seeking. Patients may have rapid weight gain for other reasons: exogenous steroid use, inactivity, overfeeding, and sympathy of relatives, high thirst and drinking of sugared drinks. Obesity in adults is defined as having a body mass index of >30 [BMI = wt(kg)/ht(m^2)] (http://nhlbisupport.com/bmi/). Overweight in children is defined as having a weight greater than the sex- and age-specific 95th percentile or BMI > 85th percentile (www.cdc.gov/growthcharts/). Evaluation of these patients includes blood pressure measurement, fasting lipid profile, fasting glucose and insulin level, and oral glucose tolerance testing with insulin levels (OGTT). In general, fasting glucose is normal and fasting insulin is elevated in patients with hypothalamic obesity. They have very high post-pyramidal insulin level as well as early and rapid insulin excursions to OGTT. However, these results may be seen in any person who becomes obese.

Hypothalamic damage from a tumor or cancer treatment can also result in hypothalamic obesity—unrelenting weight gain that does not respond to caloric restriction or exercise—attributable to ventromedial hypothalamus damage and abnormality in leptin, ghrelin, and insulin feedback (Lustig 2001). In rodents, hypothalamic obesity can be suppressed by pancreatic vagotomy to prevent insulin hypersecretion. Recent studies in patients with cranial insult confirmed insulin hypersecretion as one of the major mechanisms for the development of hypothalamic obesity (Lustig et al. 1999). In a study of 148 survivors of childhood brain tumors, the risk factors for hypothalamic obesity included age at diagnosis of cancer (<6 years), tumor location (hypothalamic or thalamic), tumor histology (craniopharyngioma, germinoma, optic glioma, prolactinoma, or hypothalamic astrocytoma), hypothalamic irradiation (>51 Gy), and presence of endocrinopathy (deficiency of GH, sex hormones, ACTH, or vasopressin) (Lustig 2001; Lustig et al. 2003b). No effects were noted on body mass index from ventricular peritoneal shunting, steroid use (<6 months), or chemotherapy. Thus, any form of hypothalamic damage, either due to tumor, surgery, or RT, is a regional-specific primary risk factor for the development of obesity in this patient population.

9 Prevention and Management

9.1 GH Deficiency

Standard therapy for GHD is synthetic recombinant human GH. Any patient identified with GHD should be evaluated for possible ACTH deficiency and for central hypothyroidism. If ACTH is deficient, adequate cortisol therapy should be started before GH or thyroid therapy. Patients with GHD who have partial or total ACTH deficiency and are receiving suboptimal hydrocortisone replacement may be at risk of developing symptoms of cortisol deficiency when GH therapy is initiated. This includes patients who are prescribed stress-dosing only of cortisol; they may need to receive daily replacement. This is because of the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1, the enzyme that converts cortisone to cortisol (Toogood et al. 2000).

The usual dose of GH in children is 0.15–0.3 mg/kg per week divided into daily doses and administered subcutaneously in the evening. Lower doses are used in adults (Vance and Mauras 1999) and in countries such as the United Kingdom. Each dose produces a pharmacologic level of GH for approximately 12 h. The growth rate in children on GH therapy typically increases to above normal for 1–3 years and then slows to normal velocity. After 4–5 years of GH therapy, the height SD scores of leukemia survivors with GHD usually approached the height SD scores at the time of diagnosis (Leung et al. 2002). The growth response may be poorer in patients who have received total body or spinal irradiation, or in patients with particular diseases such as neuroblastoma (Olshan et al. 1993; Hovi et al. 1999). GH replacement helps many irradiated brain tumor patients to achieve mid-parental height. Patients treated with craniospinal irradiation or TBI are the least likely to achieve predicted height. Younger and short patients at the start of GH replacement therapy are also at risk (Beckers et al. 2010). Adult GH replacement studies show that irradiated patients had lower QOL and increased metabolic risks (higher fat mass, lower high-density lipoprotein cholesterol levels, and a lower bone mineral content) than nonirradiated patients (Maiter et al. 2006). There is great debate about the use of GH in adult cancer survivors. Many conclude that such survivors would benefit from GH replacement for body composition (Darzy and Shalet 2006). GH replacement may reduce cardiac risk factors (Follin et al. 2006). QOL may be improved in patients who receive GH replacement therapy. Those with severe GH appear to benefit most (Murray et al. 1999).

GHRH as therapy has been taken off the market in the USA. When available, GHRH may be used as an alternative

therapy for GH deficiency in patients without primary sellar tumors. GHRH therapy, also administered subcutaneously in daily evening doses, elicits a night-time pulsatile pattern of GH secretion that approximates the normal pattern. Experience with GHRH therapy after cranial irradiation is limited. In one study, nine children who had undergone cranial or craniospinal irradiation at least 2 years earlier were treated with twice daily subcutaneous injections of GHRH for 1 year, and then with daily GH injections for 1 year (Ogilvy-Stuart et al. 1997). Both GHRH and GH increased height velocity from baseline: GHRH increased height velocity from 3.3 to 6.0 cm/year, and GH increased it from 3.3 to 7.5 cm/year.

During GH therapy, evaluation of the growth response and adjustment of GH dose should occur every 4–6 months and include measurement of height, weight, and arm span. Arm span is a surrogate measure of height, particularly in patients in whom height measurement may not fully reflect body growth (e.g., those with scoliosis or a history of spinal irradiation). In most practice settings, GH dose is increased as weight gain occurs to maintain a stable dose per kilogram of body weight. Serum IGF-I measurements are recommended yearly (GH Research Society 2000). After the first 2 years of GH therapy, if the level of IGF-I surpasses the upper limits of normal for the patient's age and sex, the GH dose should be decreased. Evaluation of pubertal stage and screening for development of additional endocrinopathy (thyroid, gonadotropins, and ACTH) should be performed at least annually. Even with GH therapy, some childhood cancer survivors do not grow as well as expected. This finding suggests that other factors, such as thyroid hormone deficiency, are present.

The use and timing of GH replacement is an individual decision. Safety data has allowed us to administer GH earlier and gain time of exposure. When gain in height is critical, delay to GH affects final height (Brownstein et al. 2004). GH treatment in children is usually safe (Wilson et al. 2003). Adverse effects are rare, occur soon after therapy is initiated, and include pancreatitis, benign intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis, and carpal tunnel syndrome (Blethen et al. 1996). Pseudotumor cerebri and carpal tunnel syndrome are probably caused by sodium and water retention. An increase in the growth and pigmentation of nevi also has been described (Bourguignon et al. 1993). Tumor recurrence does not appear to be increased in patients treated with GH replacement therapy (Darendeliler et al. 2006; Chung et al. 2005). GH therapy also did not appear to increase the risk of secondary leukemia or solid malignancy in patients who did not receive RT in the Childhood Cancer Survivor Study (Sklar et al. 2002; Ergun-Longmire et al. 2006). Because all of the included patients who developed a second neoplasm in this study had received RT, the synergistic effects of GH and irradiation on the development of second malignancy could not be discerned (Sklar et al. 2002). The absolute number of excess solid tumors attributable to GH, including many benign meningiomas, will probably be very small (<4/1000 person years at 15 years after diagnosis).

9.2 Hypothyroidism

Standard treatment for TSH deficiency or for primary hypothyroidism is levothyroxine replacement therapy. Thyroid hormone replacement can precipitate clinical decompensation in patients with unrecognized adrenal insufficiency, because levothyroxine treatment may improve metabolic clearance of cortisol. Thus, it is necessary to evaluate patients for adrenal insufficiency, and if present, treat the patient with hydrocortisone before initiating thyroid hormone therapy. In patients who also have ACTH deficiency, cortisol replacement is usually initiated 3 days before beginning thyroid hormone therapy.

The typical thyroid hormone replacement dose for infants under 3 years of age is 5–10 mcg/kg per mouth daily. For healthy children and adolescents with TSH less than 30 mU/L, the typical thyroid replacement dose is levothyroxine 3 mcg/kg per mouth every morning. This should be started at full dose. Children over 3 years of age who have TSH greater than 30 mU/L, or about whom there are concerns about medical stability, can begin levothyroxine at a low dose (0.75 mcg/kg per mouth every morning) and have it increased by 0.75 mcg/kg per day each month to permit more gradual physiologic and psychologic adjustment to the new metabolic state. Thyroid hormone concentrations should be measured after 4 weeks of therapy, because levothyroxine has a long half-life (5–6 days).

Unlike primary hypothyroidism, it is not useful to monitor TSH in patients with central hypothyroidism. In one prospective study of 37 patients with central hypothyroidism, free T4 and free T3 were monitored during therapy and adjusted to achieve free T4 in the midnormal range without free T3 elevation and without symptoms of hypothyroidism or hyperthyroidism (Ferretti et al. 1999). We usually adjust thyroid hormone replacement therapy in patients with central hypothyroidism to maintain the level of free T4 just above the middle of the normal range (for example, free T4 of 1.4–1.6 ng/dL if the normal range is 0.78–1.85 ng/dL, free T4 of 1.8–2.2 ng/dL if the normal range is 1.0–2.4 ng/dL).

9.3 ACTH Deficiency

Patients with ACTH insufficiency require daily hydrocortisone replacement. Hydrocortisone is the preferred agent

for glucocorticoid replacement in children because it is least likely to impair growth. Patients with ACTH deficiency do not need mineral-corticoid replacement, because these hormones are produced by the adrenal gland under the influence of the renin-aldosterone system rather than under the influence of ACTH. Dexamethasone is not standard for glucocorticoid replacement therapy in the pediatric age range because it has greater potential to suppress growth than hydrocortisone. In adults, dexamethasone can be used for glucocorticoid replacement at a dose of 0.25–0.5 mg once each morning.

The dose of hydrocortisone for replacement therapy is 7–10 mg/m^2 per day, divided into two or three doses administered by mouth. For example, a child whose body surface is 0.9 m^2 could receive 2.5 mg three times per day, or an adult whose body surface is 1.5 m^2 could receive 5 mg at breakfast and at 1500 hours plus 2.5 mg at bedtime. The glucocorticoid dose may need to be increased in patients taking drugs, such as phenytoin, barbiturates, newer anticonvulsants, rifampin, mitotane, and aminoglutethimide that accelerate hepatic steroid metabolism (Elias and Gwinup 1980). Patients with GHD deficiency who have partial or total ACTH deficiency and are receiving suboptimal cortisol or cortisone replacement may be at risk of developing symptoms of cortisol deficiency when GH therapy is initiated. This is because of the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1. Similarly, the initiation of thyroid hormone therapy in a child with unrecognized or under treated ACTH deficiency also can precipitate adrenal crisis.

Patients with ACTH deficiency must receive additional glucocorticoid during times of illness or stress (e.g., fever, gastrointestinal illness, injury, high-dose chemotherapy). Dexamethasone has no mineral-corticoid effect, so hydrocortisone should be used for stress dosing. The dose of additional hydrocortisone that is necessary during times of illness is 30 mg/m^2 per day divided into three doses administered by mouth. Patients whose illness or injury is severe enough to require emergency care or hospitalization, who are unable to retain oral medication, or who require anesthesia, surgery, or both should urgently receive hydrocortisone (100 mg/m^2 intramuscularly or intravenously), followed by hydrocortisone (10–25 mg/m^2 IV every 6 h) during management of the critical illness (Soule et al. 1996). At stress doses, hydrocortisone provides some mineral-corticoid effect. The hydrocortisone dose should be reduced to the usual replacement therapy dose as soon as the event is over or the patient's medical status improves. Tapering of the dose is not necessary if the pharmacologic stress doses are used for less than 10 days.

Patient and family education is an important component of treating patients with ACTH deficiency. The patient and responsible family members should be instructed about the following:

- The nature of the hormonal deficit and the rationale for replacement therapy
- Maintenance medications and the need for changes in medications during minor illnesses
- When to consult a physician
- The need to keep an emergency supply of glucocorticoids
- The proper *stress* dose for the patient's body weight
- When and how to inject glucocorticoids for emergencies.

Every patient should have at least three pre-prepared syringes of hydrocortisone (Solu-cortef®): one at home, one at work or school, and one in the car. In addition, it is wise for the patient to carry such a syringe at all times. The syringes can be obtained as 100 mg/2 mL vials, 250 mg/2 mL vials, or can be prepared by a pharmacist in regular 1-mL syringes from a multidose vial. The patient and parents must be instructed regarding the correct dose. The injectable stress dose is 5–10 times the daily hydrocortisone dose. Thus, typical doses for children would be 50–125 mg (0.4–1.0 mL of a 250 mg/2 mL solution). Unused syringes should be replaced each year or if the solution inside becomes cloudy or colored.

The patient and one or more responsible family or household members should be instructed to inject the contents of a syringe subcutaneously or intramuscularly anywhere on the patient's body during any one of the following circumstances:

- The patient has a major injury with substantial blood loss (more than one cup), fracture, or neurogenic shock
- The patient has nausea and vomiting and cannot retain oral medications
- The patient has symptoms of acute adrenal insufficiency
- The patient is found unresponsive.

Instructions should include the need to obtain medical help immediately after the injection of the stress dose. The patient should be instructed to have a low threshold for injecting the hydrocortisone: if the patient feels the injection *might* be necessary, then it *should* be injected, and medical attention should be sought. It is unlikely, however, that a patient will need the stress dose of hydrocortisone more than two or three times per year, and most patients go for years without needing it. Used hydrocortisone syringes should be replaced immediately.

Every patient should wear a medical alert (Medic Alert®) bracelet or necklace and carry the Emergency Medical Information Card that is supplied with it. Both should indicate the diagnosis, the daily medications and doses, and the physician to call in the event of an emergency. Patients can enroll in Medic Alert by calling 800-432-5372 or through the internet at www.medicalert.org (U.S.) or www.medicalert.ca (Canada).

9.4 LH/FSH (Gonadotropin) Deficiency

The use of estrogen or testosterone therapy should not be initiated without careful attention to the survivor's growth pattern. Replacement of pubertal hormones in a short or slowly growing adolescent can cause fusion of bony growth centers and shorter than expected adult height. Such therapy should be provided only in coordination with the pediatric endocrinologist after assessment of growth potential and treatment of GH or thyroid deficiencies. Initiation of sex steroid therapy in a short adolescent may be delayed until age 15 years to permit response to GH or thyroid hormone therapy and taller adult height. In short adolescents with delayed puberty, a few years of therapy with low-dose sex steroid therapy is preferable to full replacement. Such doses simulate the sex steroid levels observed in the first year or so of puberty and are less likely than full sex steroid replacement to cause inappropriate maturation of bone age. Girls can be treated with the conjugated estrogen tablets Premarin® (0.3 mg every other day), ethinyl estradiol (5 mcg daily, one quarter of a 20-mcg tablet daily), or one-fourth to one-half of an estrogen patch changed half as often as in adults (Rose 1996). Menstrual spotting can be treated with medroxyprogesterone 10 mg per day for 10 days followed by resumption of low-dose estrogen. Boys can be treated with 45 or 50 mg/m^2 depo testosterone injected intramuscularly once each month or with topical androgen gel about one gram daily. After achievement of height acceptable to the patient, both boys and girls benefit from a gradual increase in hormone replacement therapy to the full replacement dose, if there has been no sex steroid production in recent months. The increase to full replacement should take place in 1- to 3-month steps to permit gradual adjustment to the hormonal effects.

Full hormone replacement in adolescent girls who have reached their adult height is easily achieved with regular use of a standard oral contraceptive (28-day pill packet) or an adult regimen of estrogen patches plus progesterone. Boys who have attained their adult height can be treated with testosterone (200 mg injected intramuscularly every 2 weeks) with androgen by patch, or by topical gel.

The primary medical risk of delayed puberty is delayed bone mineralization. Adolescents with delayed or interrupted puberty should receive 1500 mg of elemental calcium and 1000–2000 IU of vitamin D per day to improve bone mineralization.

9.4.1 Precocious Puberty

GnRH agonists are the most effective treatments for precocious puberty, rapid tempo puberty, or normally timed puberty that is inappropriate relative to height. GnRH agonists suppress LH and FSH release from the pituitary gland through the provision of a steady rather than a pulsatile level of GnRH; the pituitary gland stops responding to GnRH when GnRH concentrations are steady or unchanging. The use of GnRH agonists to delay pubertal progression optimizes adult height potential by permitting the child to grow taller without experiencing a rapid change in bone maturation (Cassorla et al. 1997).

Treatment with GnRH agonists should be prescribed and monitored by a pediatric endocrinologist (Yanovski et al. 2003). GnRH agonists can be administered as a daily subcutaneous injection, every 4 weeks or every 3 months in a sustained or depot preparation or as a yearly implant. GnRH agonist therapy is usually continued until patients attain the third percentile for adult height: 152 cm (60 in.) in girls and 162 cm (64 in.) in boys.

9.5 Hyperprolactinemia

In event of a prolactin level in excess of 100 ng/mL, prolactin elevation may lead to symptoms (galactorrhea, amenorrhea, impotence). Dopamine agonists such as bromocriptine and cabergoline are the treatment of choice to suppress PRL secretion and to restore normal gonadal function. Cabergoline is, in general, more potent, much longer acting, and better tolerated than bromocriptine. The usual starting dose is 0.25 mg twice a week.

9.6 Diabetes Insipidus

The drug of choice for hormone replacement is desmopressin acetate or DDAVP®, which can be given by subcutaneous injection, by nasal insufflations, or orally in one or two daily doses. Oral desmopressin is available in tablets containing 0.1 or 0.2 mg. To avoid water intoxication, successive doses should not be given until a brief diuresis has occurred at least once daily. By giving a dose at bedtime, sleep disturbance by nocturia can be avoided. The usual dose of 1.25–5.0 μg intranasally, or 0.1–0.6 mg orally, will usually achieve rapid urinary concentration that lasts approximately 8–24 h. The process of starting desmopressin therapy may require close monitoring: volumetric fluid intake and urine output. Several weeks of dose adjustment may be required before achieving a stable dose. In patients with partial diabetes insipidus, chlorpropamide may be used to enhance the effect of the limited antidiuretic hormone that remains.

9.7 Osteopenia

Osteopenia after cancer therapy, including radiation and chemotherapy, and directly associated with multiple

endocrine deficiencies, may be prevented by maintaining optimal calcium (1500 mg daily) and vitamin D (1000 units daily) in the diet. Nutritional supplements may be needed in cases of osteopenia unresponsive to behavioral and dietary management. In addition, early diagnosis and replacement of hormone deficiencies will benefit bone mineralization. In the event of fractures, bisphosphonates may be beneficial. More aggressive measures have been investigated to prevent premature ovarian failure and address osteoporosis including ovarian transplantation (Feng et al. 2010).

9.8 Hypothalamic Obesity

Part of the therapy for hypothalamic obesity involves early identification and initiation of preventive measures including caloric and dietary control and maintenance of regular exercise. In addition to maintaining these lifestyle choices, pharmaceutical agents have been used pragmatically or in research efforts including Dexedrine, Ritalin, metformin, and octreotide. Dexedrine and Ritalin are taken orally and act as stimulants with the side effect of appetite suppression. Metformin is taken orally twice a day and acts as a sensitizer to insulin effects and may serve to probe the etiology of obesity in individual patients. If the obesity is exogenous, and hyperinsulinemia is a consequence of the obesity and insulin resistance, lifestyle changes with or without metformin will diminish obesity. If the obesity is hypothalamic and the hyperinsulinism is the cause of the increased appetite, metformin use may lead to hypoglycemia with no reduction in striving for food. Octreotide is a somatostatin analog that binds to the somatostatin receptor. It serves to decrease insulin secretion from pancreatic β-cells and GH and TSH secretion from the pituitary gland. If the obesity is exogenous and high insulin levels reflect insulin resistance, the patient may become diabetic with octreotide therapy. If the obesity is hypothalamic, octreotide will decrease insulin secretion leading to reduced appetite, weight control, and improved sense of well being (Lustig et al. 1999, 2003a, b). Octreotide is administered as 2 or 3 injections daily. Side effects may include gallstones and fluid retention. Patients treated with octreotide may also require therapy with GH and thyroid hormone.

Bariatric surgery has been used with mixed results to treat hypothalamic obesity in patients with craniopharyngioma (Rottembourg et al. 2009). Favorable outcomes have resulted in decreased food cravings and weight loss (Inge et al. 2007). It is critical to evaluate candidates carefully and determine that they have maximized life style conditions and have been thoroughly evaluated for treatable endocrine deficiencies.

10 Future Research Directions

In research efforts focused on improving our understanding of radiation and cancer treatment-related endocrine effects, baseline and longitudinal assessments should be prospectively planned and include, at a minimum, the somatic assessments of height, weight, and body mass index. More advanced research should address the impact of specific hormone deficiencies on QOL and be tailored to individual research effects seeking to determine the relationship between endocrinopathy and QOL, cognitive and neurological function, or biometric outcomes including neurostructural measures. Understanding radiation dose-volume effects on the hypothalamus-pituitary, thyroid, adrenal, and gonadal axes will serve to improve RT planning and delivery and measures to protect normal tissues. The same information will enable secondary prevention through early intervention. Collecting these data, now and in the future, will provide critical information to refine standard of care screening guidelines, reduce late effects and determine the benefit of old and new treatment methods including brachytherapy to hypo- and hyper-fractionated external beam irradiation and proton therapy.

The primary goal of radiation oncology is to achieve disease control with minimal side effects. Side effects may be attributed to a number of factors including the quality of RT and should be understood in the context of a multidisciplinary treatment approach. There are significant differences when considering the importance of endocrine effects in adults and children. With the exception of severe growth deformity that might result from craniospinal irradiation in a very young child, RT is generally not contraindicated when endocrine effects are considered treatable. Although the incidence and time to onset of hormone deficiencies should be the same for adults and children, there are number of differences between adult and pediatric oncology when endocrine management is considered. There is an emphasis in growth and pubertal development in children. In adults, including those transitioning from adolescent to adult, GH replacement therapy is often not undertaken or pursued because the relative risks and benefits have not been clearly understood. Often, the expense of treatment is a major barrier in a patient population that tends to be underemployed and underinsured. The prognosis may be better understood for children; however, there is a variety of tumor types and anatomic locations with a broad range of possible side effects. Age, duration since tumor therapy, and preexisting conditions are primary factors in development of late effects and differ between adults and children. Most pediatric patients receive polychemotherapy and most are

subject to long-term follow-up because survivorship is generally good. Current trends in pediatric oncology include increasing the indications for RT: younger patients are more likely to be irradiated and combined modality effects of therapy are now being recognized. The importance of the volumetric effect of radiation dose cannot be overlooked and must be considered in clinical trials and when developing treatment guidelines for adults and children.

11 Review of Literature and Landmarks

1954 Mateyko and Edelmann: Noted changes in gonadotropin, thyrotropin and adrenotropin 24 h after pituitary irradiation as above.

1957 McCombs: Presented a time-dose plot of the onset of changes resembling hypophysectomy induced by irradiation.

1959 Van Dyke et al.: Conducted an excellent study on the long-term effects of deuteron irradiation of the rat pituitary.

1960 Cleveland et al.: Made the latest metabolic analysis of proton irradiation of the pituitary. Ablative effects indicated that a fall in gonadotropins is the most sensitive index, followed by reduced thyroid and adrenal function.

1964: Tobias et al.: Analyzed pituitary endocrine alterations in humans after intense pituitary irradiation.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

1995 Rubin: Presented the LENT-SOMA toxicity scales for radiation effects to evaluate the grade of severity.

2003 Trotti and Rubin: Modified and developed the Common Toxicity Criteria CTC V3.0 which applied similar scales to grade adverse effects of all major modalities—surgery and chemotherapy in addition to irradiation.

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Eye and Orbit

Jasmine H. Francis, Hanna Y. Kim, and David H. Abramson

Contents

Abstract

- *Introduction*: Radiation-induced eye damage occurs from direct ocular irradiation, or when the eye is in the treatment field of another malignancy.
- *Eyelids*: Madarosis is common at low radiation doses, while a number of lid deformities may result from higher doses of radiation in the range of 60–75 Gy, such as ectropion (out-turning of lid margin) or ectropion (in-turning of lid margin). Aberrations in eyelid structure may result in ocular surface compromise.
- *Conjunctiva*: Severe complications include symblepharon formation (adhesions between the bulbar and palpebral conjunctiva following denuded epithelium) and subsequent forniceal shortening, trichiasis (inward turning of the lashes on the ocular surface) and other eyelid malpositions.
- *Sclera*: Fractionated doses of 20–30 Gy can cause thinning, melting or atrophy of the sclera, while its perforation is a rare complication (Brady et al. 1989).
- *Cornea*: The frequency of radiation-induced corneal damage is dose-dependent and most likely at doses greater than 40 Gy (Parsons et al. 1994, 1996). Effects include keratoconjunctivitis sicca (dry eyes) and, less frequently, the end result of ocular surface dysfunction such as corneal ulceration.

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- *Lens*: Cataracts are the most common effect to the lens induced by radiation and are dependent upon dose, dose rate, energy of the source, age of the patient and fractionation.
- *Uvea*: Iris neovascularization, or rubeosis iridis, may occur several months to years following radiation and could result in neovascular glaucoma, permanent nerve damage and visual loss.
- *Optic Nerve*: Optic nerve is deemed to have a radiation threshold of approximately 50–60 Gy, at which point optic neuropathy may develop.
- *Retina*: The threshold for radiation retinopathy is approximately 40 Gy and typically develops at 6 months to 3 years post-radiation. It can be influenced by concomitant vasculopathies such as diabetes and previous chemotherapy.
- *Orbital Bone*: Radiotherapy to ossification centers of children can result in boney deformities from bone growth arrest.
- *Chemotherapy and biologicals*: Chemotherapeutic agents and biologicals can cause a number of ocular side-effects at various levels of the eye.
- *Special Topic- Corticosteroids*: Corticosteroids have a wide range of side effects on the different ocular tissues comprising the eye.
- *Special Topic-Bone Marrow Transplant*: Ocular complications have been reported in 22–82 % of patients with GvHD affecting all layers of the eye (Kerty et al. 1999; Livesey et al. 1989; Franklin et al. 1983).
- *Special Topic- Secondary Cancers*: Retinoblastoma (Rb) patients are at risk for secondary cancers particularly if they harbor the germline Rb mutation.

Abbreviations

BMT	Bone marrow transplant
CSCR	Central serous chorioretinopathy
COMS	Collaborative Ocular Melanoma Study
CTCAE v3.0	Common terminology criteria of adverse events version 3
EGFR	Epidermal growth factor receptor
GvHD	Graft versus host disease
KCS	Keratoconjunctivitis sicca
LENT	Late effects of normal tissues
SOMA	Subjective, objective, management, and analytic descriptors
Rb	Retinoblastoma
SCC	Squamous cell carcinoma
VEGF	Vascular endothelial growth factor

1 Introduction

The eye is a palindrome reflecting both its three part architectural anatomy, and its embryonic origin. The tissues of the eye and orbit "derived from" the trigerminal elements neuroectoderm, surface ectoderm, and mesoderm. Its histogenesis determines its unique construct designed for perception of light, color, and distinguishing different forms and their motion. Different neoplasms arise in each component and vary as a function of age. Both radiation therapy and chemotherapy are often utilized for eye preservation. However, all treatment modalities as well as various cancers arising in and around the eye and orbit can result in loss of vision (Fig. 1).

The embryogenesis determines its histogenesis:

- Neuroectodermal outpouching of the optic cup forms the *retina* and *optic nerve*.
- Surface ectoderm forms the *eyelid epidermis* and its epithelial extensions which become the *conjunctival* cover inside the eyelid and cover the eye globe. As in skin epithelial cells give and cover the eye globe.
- Mesoderm forms the connective tissue and mesenchyme of eye and includes the *sclera* of the eye, the *vasculature in retina and choroid*, its arterial and venous drainage, as well as the *extraocular muscles* and orbital soft tissues, and boney orbit.

Many tissues compose the eye, and each varies greatly in its sensitivity to cytotoxic cancer therapy. Radiation-induced eye damage can occur following direct ocular irradiation for a malignancy of the eye, or incidentally when the eye is in the treatment field of another malignancy, such as paranasal sinus or central nervous system. Chemotherapy, biologics, and bone marrow transplantation cause ocular side effects via systemic exposures and consequential tissue effects. The chapter section begins with relevant anatomical and physiological descriptions of the ocular or adnexal structure—thereby providing a basis for the discussion on the late effects of cancer treatment on the various eye structures. The effects of radiation, chemotherapy, and biologicals are discussed along with a description of the late effects of steroids, bone marrow transplantation, and the concept of secondary cancers. Finally, the later part of the chapter describes therapeutic management and preventative measures.

A toxicity scoring system for the eye was created by the EORTC/RTOG (Rubin et al. 1995) in 1995 as a component of the combined late effects of normal tissues (LENT)/subjective, objective, management, and analytic descriptors (SOMA) grading system for radiation-induced late effects of normal tissue. As part of that effort, Gordon et al.

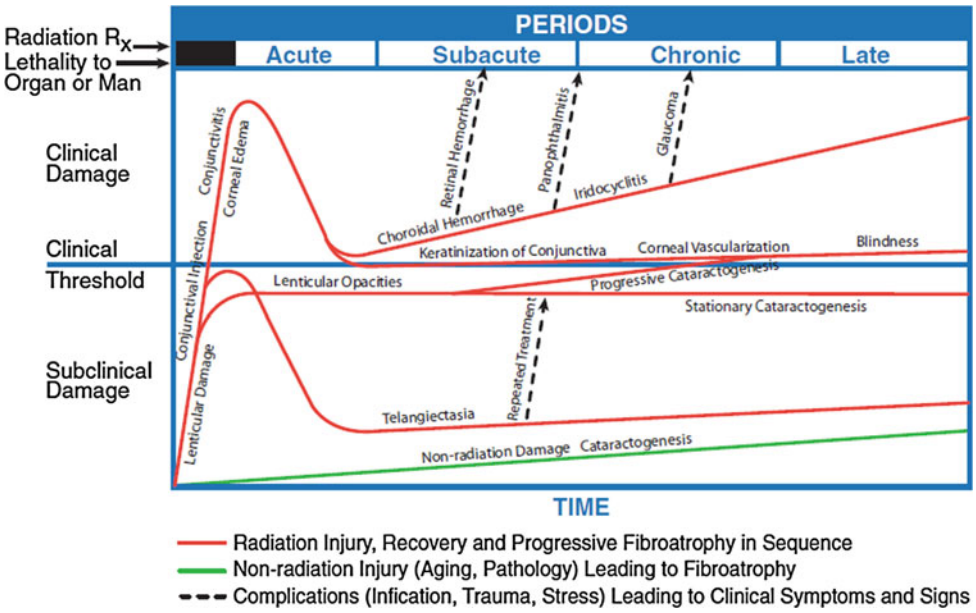


Fig. 1 Biocontinuum of adverse early and late effects of the eye and orbit (with permissions from Rubin and Casarett 1968)

proposed a clinically useful classification system to be used in prospective trials to evaluate the effects of radiation on the visual system (Gordon et al. 1995). Like the LENT/SOMA of other tissues, the purpose of this ocular focused grading system was to standardize and improve data recording on the radiation effects of the eye and ocular adnexa. The National Cancer Institute also created a series of grading systems that best describe chemotherapeutic effects, of which the Common Terminology Criteria of Adverse Events version 3 (CTCAE v3.0) is most recent. Ocular and adnexa tissue is one of the 35 anatomic sites and includes 21 eye-specific adverse event criteria for grading. By providing a system for standardized data, both the LENT/SOMA and CTCAE v3.0 offer a format through which to develop and compare the toxicity profiles of different cancer regimens, and to enhance future treatments (CTE 2006). Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The eye globe is the anatomic isocenter with the anterior component containing the eyelid, the lacrimal gland, and the posterior component containing the orbital content of muscles and nerves (Fig. 2).

The orbital contents consist of the globe, adipose tissue, extraocular muscles (medial, lateral, superior, inferior recti and the superior and inferior obliques). These muscles are innervated by cranial nerves III, IV and VI.

2.2 Histology

The histology of the eye can be described as follows (Fig. 3a, b, c):

- The eyelid can be partitioned into the anterior and posterior lamella.The anterior lamella consists of the skin and orbicularis muscle while the posterior lamella is made up of the eyelid retractors, tarsus and conjunctiva.
- The tear film is made up of three layers: mucous, aqueous and lipid layers. The inner mucous layer is produced by the goblet cells of the conjunctiva and helps tears adhere to the eye. The middle aqueous layer is predominantly produced by the accessory lacrimal glands, while the outer lipid layer is produced by meibomian glands and prevents evaporation.
- The nasolacrimal system is composed of upper and lower puncta in the medial eyelids which collect tears, descend into the canaliculi, then into the lacrimal sac and the nasolacrimal duct which opens below the inferior turbinate of the nares.
- The outer portion of the globe is composed of the sclera and cornea, while the posterior segment is lined with retina and retinal pigment epithelium (RPE). The choroid is a vascular bed that lies between the RPE and sclera.
- Chambers of the eye consist of (i) the anterior chamber, between the cornea and iris, (ii) the posterior chamber is between the posterior surface of the iris and anterior surface and equator of the lens, and (iii) the vitreous chamber, the space between the lens and retina. The vitreous is a gelatinous substance (Fig. 3b, c).
- Uvea contains the iris, ciliary body, and choroid with special emphasis on the canal of Schlemm which drains

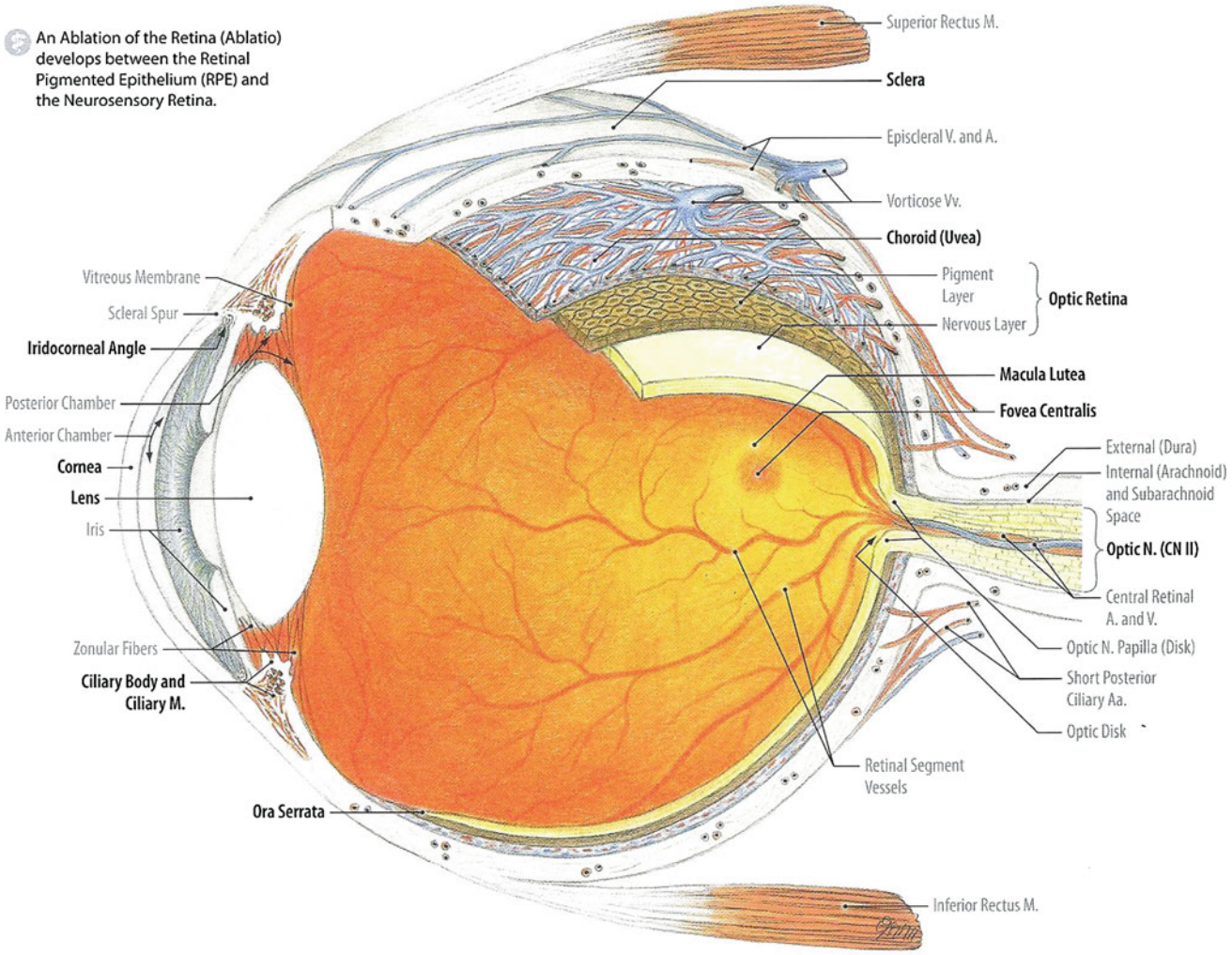


Fig. 2 Illustation (in layers) of the Retina, Choroid, and Sclera in the Outer Area: Median Sagittal Section through the Anterior Eye (with permissions from Tillman 2007)

into episcleral venous system via minute channels through sclera. Obstruction to drainage of aqueous humor through the trabecular meshwork results in increased intraocular pressure, which may lead to optic nerve damage and glaucoma.

- Pupil of the eye consists of 3 sets of circular muscles: outer ciliary muscle, mid-dilator pupillae, and inner sphincter pupillae innervated by 3 different nerves: parasympathetic (outer), sympathetic (mid), and V1 (inner).

3 Physiology and Pathophysiology

3.1 Physiology

The physiology of each component of the eye will be correlated with its anatomy and histology (Fig. 4a, b).

3.1.1 Eyelids, Periorbital Skin, Lacrimal Apparatus

The thinnest skin in the body is located on the outer surface of the eyelids. It is devoid of subcutaneous fat allowing for the accumulation of fluid to manifest rapidly as swelling. The upper and lower eyelids contain fibrous connective tissue, known as the tarsal plates, which function as structural support. The eyelashes are located on the anterior portion of the eyelids and aid in protection of the eye.

The tears drain from the ocular surface via two puncta located on the medial aspect of the upper and lower lid margin. The puncta lead to the canaliculi that empty into the lacrimal sac and, in turn, into the nose via the nasolacrimal duct.

3.1.2 Conjunctiva and Sclera

The conjunctiva is a thin, transparent mucous membrane that lines both the posterior aspect of the eyelids (palpebral

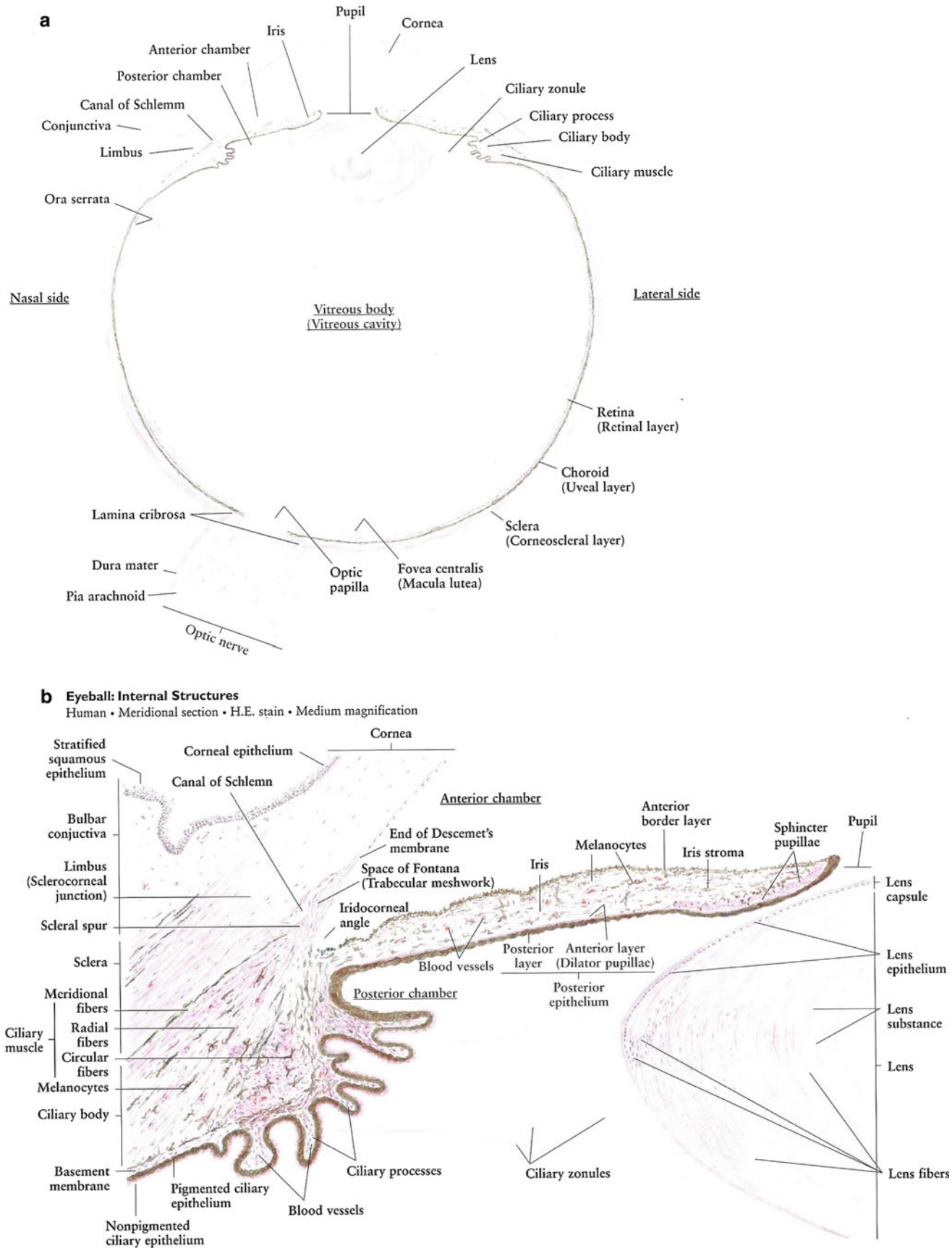
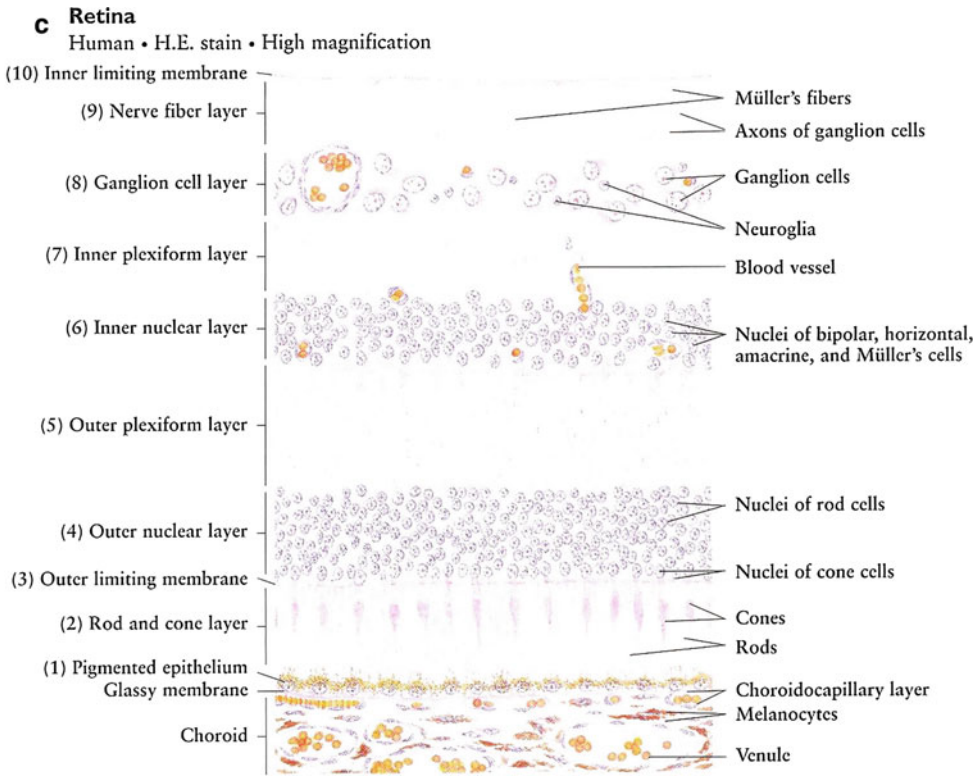


Fig. 3 **a** Eye globe: low magnification. **b** Iris and ciliary body. **c** Retina (with permissions from Zhang 1999)

Fig. 3 (continued)



conjunctiva) and the anterior surface of the eye (bulbar conjunctiva). The folds between the palpebral and bulbar conjunctiva are known as the superior and inferior fornices, respectively. Tissue is redundant in the fornices to allow for adequate movement of the globe. The main lacrimal gland, which functions during reflex tearing, empties into the superior fornix, while the accessory lacrimal glands, supplying basal tear secretion, are found throughout the conjunctiva, concentrating in the fornices.

The conjunctiva contains a stratified non-keratinized epithelium overlying a stroma, known as the substantia propria. Goblet cells supplying the mucin layer of the tear film are found intermixed with the epithelial cells. The mucin produced by goblet cells contains a mucopolysaccharide which is crucial in allowing for adherence of tears to the corneal epithelium. With goblet cell damage and a lack of this mucin substance, the tears lose their adhering qualities, become unstable and contribute to surface desiccation even in the presence of adequate aqueous production. Besides acting as a physical barrier, the conjunctiva aids in host defenses by hosting immune cells as well as colonizing bacteria.

The sclera is an acellular, avascular, collagenous protective layer of the eye. It is continuous with the cornea at the limbus and covered anteriorly by the conjunctiva. The superficial coating of the sclera, known as the episclera, consists of a loose, transparent, vascular coating.

3.1.3 Lacrimal Gland, Conjunctiva, Cornea

The tear film covers the anterior surface of the conjunctiva and cornea. It serves the vital role of supplying the cornea with moisture and nutrients in the form of mucins, enzymes, immunoglobulins antimicrobial proteins, and growth factors. It also allows for the maintenance of a clear, non-keratinized epithelium in the visual axis. Furthermore, the tear film comprises the smooth outer refractive coating essential to vision by filling in corneal irregularities. The tear film consists of three layers. The aqueous layer is produced by the lacrimal gland and accessory lacrimal glands found in the conjunctiva. Meibomian glands located within the tarsal plates produce an oily layer that sits on top of and acts to stabilize the aqueous layer. The goblet cells of the conjunctiva produce the third, or mucous, layer. The overall function of the tear film is vitally dependent on each of these individual layers, and a deficiency in any layer will adversely affect the entire ocular surface.

The cornea is the transparent, avascular anterior portion of the eye that refracts and transmits light to the inner structures of the eye, while also absorbing some of the harmful UV radiation. Along with the overlying tear film, it provides approximately two-thirds of the refracting power of the eye. The conjunctiva borders the cornea in an area known as the limbus. This region contains corneal stem cells; therefore, compromising this zone leads to the loss of corneal transparency and often its integrity. The cornea is an avascular

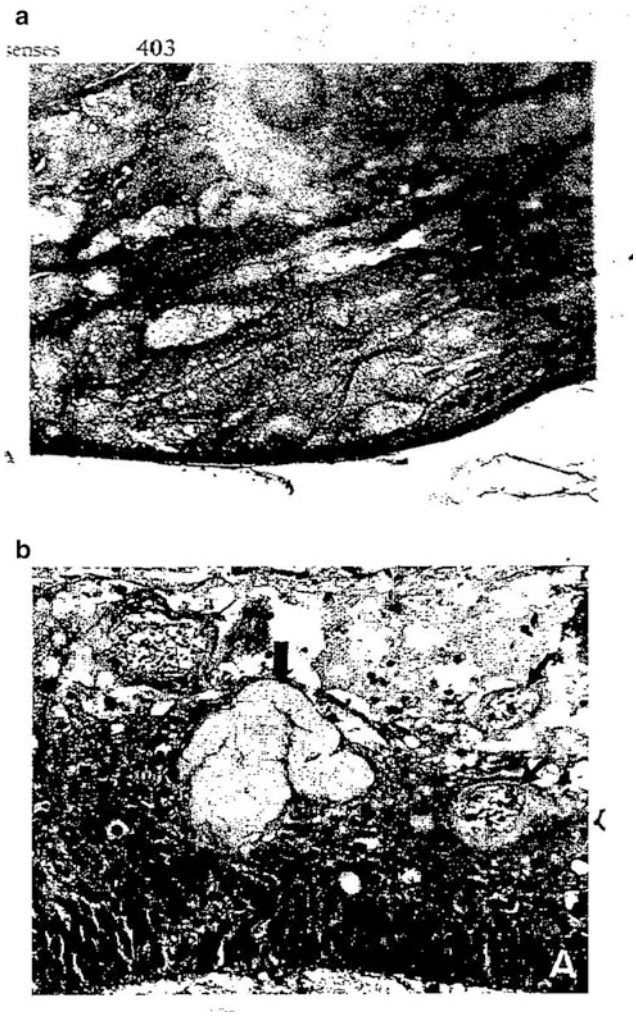


Fig. 4 **a** Lens-cataract: posterior subcapsular cataract in an irradiated lens. Notice the epithelial cells (*lower right*) that have migrated to the posterior pole. Prominent "Morgagnian globules" derived from preexisting fibers appear in the lower center as sharply demarcated polygonal spaces of variable gray density. **b** Retina-atrophy: eye resected 6 months after irradiation with 60 Gy in 25 fractions over 44 days. There is marked atrophy in the innermost layers, with irregular thickening and dilation of capillaries (*small arrows*). An arteriole in the center (*large arrow*) is totally replaced by convoluted fibrillary material (mostly collagen) (with permissions from Fajardo et al. 2001)

tissue and thus depends on the limbal vessels along with the tear film and aqueous fluid from the anterior chamber for nutrients and waste removal. The direct derivation of oxygen from air gives the cornea a unique characteristic compared to other body tissues. The cornea consists of five specialized layers, including, from anterior to posterior: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The epithelium is stratified, non-keratinized and replaces itself every 5–7 days. The stroma contains approximately 90 % of the overall corneal thickness, including a specialized superficial region known as Bowman's membrane. Descemet's membrane is a tough, thickened basement membrane secreted by the endothelium. The endothelial cells form a monolayer, which controls corneal hydration via ionic pumps. Small changes in corneal hydration (thickness) drastically change the optical properties of the cornea; therefore, the endothelial pumps are essential to maintain clear vision. Endothelial cells can migrate to fill a damaged area, but they do not regenerate; therefore, all loss of endothelial cells is permanent. Inflammation of the cornea, known as keratitis, may cause edema, increased corneal thickness and blurred vision.

3.1.4 Lens

The crystalline lens is a biconvex refractive structure that provides the second major refractive surface of the eye after the cornea. It is located behind the iris and pupil and is suspended circumferentially by ligaments known as zonule fibers. Anteriorly it is immersed in aqueous humor and posteriorly in vitreous humor. The encapsulated structure is devoid of blood vessels and nerves and depends on nutrients from the aqueous and vitreous humor. The lens is composed of densely packed fibers that arise from lens epithelial cells. These cells, located within the anterior periphery of the lens, undergo mitotic division at the germinative zone (the most mitotically active zone), elongate, lose their nuclei, and extend anteriorly and posteriorly to meet at the "Y" shaped suture lines in the center of the lens. The fiber cells contain specific proteins called crystallins that keep the lens transparent by inhibiting aggregation of proteins (Yanoff et al. 2004). The avascular nature of the lens prevents dispersing heat efficiently and the arrangement of the lens does not allow for removal of cells. Thus, any injured cells leave a permanent, visible defect; and like the rings of a tree, the timing of the insult is evident and irreparable.

3.1.5 Uvea: Iris, Ciliary Body, and Choroids

The uvea consists of three structures with a common embryologic origin: the iris, ciliary body, and choroid. The iris acts as the light aperture of the eye. It is a muscular membrane with a central circular opening (the pupil). Despite the wide variation in iris color on the anterior surface, the posterior surface of the normal iris characteristically contains a thick layer of heavily pigmented cells that act to absorb and thus limit the influx of light. The size of the pupil is controlled by the autonomic nervous system with input from both sympathetic and parasympathetic systems.

The ciliary body is a muscular structure located posterior to the iris and peripheral to the lens. The ciliary body produces the aqueous humor, the fluid that fills the anterior segment of the eye. This fluid drains through a structure known as the trabecular meshwork located anterior to the iris. As a result, the fluid must travel through the pupil in order to exit the eye. Any disruption to this flow will result in a backup of fluid and increased pressure within the eye,

known as glaucoma. The ciliary body is also responsible for adjusting the tension on the zonule that allows for lens accommodation. The choroid, located between the retina and sclera, is the posterior segment of the uveal tract. It is a highly vascular structure that supplies the outer retina with oxygen and acts as a heat sink to the highly active photoreceptors; thereby preventing them from getting overheated when converting light energy to electrical stimuli.

3.1.6 Optic Nerve and Retina

The retina is a thin, transparent structure that functions to convert light energy into electrical stimuli for the brain to interpret. The macula, located temporal to the optic disc, is responsible for central vision and contains the highest concentration of photoreceptors. It is thought the retinal vasculature contributes roughly 5 % of the oxygen used by the retina, while the choroid provides the rest. The retinal vessels are sensitive to changes in vascular permeability which may lead to swelling of the retinal layers (i.e., macular edema). The nine layers spanning from the inner to outer aspect of the retina are histologically distinguishable, and may distort retinal pathologies in characteristic ways depending on their location.

The optic nerve contains 1,100,000 axons from the superficial layer of the retina. These axons leave the eye through an area known as the optic disc and comprise the pathway through which visual stimuli reach the brain.

3.1.7 Orbital Bones and Tissue

The orbital cavity is composed of seven bones: the maxilla, palatine, frontal, sphenoid, zygomatic, ethmoid, and lacrimal bones. They form the shape of a quadrilateral pyramid with the apex forming posteriorly and the medial walls parallel. The soft tissues of the orbit consist of the extraocular muscles, orbital fat, fascia, and vascular structures. The function of the orbital bones is to protect the eye, while the soft tissues act to cushion the eye and optic nerve during movement.

3.2 Pathophysiology

Each structure of the eye, because of its complex structure will be described separately:

3.2.1 Eyelids, Lacrimal Gland

Eyelid reaction to irradiation is similar to skin and its appendages, depending on dose/time factors. It may result in acute erythema to desquamation, loss of eyelashes, inward turning of re-grown lashes and meibomian gland disturbance. Late effects include keratoconjunctivitis sicca and squamous metaplasia of the conjunctiva.

3.2.2 Lens

The formation of cataracts is most often cited as an adverse event due to radiation. The lens is an ectodermal structure, as is the skin. The germinal epidermal cell (stratum granular) is located at the equator of the lens, migrates posteriorly, and loses its nucleus to form clear epithelial layers (stratum clear) to the lens. Radiation has been primarily associated with posterior sub-capsular cataracts owing to abnormal epithelial cells migrating posteriorly and centrally. The exact mechanism of damage remains unclear, but proposals have included free radical formation or thermal effects of radiation.

3.2.3 Uvea

Inflammation can result in synechiae or scarred attachments between the iris and anterior lens capsule. Scarring of these structures can lead to narrow angles, obstruction of trabecular meshwork outflow, elevated intraocular pressure and possibly glaucoma.

3.2.4 Retina

The mechanism of radiation retinopathy is still debated. One proposal suggests the primary site of damage is the vasculature. Endothelial cell damage with secondary loss of pericytes leads to leaky vasculature and retinal edema, while microaneurysm formation can cause intraretinal hemorrhage. Capillary loss leads to ischemia, instigating release of vasoproliferative factors and eventual neovascularization of the retina and optic disc. In very advanced cases, proliferative retinopathy can result in a tractional retinal detachment.

3.2.5 Optic Nerve

Radiation to the optic nerve may result in free-radical mediated damage to the glial cells and vascular endothelium of the white matter. With time this may result in a pale optic disc from degenerated nerve fibers.

4 Clinical Syndromes: Radiation-Induced

4.1 Eyelids, Periorbital Skin, Lacrimal Glands

Radiation can cause a number of insults to the eyelids including pigment changes, telangiectasia, madarosis (or eyelash loss), lymphedema, and architectural alterations to the eyelids and nasolacrimal system. Hyperpigmentation may follow the acute stages of erythema within a year of treatment. It is speculated that activation of angiogenic factors may contribute to telangiectasia formation (Riekki et al. 2001), which occurs at doses greater than 55 Gy, and typically at 1–5 years post treatment. In one study, lid

Table 1 Clinical syndromes (LENT SOMA) of the Eye-orbit

Eye				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Vision	Indistinct color vision	Blurred vision, loss of color vision	Severe loss of vision, symptomatic visual field defect with decrease in central vision, some ability to perform daily living activities	Blind, inability to perform daily living activities
Light sensitivity	Photophobia, no change in vision	Increased photophobia, decreased vision	Photophobia, major loss of vision	
Pain/ Dryness	Occasional & minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Tearing	Occasional	Intermittent	Persistent	
Objective				
Best corrected vision	>20/40	20/50–20/200	<20/200 count fingers at 1 meter	Cannot count fingers at 1 m
Cornea	Increased tearing on exam	Non-infectious keratitis	Infectious keratitis, corneal ulcer	Panophthalmitis, corneal scar, ulceration leading to perforation/loss of globe
Iris	Rubeosis only	Rubeosis, increased intraocular pressure	Neovascular glaucoma with ability to count fingers at 1 m	Neovascular glaucoma without ability to count fingers at 1 m, complete blindness
Sclera	Loss of episcleral vessels	≤50 % scleral thinning	>50 % scleral thinning	Scleral or periosteal graft required due to perforation
Optic nerve	Afferent pupillary defect with normal appearing nerve	≤1/4 pallor with asymptomatic visual field defect	>1/4 pallor or central scotoma	Profound optic atrophy, complete blindness
Lens	Asymmetric lenticular opacities, no visual loss	Moderate lenticular changes with mild-moderate visual loss	Moderate lenticular changes with severe visual loss	Severe lenticular changes
Retina	Microaneurysms, nonfoveal exudates, minor vessel attenuation, extrafoveal pigment changes	Cotton wool spots	Massive macular exudation, focal retinal detachment	Opaque vitreous hemorrhage, complete retinal detachment, blindness
Facial bones	Cosmetically undetectable facial asymmetry	Minimal cosmetic asymmetry	Moderate orbital contracture	Severe hypoplasia of orbital bones

margin epilation occurred in 20 % of patients receiving external beam radiation at doses of 60 Gy, followed by regrowth of sparse and differently pigmented cilia (Nakissa et al. 1983). In the Collaborative Ocular Melanoma Study (COMS), madarosis was the only complication that was significantly greater in those patients whom had received pre-enucleation external beam radiation therapy compared to those whom received enucleation only (COMS 1998) (Tables 1, 2, 3).

A number of lid deformities may result from higher doses of radiation in the range of 60–75 Gy, such as ectropion (out-turning of lid margin) or entropion (in-turning of lid margin) (Nakissa et al. 1983). However, these complications are rare and seldom seen today. Radiation to the tarsus may result in its atrophy or contracture. Lid necrosis may develop months to years after treatment and is exacerbated by excess sun to previously irradiated tissue (Brady et al. 1989; Ober et al. 2012). Aberrations such as these can impair the eyelids' ability to adequately cover and maintain the integrity of the ocular surface, leading to its possible compromise (see next section on ocular surface).

Destruction or occlusion of the puncta may occur when the medial portions of the eyelid are irradiated. Radiation induced canaliculitis leads to fibrosis and obstruction,

Table 2 Detection: analytic (LENT SOMA eye-orbit)

Management				
Tearing, Cornea, Lacrimation	Lubrication as needed	Lubrication with or without pressure patch, antibiotics	Topical antibiotics with or without cycloplegia	Corneal graft, Enucleation
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Parenteral narcotics
Neovascularization	Pan-retinal photocoagulation for neovascular changes	Medical management of glaucoma, pan-retinal photocoagulation	Surgical management of glaucoma, Cytodestructive procedure	Enucleation
Lens			Cataract extraction depending on visual potential	
Retina		Medical management of glaucoma, focal photocoagulation	Surgical management of glaucoma, with or without pan-retinal photocoagulation	Cytodestructive procedure, repair of retinal detachment
Facial bones			Cosmetic repair ± orbital augmentation for anophthalmic socket	Enucleation, orbital augmentation for anophthalmic socket
Analytic				
Slit lamp exam	Assessment of intraocular pressure, pupils, ocular motility, dilated fundoscopic exam, and gonioscopy			
Cultures and stains	Assessment of corneal infiltrates			
Ultrasound	Examination of posterior pole if opaque media, i.e., cornea, lens, vitreous			
Fluorescein angiogram	Evaluation of retinal neovascularization, macular edema/exudates			
Color vision	Assessment if afferent pupillary defect, or optic nerve asymmetry			
Automated visual field	Bilateral-assessment of optic nerve, pupillary or color vision abnormality			
MRI	Assessment of sudden visual loss and abnormal optic disc or normal appearing optic disc and no other visible reason for visual loss			

Table 3 Examples of clinical and subclinical endpoints of radiation induced eye toxicity

	Focal	Diffuse
Subclinical	Telangiectasia	
	Pigment deposition	–
	Neovascularization	
	Asymptomatic keratopathy	
	Asymptomatic cataract	
	Asymptomatic glaucoma	
	Iris atrophy	
	Asymptomatic retinopathy	
	Asymptomatic optic neuropathy	
Clinical	Eyelid deformities	Vision loss
	Symptomatic keratopathy	Diplopia
	Symptomatic cataract	Sympathetic ophthalmia
	Uveitis	Endophthalmitis
	Symptomatic glaucoma	
	Visual field defect	
	Symptomatic retinopathy	
	Symptomatic optic neuropathy	
	Boney deformities	

typically to the lateral one-third of the nasolacrimal system (Buatois et al. 1996). Stenosis or obstruction along any part of the nasolacrimal ductal system can cause impaired tear drainage and symptoms of epiphora.

Lacrimal gland dysfunction can lead to a dry eye and associated chronic symptoms such as pain, and may result in corneal ulceration and visual loss. A series of analyses from the University of Florida and elsewhere relate the incidence of dry eye to the dose of radiation delivered to the lacrimal gland. Dry eye is unusual at doses <30 Gy, is occasionally seen at slightly higher doses, is very common following doses >40–45 Gy, and can be severe at doses >57 Gy (doses usually delivered at 1.8–2.0 Gy per fraction). The interval between RT and the onset of dry eye can be years following modest doses (e.g., >4 years after 30–40 Gy), but are often shorter at higher dose levels (e.g. 9–10 months after >57 Gy) (Parsons et al. 1994, 1996; Jeganathan et al. 2011).

4.2 Conjunctiva and Sclera

Radiation effects to the conjunctiva may occur via direct damage or through secondary effects on the ocular surface. At 1–2 years post-treatment, prolonged conjunctival injection may develop, particularly at exposures of 30–50 Gy. Also at doses of 30 Gy, telangiectatic vessels may follow at 3–6 years. With minor trauma or valsalva efforts, the fragility of these vessels may result in their rupture and accumulation of subconjunctival hemorrhage (Fig. 5).

At radiation doses over 50 Gy, keratinization of the epithelium has been observed (Gordon et al. 1995). These eyes should be evaluated for cornea irritation from adjacent keratin plaques. In severe cases and exposures of 60 Gy, chronic conjunctival ulceration may develop. Feared complications include symblepharon formation (adhesions between the bulbar and palpebral conjunctiva following denuded epithelium) and subsequent forniceal shortening, trichiasis (inward turning of the lashes on the ocular surface) and other eyelid malpositions. Conjunctival necrosis has also been observed in retinoblastoma patients when radioactive plaque therapy provided conjunctiva doses of 90–300 Gy (Haik et al. 1983; Brady et al. 1989; Ober et al. 2012; Donnenfeld et al. 1993). Loss of goblet cells may occur and exacerbate dry eye symptoms through the subsequent dearth of mucin.

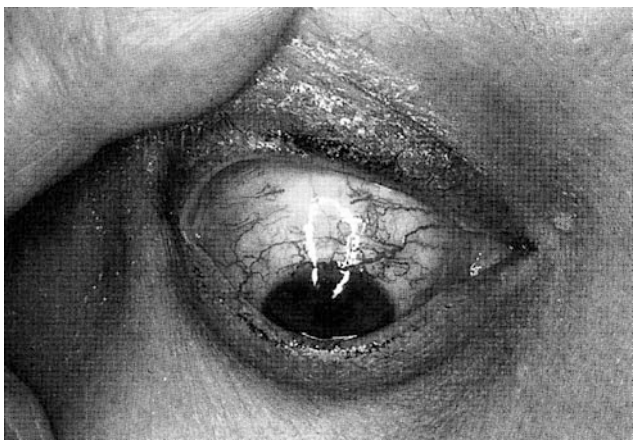


Fig. 5 Clinical syndromes: telangiectasia of conjunctival blood vessels

The avascular property of sclera renders it relatively radioresistant. For example, the sclera is able to tolerate doses of radiation up to 900 Gy from an iodine or cobalt plaque when administered over 4–7 days. However, scleral atrophy and necrosis has been documented in irradiated eyes, and is most common following the use of brachytherapy. In fact, scleral atrophy is a dose-limiting factor in ocular plaque dosing. Fractionated doses of 20–30 Gy can cause thinning, melting or atrophy of the sclera, while its perforation is a rare complication (Brady et al. 1989). Sclera atrophy should be monitored for infection, corneoscleritis (concomitant inflammation of the sclera and cornea) and perforation.

Pigmented deposits on the episclera have been reported following brachytherapy for uveal melanoma. They developed within 6 months of treatment, occurred in 85 % of patients at 1 year and their quantity was associated with proximity to the tumor or irradiated area (Toivonen and Kivelä 2006).

4.3 Lacrimal Gland, Conjunctiva, Cornea

The health of the ocular surface relies greatly upon the tear film, which is generated by a careful balancing of three components: the aqueous, mucin, and lipid layers. Deficiencies in any one of these may result in a compromised tear film and risk the maintenance of the ocular surface. Radiation can disrupt many of the key structures that produce these tear film elements, and place the eye at risk for ocular surface damage (or dry eyes) via a number of mechanisms. For example, radiation induced atrophy of the lacrimal gland, which occurs at 50–60 Gy, causes a decrease in aqueous tear substance. Furthermore, atrophy of meibomian glands at doses less than 30 Gy (Roth et al. 1976) and damage to conjunctival goblet cells (which also have low radiation tolerance) cause reductions in the lipid and mucin constituent of tears, respectively. The subsequent instability of the tear film and its surface tension results in an evaporative dry state. When all of the three tear film constituents are compromised by radiation, it is inevitable that a dry eye state will follow. The frequency of radiation-induced dry eye is dose-dependent and most likely at doses

greater than 40 Gy (Parsons et al. 1994, 1996). However, while changes are evident within 9–10 months at higher doses (>57 Gy), it is suggested that low doses (30–45 Gy) cause later-onset ocular surface disease at an estimated 4–11 years post-treatment (Durkin et al. 2007). Symptoms of keratoconjunctivitis sicca (KCS), or dry eyes, include foreign body sensation, burning, photophobia and blurry vision. High dose radioiodine used in the treatment of thyroid carcinomas results in reduction of lacrimal gland tears; however, the subsequent association to dry eye symptoms is unclear (Fard-Esfahani et al. 2007).

The anterior surface of the cornea can likewise be affected by a number of radiation-induced pathologies. The tear film baths the cornea but when altered by radiation, can lead to an epitheliopathy. Radiation-induced impairment of the fifth cranial nerve causes decreased corneal sensation and neurotrophic harm, while decreased blink mechanism and exacerbation of surface changes can result from aberrations of the seventh cranial nerve. Furthermore, radiation can damage the corneal stem cells located at the limbus (the transition between cornea and conjunctiva along the peripheral edge of the cornea), thereby injuring the cornea's source of epithelial turnover (Dua et al. 2003). This may cause chronic epithelial defects or filamentary keratitis, which share the symptoms of irritation, photophobia, pain, and epiphora. Without an intact epithelium, the underlying stroma is at risk for damage. In fact, either epithelial or endothelial dysfunction can cause stromal edema. In addition, stromal ulceration results from direct radiation damage to the stromal keratocytes at doses of greater than 60 Gy (Nakissa et al. 1983). Both epithelial and stromal defects can elicit vision-limiting neovascularization and opacification. Years after treatment, keratinization and even lipid deposition in the stroma can occur, both of which further compromise vision. A nonhealing ulcer can be a treatment dilemma and requires close observation for panophthalmitis and perforation.

Without an adequate tear film, the ocular surface has limited contact to the accompanying nourishment, lubrication, immunoglobulins, and enzymes. This may increase the cornea's susceptibility to colonization or microbial invasion and thereby accelerate ulceration and perforation (Haik et al. 1983; Brady et al. 1989; Donnenfeld et al. 1993; Barabino et al. 2005; Blondi 1958).

4.4 Lens

Cataract is a well known complication following radiation to the eye. A cataract is a loss of optical clarity within the lens. It is usually attributed to a disruption of the regular structure of the lens fibers. Radiation has been primarily associated with posterior subcapsular cataracts secondary to the abnormal epithelial cells migrating posteriorly and centrally. Damage to the radiosensitive germinative epithelium is likely responsible for most post radiation cataracts. The exact mechanism of damage remains unclear. However, evidence exists for free radical formation causing DNA and cell membrane damage and mitotic arrest. Thermal effects of radiation are also likely to contribute to injury of lens fiber cells secondary to the heat being inefficiently dissipated (Fig. 6).

An association between cataract formation and exposure to ionizing radiation was first recognized in 1897. In humans an increased incidence of cataracts was noted in nuclear plant workers, survivors of atomic bombs, and later in patients treated with local radiation for head and neck cancers (Abelson and Kruger 1949; Cogan et al. 1949; Merriam and Focht 1957). Cataract formation ranges from a latency period of 6 months to over 30 years with an approximate average of 2–3 years. The development of lens opacity is heavily influenced by patient age, the method of delivery, size and location of the tumor, and total dose, fractionation, energy of the source, and dose rate of radiation.

In patients with choroidal melanoma, tumor size is a risk factor for the development of cataracts with either brachytherapy or external beam radiation. Tumor basal diameter greater than 10–15 mm (Summanen et al. 1996), and height greater than 4–6 mm (Summanen et al. 1996; Beitler et al. 1990; Gunduz et al. 1999a, b, c; Gragoudas et al. 1995), are strong predictors of developing radiation cataracts. Tumor height, which is believed to be a good approximation of tumor volume, has been found to be an independent risk factor and associated with time to cataract formation (Summanen et al. 1996; Kleineidam et al. 1993; Puusaari et al. 2004a). This could be partially secondary to elevated tumors undergoing more necrosis contributing to increased intraocular inflammation, which is known to cause cataracts.

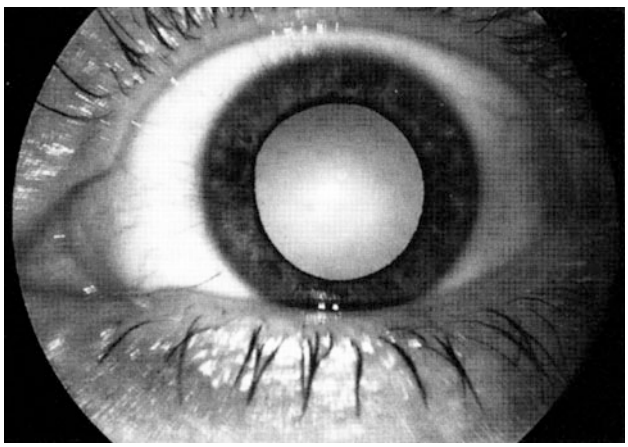


Fig. 6 Clinical syndromes: cataract

Tumor location also influences cataract formation. It is well accepted that anterior tumors are more likely to develop cataracts after brachytherapy than posterior tumors, secondary to the difference in radiation dose to the lens. For example, one study found cataract rates to be as high as 85 % in anterior tumors treated with Pd^{103} brachytherapy compared to 17 % for posterior tumors (Finger 1997). Additionally, there is a lower rate and longer time to onset of cataract formation for tumors located posterior to the equator (Fontanesi et al. 1993; Summanen et al. 1996). Cataracts have been noted after an average of 11 months in patients with anterior, iris, or ciliary body lesions compared to 26 months in patients with posterior based lesions (Summanen et al. 1996).

Several studies have investigated the minimal amount of radiation that would induce cataract development. Merriam and Foch, the first to describe the relationship between radiation dose and cataract formation, suggested that the amount of radiation delivered at a single period may be as important as the total dose (Merriam and Focht 1957). A single dose of 2 Gy or a cumulative dose of 5.5 Gy given over longer than 3 months was enough to induce cataract formation. Subsequent studies have reported a slightly higher threshold of single dose of 5 Gy or lower (Henk et al. 1993). In brachytherapy, eyes treated with doses less than 12 Gy of iodine 125 have a significantly lower rate of cataract and cataract surgery compared with doses greater than 24 Gy (COMS 2007). Additionally, for each 10 Gy increase of iodine 125 to the center and posterior pole of the lens, the rate of cataract formation has been reported to increase around 15 % (Puusaari et al. 2004b).

The effect of fractionation can influence cataract incidence. For example, Benyunes et al. reported 85 % of their patients developing cataracts when exposed to a single dose of 10 Gy versus 34–50 % when given fractionated doses of 2 Gy even to a higher total dose of 12 Gy or greater (Benyunes et al. 1995). Fractionation is also associated with delaying the development of cataracts, the severity of lens opacification, and the need for cataract surgery (Tichelli et al. 1993; Aristei et al. 2002; Benyunes et al. 1995). In addition, hyperfractionation with greater than 6 fractions can decrease the incidence of cataracts (Belkacemi et al. 1998).

Dose rate is another known risk factor that affects cataract formation. Low exposure rates, ranging from less than 0.035–0.06 Gy/min, may have significant sparing effect in the form of lower incidence of cataracts and cataract surgery (Belkacemi et al. 1998; Ozsahin et al. 1994; Fife et al. 1994).

4.5 Uvea: Iris, Ciliary body and Choroid

Iris neovascularization, or rubeosis iridis, occurs several months to years following RT, particularly with fractionated doses of 70–80 Gy over 6–8 weeks. Ocular ischemia instigates new, abnormal vessel formation through the release of vascular growth factors from ischemic retina, irradiated tumor tissue or direct damage to iris vessels. Without abatement, it is feared these vessels will grow into the anterior-chamber angle accompanied by myofibroblasts. The latter contract, form fibrous adhesions within the angle, and thereby obstruct aqueous outflow and increase pressure in the eye. High intraocular pressure may cause damage to the optic nerve, resulting in neovascular glaucoma, which is thought to occur in 35 % patients treated with brachytherapy (Shields et al. 2003). In plaque brachytherapy treatment, both iris neovascularization and glaucoma may be influenced by involvement of the anterior tumor with the iris, and with high intraocular pressures at diagnosis (Gunduz et al. 1999a, b, c; Puusaari et al. 2004a, b). With helium-ion irradiation in uveal melanoma patients, Daftari et al. found development of neovascular glaucoma correlated with amount of lens and anterior chamber exposed, tumor volume, proximity to the fovea, history of diabetes, and development of vitreous hemorrhage (Daftari et al. 1997).

Another mechanism for radiation-induced glaucoma involves the formation of posterior synechiae, which are iris adhesions to the lens caused by inflammation. They prevent fluid from moving behind the iris to the more anteriorly placed trabecular meshwork; thus placing the eye at risk for glaucoma due to high intraocular pressures. Although of little clinical consequence, iris atrophy has been reported 3 years after high doses of beta-irradiation with 170–250 Gy (Brady et al. 1989; Ober et al. 2012).

While anterior uveitis may be an acute complication following radiation, sympathetic ophthalmia is an autoimmune hypersensitivity phenomenon, which can occur between 10 days to 50 years after injury. It involves antibodies that are produced to exposed uvea of an injured (exciting) eye, which are then directed against the fellow (sympathizing) eye. This response has been reported in eyes treated with both irradiation and plaque brachytherapy for ocular melanoma (Ahmad et al. 2007; Fries et al. 1987). While a rare phenomenon, a suspicion of sympathetic ophthalmia warrants prompt management of the exciting (responsible) eye, since its enucleation within 2 weeks is most influential in preserving the health of the sympathizing eye.

4.6 Retina and Optic Nerve

In 1933, Stallard was the first to describe radiation retinopathy, and it has since been extensively described following external bean radiation, proton beam radiation and brachytherapy (Stallard 1933). The macula is the most visually ominous location for radiation pathology, and results from damage to the vessels that course around the

macula and feed the foveal area (which is essential for central vision). The risk for retinopathy is reported at exposures as little as 15 Gy, although the threshold is regarded at 40–50 Gy and others have suggested the threshold is higher. Monroe et al. propose that the incidence can be significantly reduced by hyperfractionated external beam radiation, with twice daily doses of 1.1–1.2 Gy; with this protective effect being most profound when the retina receives more than 50 Gy (Monroe et al. 2005) (Fig. 7).

On histology, there is pigment epithelial cell reduction and corresponding areas of photoreceptor atrophy. The choriocapillaris vessels are occluded, the retinal vessels are ensheathed in collagen fibrils, the retinal tissue is invaded with macrophages, and the nerve fiber layer is attenuated (Krebs et al. 1992). The ocular features of radiation retinopathy mimic other hypoxic etiologies of retinal damage with findings such as: microaneuryms, angiographic leakage, capillary nonperfusion, hard exudates, telangiectasia, retinal pigment epithelial changes, macular edema, hemorrhages, and neovascularization. These pathologies accumulate over time, while foveal retinal detachments and cotton wool spots (a marker for ganglion cell destruction and retrograde axonplasmic flow) predominate at 2 yrs post-treatment (Boldt et al. 2009). Retinopathy may develop as early as 3 weeks and as late as 15 years post-treatment, although it typically develops between 6 months and 3 years. The prevalence of radiation retinopathy at 5 years following plaque brachytherapy is close to 50 % (Gunduz et al. 1999a, b, c; Puusaari et al. 2004a) and is associated with tumor height and tumor distance to the macula; both possible indicators for radiation dose.

COMS found that radiation retinopathy is worse in those patients with underlying vascular disorders such as diabetes, which is not surprising given the risk of microvascular changes and retinopathy in uncontrolled diabetes. Researchers have also found that chemotherapy may exacerbate radiation retinopathy (Boldt et al. 2009). Poor prognostic factors for radiation retinopathy include papillopathy and proliferative retinopathy. The latter which causes the visually impairing complications of vitreous hemorrhage and tractional retinal detachment.

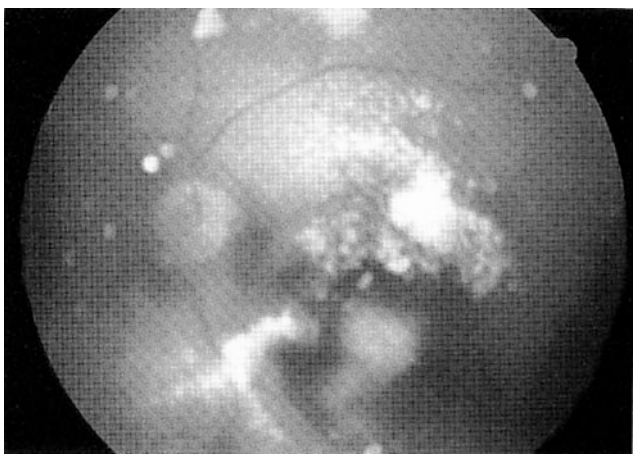


Fig. 7 Radiation retinopathy

Irradiation to tumors in proximity to the optic nerve, chiasm, and retrogeniculate visual pathways can cause optic neuropathy and vision loss. DNA exposure to radiation is thought to generate free radicals, which induce vascular endothelial damage and result in white matter injury (Lessell 2004). In fact, optic nerve pathology reveals narrowed, occluded blood vessels with decreased endothelial cells, and fibrin exudates (Levin et al. 2000). Demyelination and neuronal degeneration may result from the ionizing effects on replicating glial cells (Fike and Gobbell 1991).

The range of the reported prevalence of optic neuropathy is broad at 11–57 % (Boldt et al. 2009) due to the use of different endpoints and co-medical morbidities in treated patients. While the optic nerve is deemed to have a threshold of approximately 50 Gy, this threshold is lower in patients with coexistent diabetes, Cushing syndrome or previous chemotherapy (Lessell 2004). Typically, the radiation-induced neurological damage will result in presentation of vision loss on an average of 18 months after treatment, although the latency is shorter with higher radiation dosage (Lessell 2004). At exposures greater than 60 Gy, the fractioned dose becomes influential in optic nerve injury, with more risk for injury with larger daily fraction size (Durkin et al. 2007).

Other neurophthalmological complications of radiation exist. Four children who received periocular carboplatin injections for intraocular retinoblastoma developed ischemic optic neuropathy. One of these children received prior radiation, which may have been a contributing factor (Schmack et al. 2006). Ocular neuromyotonia is a rare syndrome and is characterized by episodic involuntary discharge of cranial nerves 3, 4, and 6 which control extraocular movements. It occurs months to years post-radiation and causes recurrent short-lived episodes of diplopia (Shults et al. 1991).

4.7 Orbital Bones and Tissue

Radiotherapy to ossification centers of children can result in boney deformities from bone growth arrest, necrosis of cartilaginous structure, and lead to hypotelorism (abnormally close eyes) and other orbital deformations (Raney et al. 1999). Anophthalmic socket syndrome, or soft tissue atrophy, and contracture of the socket following removal of the eye, has been documented after radiotherapy in patients treated for retinoblastoma (Abramson 1988). Osteonecrosis is rare and only results after very high doses of radiotherapy, but may be associated with concurrent orbital infections.

Table 4 Radiation effects on the eye and orbital tissues (LENT SOMA, Int. J. Radiation Oncology, Biology, Physics Volume 31, Number 5, 1995)

Tissue	Effect	Dose (Gy)	References
Conjunctiva	Conjunctivitis	5500–7500	Buatois et al. (1996)
	Telangiectasis	3000	Buatois et al. (1996), Parsons et al. (1994)
Cornea	Keratitis, edema, mild ulcer	3000–5000	Parsons et al. (1994)
	Ulcer, scarring, perforation	>6000	Buatois et al. (1996), Parsons et al. (1994)
Lens	Cataract	200 (threshold)	Ozsahin et al. (1994)
		1600	Buatois et al. (1996)
Retina	Retinopathy	>4650	Fife et al. (1994)
Optic nerve	Optic neuropathy	>5500	Buatois et al. (1996), Bajcsay et al. (2003)
Lacrimal system	Atrophy	5000–6000	Buatois et al. (1996)
	Stenosis	6500–7500	Buatois et al. (1996), Parsons et al. (1994)
Eyelid	Lash loss	4000–6000	Buatois et al. (1996), Parsons et al. (1994)
	Erythema	3000–4000	Buatois et al. (1996), Parsons et al. (1994)
	Telangiectasis	>5000	Buatois et al. (1996)
Orbit	Implant extrusion	Not specified	Bajcsay et al. (2003)

Note these are effects seen with conventionally fractionated (<250 Gy/day) megavoltage photon therapy. Adapted from Bardenstein and Char, with permission

5 Radiation Tolerance

The tolerance doses have been discussed in the clinical syndromes section and are summarized noting important studies (Table 4).

5.1 Dose Time Fractionation

The Tolerance Doses utilized 250 Gy fractions are summarized in Table 4. Important contributions to understanding the radiation time dose factors for cataract formation is due to the meticulous studies of Merriam and Focht, the extremely low level of radiation dose TD_5:200 Gy and $TD_{50} \geq 1000$ cGy, establishing the lens of the eye as one of the most radiosensitive tissues (Fig. 8).

6 Chemotherapy Tolerance

Chemotherapeutic agents and biologics can cause a number of ocular side-effects at various levels of the eye (Table 5). These complications are illustrated in Fig. 9.

Beginning with the anterior aspect of the orbit and eye, chemotherapeutic agents have been associated with stenosis of the punctum and tear (canalicular) drainage system, while other agents can rarely cause excessive lacrimation, cicatricial eyelid malpositioning or pallor of the periorbital skin. Conjunctivitis is a commonly reported symptom with chemotherapy use, while scleral complications from systemic chemotherapy applications are mild and uncommon. However, scleral ulcerations, scleritis and scleral calcifications are a known side effect of topical mitomycin C, which is used as an adjunct treatment for ocular surface tumors (Al-Tweigeri et al. 1996).

Many chemotherapeutic agents alter the normal tear film physiology either by causing inflammation of the lacrimal glands or by being excreted directly into tears, which leads to dry eye symptoms and inflammation around the eyelids and anterior segment of the eye (Al-Tweigeri et al. 1996). Following the use of chemotherapy, patients may develop keratitis, punctate corneal opacities, corneal hypoesthesia, other surface keratopathies, and whirl-like corneal inclusions known as verticillata (Albert et al. 1967; Al-Tweigeri et al. 1996; Kaiser-Kupfer and Lippman 1978). Severe uveal reactions have been described following intracarotid treatment with chemotherapeutic agents, including one reported patient treated with intracarotid cisplatin infusion who developed serous retinal detachment (Anderson and Anderson 1960; Margo and Murtagh 1993) likely from choroidal disturbance. Moving to the posterior segment, chemotherapeutic insult to the retina can result in retinal hemorrhages, cotton wool spots, optic disc edema, exudative retinal detachment, retinopathy (including pigmentary and crystalline), retinal edema and ischemia (Ashford et al. 1988; Margo and Murtagh 1993; Millay et al. 1986; Miller and Pecxon 1965; Miller et al. 1985; Ostrow et al. 1978; Rankin and Pitts 1993). Optic nerve damage includes optic neuritis, papilledema, optic nerve ischemia, optic neuropathy, color blindness and optic nerve atrophy (Albert et al. 1967; Al-Tweigeri et al. 1996; Ashford et al. 1988; Capri et al. 1994; Chun et al. 1986; Margileth et al. 1977; Margo

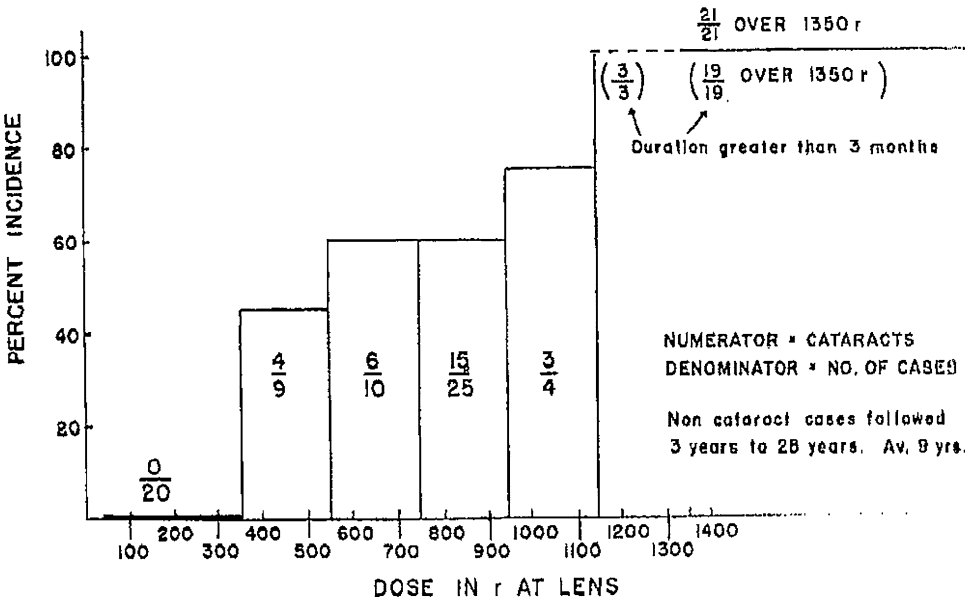


Fig. 8 Dose time: incidence of cataracts. The eye, variable factors; time-dose, incidence of cataraclx x- and gamma irradiation. **a** doses of x-gamma radiation of lous in 07 errors of radiation comfort and 70 errors without lens opacities. **b** Incidence of entararts. The treatment period was three weeks to three months (with permissions from Rubin and Casarett 1968)

and Murtagh 1993; Millay et al. 1986; Miller and Pecxon 1965; Miller et al. 1985; Ostrow et al. 1978; Porges et al. 1998; Rankin and Pitts 1993; Shurin et al. 1982). Paralysis of the eye muscles (ophthalmoplegia) has been reported with some agents due to cranial nerve palsy (Albert et al. 1967; Bixenman et al. 1968).

6.1 Biologicals

Biologicals comprise a relatively emerging field of medicine and a number of ocular complications have been associated with these agents. For example, the epidermal growth factor receptor (EGFR) inhibitors produce complications in cell types specific for EGFR including the periorbital skin, cilia, conjunctiva and cornea. Paradoxically, some agents concomitantly demonstrate both adverse and favorable effects on the eye, leading to their use for the treatment of ocular pathology in certain situations. As their use widens and new therapies are added to the compendium, more complications are likely to be documented and our understanding of their affects on the eye, both good and bad, will continue grow.

7 Special Topics

7.1 Effects of Corticosteroids

Corticosteroids inhibit the release of arachidonic acid, thereby exerting an anti- inflammatory and immunosuppressive effect. It is well documented that corticosteroids cause a host of ocular complications whether administered systemically (orally or intravenously) or locally via topical, intranasal, inhaled, or injected applications. These side effects target the eye at various tissue, anatomical and functional levels.

Corticosteroids are known to cause complications of the adnexa and anterior segment. Long-term corticosteroid use can cause ptosis, or a drooping of the upper eyelid, as a result of levator muscle myopathy (Carnahan and Goldstein 2000; Miller and Pecxon 1965; Miller et al. 1985). Exophthalmos, or protrusion of the globe is a known cause of endogenous steroids in Cushing's disease, but also rarely arises from long-term systemic exogenous use (Van Dalen and Sherman 1989). Slight mydriasis of the eye receiving topical steroids has been observed, and a few instances of myopia during systemic corticosteroids have been documented (Grant 1974). Corticosteroids may cause retardation of corneal healing and delay in generation of tensile strength, but these impairments are temporary (Grant 1974). Phosphate preparations of topical steroids show development of corneal stromal opacification likely via calcium phosphate precipitation (Schlotzer-Schrehardt et al. 1999); but this can be avoided with non-phosphate formulas. In addition, systemic administration of corticosteroids has been associated with scleral thinning and discoloration.

In 1960, Black et al. were the first to suggest that systemic steroids could lead to posterior subcapsular cataract formation (Black et al. 1960). Now, it is perhaps, the most frequently reported side-effect. While steroid-induced cataracts are highly variable and dependent on dose and duration, the incidence ranges from 15 to 52 % of patients and the threshold for formation is approximated at 10 mg oral prednisone daily for 1 year (Braver et al. 1967; Loredo et al. 1972). However, steroid-induced cataracts have been

Table 5 Chemotherapy agents and associated toxicities (with permission from Abramson 2008)

reported to develop after as little as 5 mg of daily oral prednisone for 2 months duration (Black et al. 1960; Urban and Cotlier 1986). For example, 30–40 % of patients with rheumatoid arthritis treated for 2 years with 10 mg prednisone develop cataracts, while this incidence approaches 80–100 % at an increased dose of 15 mg prednisone over 4 years (Becker 1964). The mechanism for steroid-induced cataract formation is still under investigation, but proposals include: glucocorticoid receptor-mediated mechanisms present on the lens, disruptions in lens structure by steroid binding of lens proteins, altered growth factor effects on epithelial cell differentiation, and increased susceptibility to oxidative stress (Bucala et al. 1985; James et al. 2003;

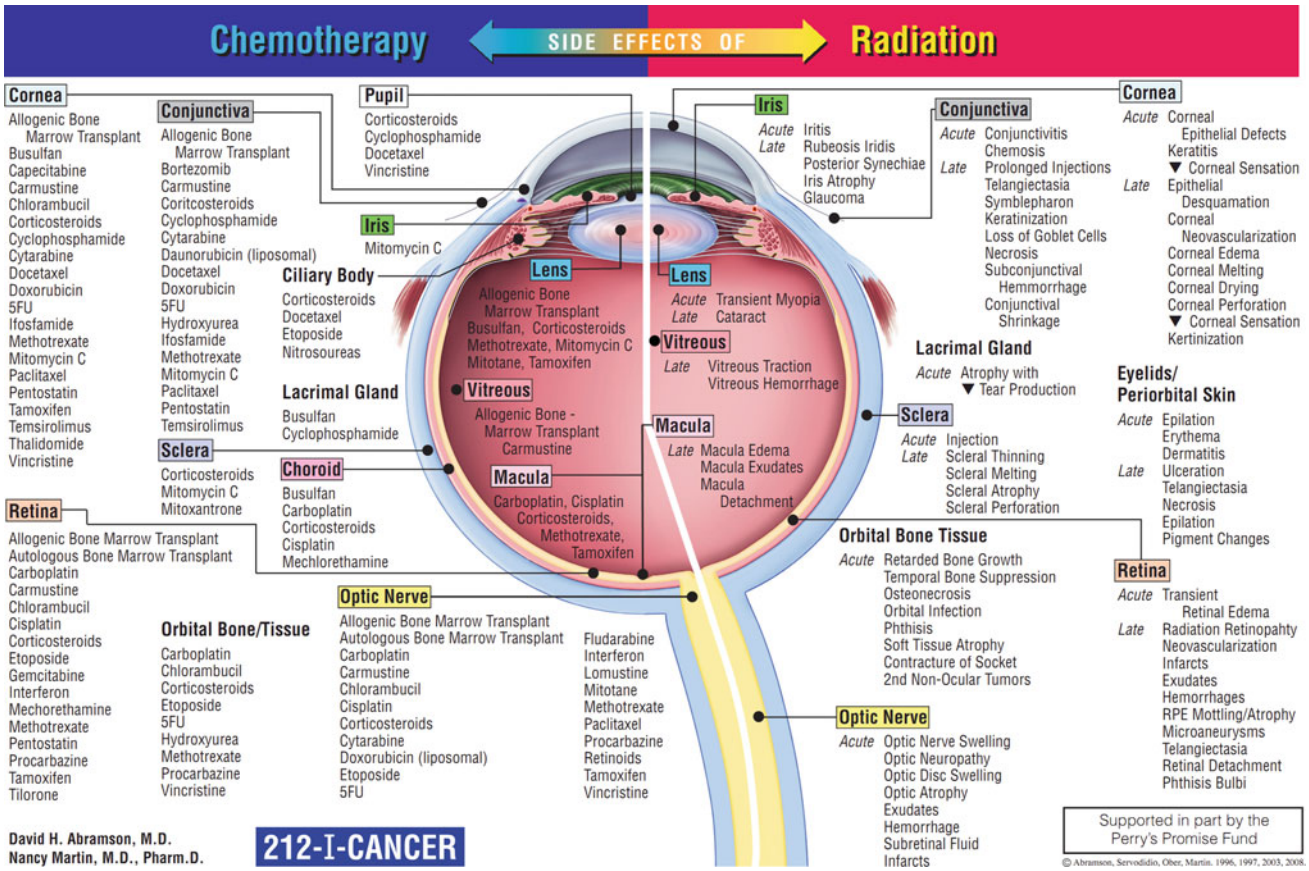


Fig. 9 Side effects of chemotherapy and radiation (with permission from Abramson 2008)

Jobling and Augusteyn 2002). Cataracts can be removed and vision typically improved with surgical extraction.

Some patients have corticosteroid-associated increased intraocular pressures, which may predispose them to glaucoma. For instance, about one-third of patients have been shown to generate elevated intraocular pressures with steroid eyedrops (Becker 1964). Systemic use can have a similar effect and has been estimated to cause elevated pressures at a little over 50 % of topical treatments (Carnahan and Goldstein 2000). Elevated intraocular pressures may be influenced by existing glaucoma, hypertension, high myopia, diabetes mellitus, family history, ethnicity, and rheumatoid arthritis (Carnahan and Goldstein 2000). Patients who are "steroid-responders" are more vulnerable to glaucoma progression when combined with other factors such as older age, ocular architecture, genetic predisposition, and length and increased dose of treatment (Armaly 1963a, b, 1966). Increased intraocular pressure is typically reversible within 2–4 weeks of steroid cessation (Tripathi et al. 1999). The mechanism for steroid-induced glaucoma is under debate but theories include receptor-mediated mechanisms via steroid-specific receptors in the trabecular meshwork, altered genes, or stabilization of lysosomal membranes leading to an accumulation of materials in the trabecular meshwork that increase resistance to flow (Carnahan and Goldstein 2000).

Steroids have been implicated in posterior segment pathologies. For instance, they have been associated with pseudotumor cerebri and accompanying papilledema, particularly during steroid withdrawal or tapering of dose (Newton and Cooper 1994; Liu et al. 1994; Ray et al. 2008). They are believed to be a possible contributing factor in central serous chorioretinopathy (Koyama et al. 2004) and have been reported to cause multiple retinal hemorrhages and transient vision loss of lumbar epidural injection (Young 2002). In addition, the immunosuppressive effects of corticosteroids can have an impact at multiple levels of the eye by facilitating opportunistic infections; this includes bacterial, viral and fungal derivatives of conjunctivitis, keratitis, corneal ulcers, uveitis, and retinitis (Palmer and Hyndiuk 2000).

7.2 Effects of Bone Marrow Transplant

Long-term ocular complications following bone marrow transplant (BMT) are well described. Aside from the complications that arise from exposure to high dose

chemotherapy and/or radiation, ocular changes associated with graft versus host disease are unique and are not uncommon among patients who undergo BMT. Graft versus host disease (GvHD) is a cell-mediated immune reaction in which the donor T cells mount an attack against the recipient tissue. The acute form of GvHD occurs within 3 months after transplantation and generally carries a better prognosis than the chronic form that is ongoing from 3 months after transplantation.

Ocular complications have been reported in 22–82 % of patients with GvHD affecting all layers of the eye (Kerty et al. 1999; Livesey et al. 1989; Franklin et al. 1983). Keratoconjunctivitis sicca (KCS) is the most frequent manifestation of ocular GVHD. The primary etiology of dry eyes in GVHD is thought to be secondary to lacrimal gland dysfunction. Histopathologic evaluation by Jabs et al. revealed PAS-positive material deposited within the lumina of acini and ductules of lacrimal glands in GvHD patients causing luminal obliteration and ductal dilatation (Jabs 1989). The typical time from transplantation to diagnosis of dry eye can range from around 100 to 200 days (Ogawa et al. 1999). KCS may cause corneal breakdown which leads to epithelial defects, peripheral neovascularization, keratinization, punctuate keratitis with sterile or infectious ulcerations, and perforation. Additionally, cutaneous manifestations of GvHD such as cicatricial lagophthalmos, ectropion, and eyelid stiffening may contribute to or exacerbate these corneal changes.

Pseudomembranous conjunctivitis is a cardinal ocular complication in GvHD, occurring in 12–17 % of patients with acute GvHD (Bray et al. 1991; Jabs et al. 1989) and 11 % in chronic GvHD (Jabs et al. 1989). Four stages of conjunctivitis have been described by Jabs et al. (1989). Stage 1 presents as conjunctival hyperemia. Stage 2 includes hyperemia with chemosis or serosanguinous exudates. Stage 3 manifests as conjunctival pseudomembrane which can lead to cicatricial fibrotic scarring of the tarsus. Stage 4 involves corneal epithelial sloughing in the setting of pseudomembrane conjunctivitis and usually occurs in the acute or hyperacute post transplant setting (Kim 2006). A study from John's Hopkins suggests that conjunctival involvement is a marker of severe acute GvHD and patients with lower stages of conjunctivitis without pseudomembranes have a better prognosis (Jabs et al. 1989).

Cataracts are a common ocular complication of BMT. Cataract genesis in patients with post-transplantation GvHD is caused by a combination of factors, including radiation, corticosteroids, and in some reports GvHD itself (Bray et al. 1991; Dunn et al. 1993).

Uveitis in the form of iridocyclitis and or choroiditis has been demonstrated in patients with GvHD. Hettinga et al. reported three patients who developed anterior uveitis in the setting of chronic GvHD without any other identifiable causes (Hettinga et al. 2007). Increased levels of inflammatory cytokines were found in the ocular fluid of these patients making GvHD a likely cause of the uveitis.

Posterior segment complications may also occur in patients post BMT with or without GvHD. Retinal findings, such as microvascular retinopathy, cotton-wool spots, and intraretinal and vitreous hemorrhage, have been reported in 12.8 % of patients post BMT. Most retinal and vitreous hemorrhages occur in the setting of pancytopenia and generally resolve without long-term sequelae (Coskuncan et al. 1994). Chronic GVHD has been reported to be the only significant risk factor associated with microvascular retinopathy (Coskuncan et al. 1994). Other posterior segment findings seen in the setting of GvHD include posterior scleritis, and central serous chorioretinopathy (CSCR). Posterior scleritis can be the initial manifestation of acute GvHD following BMT (Kim et al. 2002). CSCR is generally seen 50–120 days post BMT (Cheng et al. 2002; Karashima et al. 2002). CSCR development is thought to be secondary to choroidal infiltration in GvHD leading to choroidal hyperpermeability.

Drugs associated with the treatment of GVHD have characteristic ocular complications. Cyclosporine, an immunosuppressant agent used to prevent GvHD, has been linked to optic disc edema, optic neuropathy, and ischemic retinal lesions (Avery et al. 1991; Walter et al. 2000). In the setting of GvHD, BMT recipients are also highly susceptible to ocular infections secondary to persistent abnormalities of the immune system which is further inhibited by the treatment of GvHD with immunosuppressants. Pseudomonal corneal ulcers, herpes simplex keratitis, herpes zoster retinitis, toxoplasma gondii retinitis, cytomegalovirus chorioretinitis, and fungal endophthalmitis may cause permanent visual deficits following BMT (Chung et al. 2008; Coskuncan et al. 1994; Crippa et al. 2001; Robinson et al. 2004; Uchino et al. 2006).

A variety of treatments for ocular complications secondary to GvHD have been reported in the literature. The mainstay treatment is aimed toward treating the underlying GvHD while balancing the degree of immunosuppression. Systemic treatment for chronic GVHD includes corticosteroids and T-cell modulators (Cutler and Antin 2006). Recent reports have found targeting B-cells with Rituximab and photopheresis to be successful in the setting of steroid refractory GvHD (Couriel et al. 2006; Cutler et al. 2006).

7.3 Secondary Neoplasms

In some cases, the treatment modality for one malignancy increases risk for a secondary cancer. For instance, retinoblastoma patients are at risk for a secondary cancer particularly if they harbor the germline Rb mutation. It is believed

the radiation-induced chromosome instability, confers the second hit in the two-hit model of retinoblastoma. Importantly, this risk increases in irradiated patients treated before 12 months of age (Abramson and Frank 1998). For example, 50 years after radiotherapy for hereditary retinoblastoma, patients have an 8.9 % cumulative risk of developing a soft tissue sarcoma in the radiation field (Kleinerman et al. 2005, 2007). Soft tissue and osteosarcomas have significantly higher rates in the field of radiation. Therefore, periocular tumors such as these are possible in previously treated retinoblastoma patients.

Radiation can also induce DNA damage in the skin and result in a number of periocular skin neoplasms, including basal cell carcinoma, squamous cell carcinoma (SCC) and sebaceous cell carcinoma. Radiation doses greater than 20 Gy produce the malignant change necessary for SCC, which may occur 15 years or more after radiation therapy and has a higher risk of metastases in the setting of previous radiotherapy (Weedon 1997). One patient developed sebaceous cell carcinoma on all four of his eyelids following facial radiation (Rumelt et al. 1998).

8 Prevention and Management

8.1 Eyelids, Periorbital Skin, Lacrimal Drainage

During cancer treatment, skin can be cared for with the use of mild soaps and skin lubricants for hygiene and moisture. Ultraviolet protection should be established through a variety of means and skin-sensitizing drugs such as tetracyclines should be avoided. Antibiotic creams can be used to prevent superinfections while topical corticosteroid preparations may be useful in tempering skin inflammation.

Ptosis or other eyelid malpositions may require surgical manipulation and should be referred to an ophthalmologist in clinically significant cases (Seiff et al. 1985). Punctal stenosis may be relieved by punctoplasty, while nasolacrimal duct obstruction may necessitate silicone intubation or dacryocystorhinostomy (Barabino et al. 2005). Others have suggested the use of a stent before and after irradiation to prevent nasolacrimal duct obstruction (Gordon et al. 1995). Dry eye can be treated symptomatically with topical agents such as moisturizing eye drops.

8.2 Conjunctiva and Sclera

Artificial teardrops replace lost tear volume, dilute toxic chemotherapeutic metabolites, provide lubrication and thereby aid in relieving conjunctival irritation (see Sect. 4.3 for more on ocular surface management). In cases of conjunctival ulceration or even prolonged conjunctivitis, antibiotic eye drops, sometimes in combination with corticosteroids can be used. In advanced cases of inflammation, squamous metaplasia and loss of vascularization from scar formation may be reversed with vitamin A ophthalmic ointment (tretinoin 0.01 or 0.1 %) (Tseng 1986). Endstage, severe conjunctival reactions such as symblepharon and forniceal shortening should be referred for immediate ophthalmic interventions such as symblepharon lysis, mucous membrane grafting with forniceal reconstruction. Infectious conjunctivitis is highly contagious and patients should be counseled on contact precautions.

Subconjunctival hemorrhage typically reabsorbs without intervention; although patients should be warned and reassured of possible expansion, and advised to use artificial tears for alleviation of foreign body sensation.

Scleritis is treated with a number of oral anti-inflammatory agents including corticosteroids, NSAIDS and other immunomodulatory agents. Infections can be mitigated or treated with topical and systemic antimicrobials: fluoroquinolones are a common choice for their good tissue penetration. When there is significant risk for perforation, such as with scleral melting and profound thinning, scleral patch grafting can be employed. These patients should be warned about avoiding eye trauma and wearing eye protection at all times.

8.3 Tear Film, Ocular Surface, Cornea

One method in the treatment of dry eyes involves increasing the volume of tears. This can be achieved in two ways: either by reducing tear drainage or by supplementing the tear film with topical tear substitutes. The tenet of dry eye therapy is artificial tears, which contain a number of demulcents, which are polymers added to improve lubricant properties. Preservative-free formulas are preferred, given the toxic effect of preservatives on increasing corneal desquamation. These lubricants come in a variety of viscosities, with the most viscous being reserved for overnight use given its tendency to blur vision. Additives to increase viscosity include methylcellulose and hyaluronic acid; the latter promotes epithelial cell proliferation and has a longer ocular surface time to help stabilize the tear film (Troiano and Monaco 2008). Artificial tears require intermittent but persistent application, which can be tiresome for some patients. More convenient methods have been developed such as the lacrisert®, an ophthalmic insert which is placed into the inferior fornix and remains in place throughout the day to provide lubrication as it dissolves.

A number of anti-inflammatory agents are being employed to treat the inflammatory component of dry eyes. For instance, cyclosporine A is an immunomodulatory agent

that inhibits T cell activation and downregulates inflammatory cytokines. Likewise, steroid drops are used for a similar anti-inflammatory effect. Other agents under clinic trial are focused on stimulating tear components, such as the P2Y2 purinergic receptor agonist, which increases chloride, fluid and mucin secretion by the conjunctiva (Jumblatt and Jumblatt 1998). Vitamin A regulates proliferation and differentiation of corneal epithelial cells and aids in goblet cell preservation (Kobayashi et al. 1997). In one study, both cyclosporine A and vitamin A were both found to improve dry eye symptoms, but at least one month of their use is advised to obtain an adequate effect (Kim et al. 2009).

Autologous serum drops have beneficial effects on dry eyes by containing the growth factors normally present in tear fluid, which stimulates conjunctival mucous production. Environmental alterations such as humidifiers and moisture shield glasses can alleviate dry eye symptoms, as well as avoiding eye irritants such as rubbing, wind, smoke, and fans. Surgical interventions include reversible punctal occlusion with collagen or silicone punctual plus, and irreversible occlusion with cautery, hyfrecator or radiofrequency probe. Tarsorrhaphy can decrease the palpebral aperture and reduce exposure of the ocular surface, aiding dry eyes but also allowing for corneal wound healing. Finally, treatment of confounding eye diseases is imperative: for example, hot compresses and eyelid massage use in blepharitis may improve meibomian gland function and help generate a more stable lipid component to the tear film.

Epithelial defects, corneal infections, and ulcerations are treated with broad-spectrum antibiotic drops (typically a 4th generation fluoroquinolone) as frequently as every 15 min, based on severity. Non-healing epithelial defects can be treated with a bandage contact lens or tarsorrhaphy along with antibiotic drops. Corticosteroid drops (dexamethasone) are given as prophylactic treatment for corneal and conjunctival irritation in patients receiving antimetabolite treatment, especially cytosine arabinoside. Some types of sterile keratitis can also be alleviated with steroid drops. With impending or apparent corneal perforation, emergency surgical intervention is necessary.

Precaution measures during the time of radiation can help to reduce the radiation effect on key ocular structures. Selective blocking, angulations of the radiation fields and enhanced dose homogeneity with beam attenuators are examples of methods to achieve this. For instance, the accessory lacrimal glands concentrated in the upper lid can be displaced from the treatment field with a lid retractor. There is a misconception that the relatively radiosensitive lacrimal gland must be protected from the radiation field to maintain the aqueous component of the tear film. However, interestingly its removal fails to result in dry eyes, suggesting its protection is not necessary and may also be shielding micro foci of malignant cells.

8.4 Lens

Prevention of cataract formation may be accomplished by lens-sparing radiation techniques such as angle modification of external beam radiation or lens shielding. The Schipper's lens sparing retinoblastoma treatment method, which involves positioning the radiation beam to pass lateral to the orbits and beneath the lens posterior pole, has been shown to prevent radiation cataracts in patients with uveal metastases treated with external beam radiation (Bajcsay et al. 2003). Lens shielding is another effective method and has been described to decrease the total dose of radiation to the lens by as much as 50 % (Esik et al. 1996; Henk et al. 1993).

Cataract extraction is the only potential curative treatment for clinically significant radiation induced cataracts. During the early postoperative period several studies have shown an improvement in visual acuity of 2–5 lines compared with preoperative measurements (Fish 1991; Collaborative Ocular Melanoma Study 2007). However, vision-limiting complications usually lead to patients returning to either their preoperative visual acuity or worse within a few years after the surgery. The decrease in visual acuity is typically attributed to the effects of radiation rather than cataract surgery itself. In the COMS the most commonly reported complication was presumed radiation retinopathy (Collaborative Ocular Melanoma Study 2007). Complications that may be related to cataract surgery include cystoid macular edema, retinal detachment, and worsening of diabetic retinopathy.

Since free radical formation is postulated to be involved in the development of cataracts, antioxidant supplements, such as vitamin E and glutathione isopropyl ester, may help prevent or slow down the process. In animal models antioxidants have been shown to decrease oxidative stress and the risk of cataract formation (Karslioglu et al. 2004). However, to date, no compound has been identified to be effective in humans to prevent radiation related cataracts.

8.5 Uvea: Iris, Ciliary body, and Choroids

The mainstay treatment of noninfectious uveitis includes steroids. Typically, frequent dosing of topical steroid drops are used, although oral steroids maybe added in refractory cases. A number of other steroid-sparing immunomodulatory agents can be employed; although given their toxicity profile, use in conjunction with medical surveillance is advised. Cycloplegic drops are also recommended in the context of uveal inflammation: the paralysis of the ciliary body may relieve the associated pain, while also pulling the iris away from the lens and preventing posterior synechiae formation and its complications.

A number of intraocular pressure lowering agents are available, each with their unique side effects and thus patient indication. Beta-blockers, alpha-agonists, carbonic anhydrase inhibitors decrease aqueous production. Conversely, cholinergics increase trabecular outflow, while prostaglandin analogues increase uveoscleral outflow.

When medical management of intraocular pressures is inadequate, a number of surgical techniques are available. Commonly, a laser is used to create an opening in the iris (peripheral iridotomy) and thus provide an outlet for aqueous flow from the ciliary body to the trabecular meshwork. Laser is also used in trabeculoplasty to open the drainage angle and in cyclophotocoagulation to destruct the ciliary epithelium and decrease aqueous production. Other filtering procedures include goniotomy and trabeculotomy in which tissue incisions are created to provide an alternate means of outflow for aqueous drainage. In progressive cases, aqueous shunt devices can be placed to facilitate aqueous flow through a tube implanted in the anterior chamber to the subconjunctival space. Panretinal photocoagulation of the retina is used in neovascular glaucoma since it can help dissipate the ischemic retina as the inciting cause of angiogenic factors. Recently, vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) has been used as a treatment for neovascular glaucoma (Kahook et al. 2006), and these agents have since supplanted all other treatments for neovascular glaucoma and rubeosis iridis.

8.6 Optic Nerve and Retina

The management of radiation retinopathy is similar to that for diabetic retinopathy. Retinal hemorrhages and cotton wool spots are a clear indication of retinal damage, and while they typically resolve without treatment, an ophthalmologic referral for their evaluation and associated pathology is appropriate. Of note, macular edema is typically diagnosed by abnormal fluorescein angiogram or optical coherence tomography, which provides a high-resolution cross-sectional image of the retina. Panretinal photocoagulation can be applied to peripheral zones of ischemia and neovascularization. The goal of photocoagulation is to ablate ischemic tissue and thus remove the instigating factor for angiogenic growth factors. The rationale of focal laser photocoagulation to macular edema is to reduce vascular leakage via a series of laser burns at leaking microaneuryms. Intravitreal triamcinolone acetonide has also been used for macular edema; however, while the visual acuity may stabilize or improve, the effects are short-lasting (Shields et al. 2005). A number of cases have reported on the beneficial effects of intravitreal placement of a VEGF inhibitor (bevacizumab) on radiation retinopathy, citing decreased vascular leakage, improved vision, and resolving recent onset macular edema (Finger 2008; Gupta and Muecke 2008). However, despite temporary improvements with these treatments, no therapy has been proven to alter the course of the disease and most centers do not treat radiation retinopathy.

The treatment for optic neuropathy is controversial and outcomes are disappointing. Heparin and warfarin have been used in an effort to promote blood flow to irradiated tissue. Hyperbaric oxygen is thought to stimulate oxygen revascularization via alterations in oxygen gradation, but has proven useful only if employed within 72 h of visual symptoms (Lessell 2004). Some believe prompt diagnosis of optic neuropathy is crucial and early detection has been suggested through the use of magnetic resonance imaging or electrophysiological testing which may demonstrate findings that predate symptoms (Lessell 2004). While the use of systemic corticosteroids and pressure-lowering medications may be effective in optic disc edema, observation is also a viable option. Ocular neuromyotonia responds to the membrane-stabilizing medication, carbamazepine.

8.7 Orbital Bones and Tissue

Unfortunately, there is no medical treatment to reverse the bone growth retardation caused by radiation. The anophthalmic socket may be improved with orbital volume augmentation with self-inflating expanders or custom-made conformers, and with orbital reconstructive surgery in advanced cases. Anophthalmic sockets and their ocular prosthesis require frequent cleaning with mild soaps, and regular examinations for abnormal tissue or other lesions. Osteonecrosis requires aggressive antibiotic therapy and surgical debridement on occasion.

The radiation effects on bone retardation can be disfiguring and devastating for some patients, and access to counseling should be available.

9 Future Research

Ocular toxicity of cancer treatment by radiation, chemotherapy, bone marrow transplant, or biologicals is a growing field. As new therapies are being introduced and as patients are offered longer survivals times with more promising treatments, the ocular insults become increasingly important. Our collaborative efforts in understanding these toxicities, at the chemical, physiological, and clinical level will help establish safer protocols and adequate management to guide our patients through these complications.

The most promising new studies have been the use of molecular agents as, avastin, to mitigate retinal vascular alternations; the introduction of retinal stem cells are becoming available to restore radiation damaged retina.

10 Review of Literature and Landmarks

1897 Chalupecky: Noted that roentgen rays cause severe destructive changes, especially in the structures of the anterior segment of the eye.

1908 Birch-Hirschfield: Concluded that blood vessel changes due to irradiation may play some part in later phases but that corneal changes are direct effects.

1931 Desjardins: Offered a complete and exhaustive review of the experimental and clinical literature up to 1931, establishing the order of radiosensitivity of the various structures of the eye.

1933 Foster-Moore: Treatment of retinoblastoma with interstitial insertion of radiation. Moore RF: Proc Soc Med; 26:1036.

1936 Leinfelder and Kerr: Published one of the earlier reports correlating clinical and microscopic studies of non-progressive cataract, and found this opacity to be the usual result of irradiation of the rabbit lens with ordinary therapeutic doses of X-rays.

1952 Cogan, Donaldson and Reese: Published an excellent article correlating the clinical appearance of radiation cataract with histopathologic changes in humans, and evolved a thesis for their occurrence.

1955 Merriam: In an excellent article, defined the late effects of beta radiation on the eye and their relationship to the dose administrated.

1957 Merriam and Focht: Presented a classic paper on a clinical study of radiation cataracts and the relationship to dose-time factors.

1965 Perrers-Taylor, Brinkley and Reynolds: Described choroidoretinal damage of varying types as a complication of radiotherapy.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

1995 Rubin: Presented the LENT-SOMA toxicity scales for radiation effects to evaluate the grade of severity.

2003 Trotti and Rubin: Modified and developed the Common Toxicity Criteria CTCAE V3.0 which applied similar scales to grade adverse effects of all major modalities-surgery and chemotherapy in addition to irradiation.

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Radiation-Induced Ototoxicity

Niranjan Bhandare, Avraham Eisbruch, Patrick J. Antonelli, and William M. Mendenhall

Contents

Abstract

- High-dose radiation therapy for the treatment of head-and-neck tumors, including those of the central nervous system or acoustic schwannomas, can damage components of the auditory system.
- Radiation-induced morbidities to all parts of the auditory system, including external, middle, and inner ear, can occur (e.g. external otitis, cochlear-associated hearing loss), and their incidence/severity is radiation dose-related (both total dose and fraction size).
- Timing can be variable and be acute, chronic, and delayed.
- The degree of morbidity varies from mild to severe; some are easily manageable while others are irreversible and require rehabilitation.
- Chemotherapy can independently cause damage to the cochlea, and be additive to radiation-induced injury; evidence for synergism is lacking.
- Controversy exists as to whether traditionally fractionated radiation therapy is safer than hypofractionated radiation therapy when used to treat vestibular schwannomas.

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Abbreviations

ABI	Auditory brainstem implant
ABR	Auditory brain response
BAEP	Brainstem auditory evoked potential
BAER	Brainstem auditory evoked response
BCT	Bone conduction threshold
CHL	Conductive hearing loss
COM	Chronic otitis media
COME	Chronic otitis media with effusion
CSOM	Chronic suppurative otitis media
dB	Decibel
dB SPL	dB Sound pressure level
EAM	External acoustic meatus
ENG	Electronystagmography
FSRT	Fractionated stereotactic radiotherapy
GRHG	Gardner-Robertson hearing grade
HBO	Hyperbaric oxygen
HL	Hearing loss
IMRT	Intensity modulated radiation therapy
MHL	Mixed hearing loss
NF2	Neurofibromatosis type 2
NTCP	Normal tissue complication probability
OME	Otitis media with effusion
PTA	Pure tone audiometry
RT	Radiation therapy
SD	Speech discrimination
SDS	Speech discrimination scores
SNHL	Sensory neural hearing loss
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiation therapy
TEOAE	Transient-evoked otoacoustic emissions
VEMP	Vestibular evoked myogenic potential
VS	Vestibular schwannoma
VSG	Videonystagmography
WDS	Word discrimination scores

1 Introduction

Intracranial and extracranial head-and-neck malignancies are often treated with radiation both definitively (e.g., nasopharyngeal and oropharyngeal carcinomas, parotid tumors) and postoperatively (e.g., parotid tumors, high-grade brain tumors, and paranasal sinus malignancies) or combined with chemotherapy (e.g., larynx and tongue base). In these scenarios, high doses of radiation may be received by the temporal bone and associated structures, resulting in radiation-induced morbidity to the external, middle, and inner ear. This can occur after fractionated radiotherapy (RT), including conventional, conformal, or intensity-modulated RT, for head-and-neck cancers, as well as stereotactic radiosurgery (SRS) and fractionated stereotactic RT (FSRT) to treat vestibular schwannomas (VS) (Fig. 1).

Otologic structures are seldom primarily affected by malignancies. Malignancies may extend into the ear from the overlying skin or anteriorly and caudally from the parotid. Nasopharyngeal tumors may extend into the parapharyngeal space with extrinsic eustachian tube obstruction or tubal invasion. The resulting functional impairment to the eustachian tube commonly leads to the development of otitis media with effusion (OME) (Sato et al. 1988). RT-induced complications in head-and-neck cancers and VS commonly involve a range of otologic dysfunction.

RT-associated ear morbidity may be both acute and delayed and vary in degree from mild to severe. In the external ear, these morbidities range from acute otitis externa to external auditory canal stenosis (van Hasselt and Gibb 1999). Eustachian tube dysfunction, OME, and conductive hearing loss (CHL) are the most common middle ear complications (van Hasselt and Gibb 1999; Elwany 1985). Thickening of the tympanic membrane, tympanosclerosis, and perforation has also been reported (Elwany 1985). Higher doses of radiation may cause middle ear fibrosis or ossicular atrophy (Gyorkey and Pollock 1960). Morbidities associated with the inner ear include tinnitus, vertigo or imbalance, and sensorineural hearing loss (SNHL). Hearing loss and neurological deficits are the most significant of the RT-induced morbidities (Borsanyi and Blanchard 1962). Biocontinuum of adverse early and late effects is shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The ear's sensory system is primarily comprised of the auditory and vestibular systems. Anatomically and functionally, the ear is divided into three distinct regions: the external, middle, and inner ear. All three regions are involved in hearing function. Only the inner ear functions in the vestibular system (Fig. 2).

2.1.1 External (Outer) Ear

The outer ear includes the visible part commonly known as the auricle or pinna and a slightly curved short external auditory canal that extends inward from the floor of the deepest depression of the auricle, called the concha, and ends at the tympanic membrane. The auricle consists of a thin plate of cartilage and overlying skin that forms an irregular, shallow funnel that is continuous medially with the external auditory meatus. The external auditory meatus is an S-shaped canal that extends about 1.25 inches. The outer third wall of the external auditory canal is composed

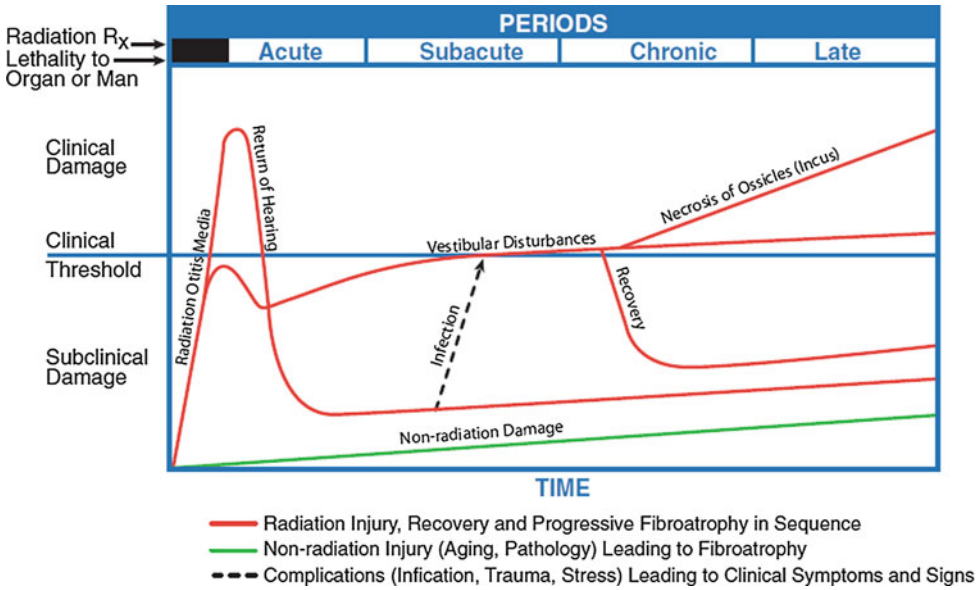

Fig. 1 Biocontinuum of adverse early and late effects of the ear (with permission from Rubin and Casarett 1968)

of cartilage, while the inner two-thirds are formed mostly by the tympanic portion of the temporal bone. The isthmus is the narrowest point of the external auditory canal and is situated just medial to the bony-cartilaginous junction. The inferior wall of the external auditory meatus is about 5 mm longer than the superior wall, conferring obliquity to the tympanic membrane. The entire length of the passage is lined with skin, which also covers the outer surface of the tympanic membrane. The outer cartilaginous portion is covered by thicker skin with fine hairs directed outward and lined with secretory glands that produce cerumen. The ear canal is bound superiorly by the middle cranial fossa, anteriorly by the temporomandibular joint and parotid, medially by the tympanic membrane, posteriorly by the mastoid (a confluence of the squamous and petrous portions of the temporal bone), and inferiorly by the skull base and soft tissues of the neck. The tympanic membrane is a thin, semitransparent oval, and obliquely placed membrane that separates the external and middle ear. The long process of the malleus is attached to the tympanic membrane, resulting in concavity toward the external auditory meatus (Fig. 2).

2.1.2 Middle Ear

The middle ear is an air-filled cavity in the petrous portion of the temporal bone located directly internal to the tympanic membrane. It is connected anteriorly to the nasopharynx via the eustachian tube and posteriorly with mastoid air cells via the mastoid antrum. The labyrinth of the inner ear forms much of the internal surface of the middle ear, with the basal turn of the cochlea representing the bulk of the surface directly medial to the tympanic membrane (a.k.a., the mesotympanum). The carotid artery passes through the medial face of the junction of the middle ear and eustachian tube (a.k.a., the protympanum). A complex air-cell system surrounds the labyrinth, connecting the middle ear to the petrous apex. The middle ear is lined by respiratory mucosa and contains three bones (malleus, incus, and stapes) and two muscles (tensor tympani and stapedius). The facial nerve passes from the internal auditory canal, over the cochlea, around the stapes, and caudal to the lateral semicircular canal en route to the stylomastoid foramen at the skull base. In the process, it emanates branches, most importantly, the greater superficial petrosal and chorda tympani nerves. Primary sensory innervations to the middle ear travel by way of Jacobsen's nerve, or the tympanic plexus, a branch of the glossopharyngeal nerve, as it exits the jugular foramen just caudal to the cochlea (a.k.a., the hypotympanum). A branch of the vagus nerve (Arnold's) similarly passes across the middle ear to contribute sensory fibers to the external auditory canal and pinna.

2.1.3 Inner Ear

The inner ear is located in the petrous portion of the temporal bone. This is grossly divided into the cochlea, the vestibule, and the semicircular canals. Within the vestibule are the otolithic organs, the utricle, and the saccule. The inner ear consists of a bony capsule that is filled with perilymph. Within the bony labyrinth is the membranous labyrinth that is filled with endolymph. The membranous labyrinths contain the hair cells that are responsible for the detection of sound, movement, and gravity. A detailed description of the microanatomy of the inner ear is beyond the scope of this text. The internal auditory canal passes from the petrous apex to the labyrinth, just medial to the vestibule. This contains the cochlear, facial, superior vestibular, and inferior vestibular nerves. The petrous apex may contain air cells contiguous with the middle ear or bone marrow.

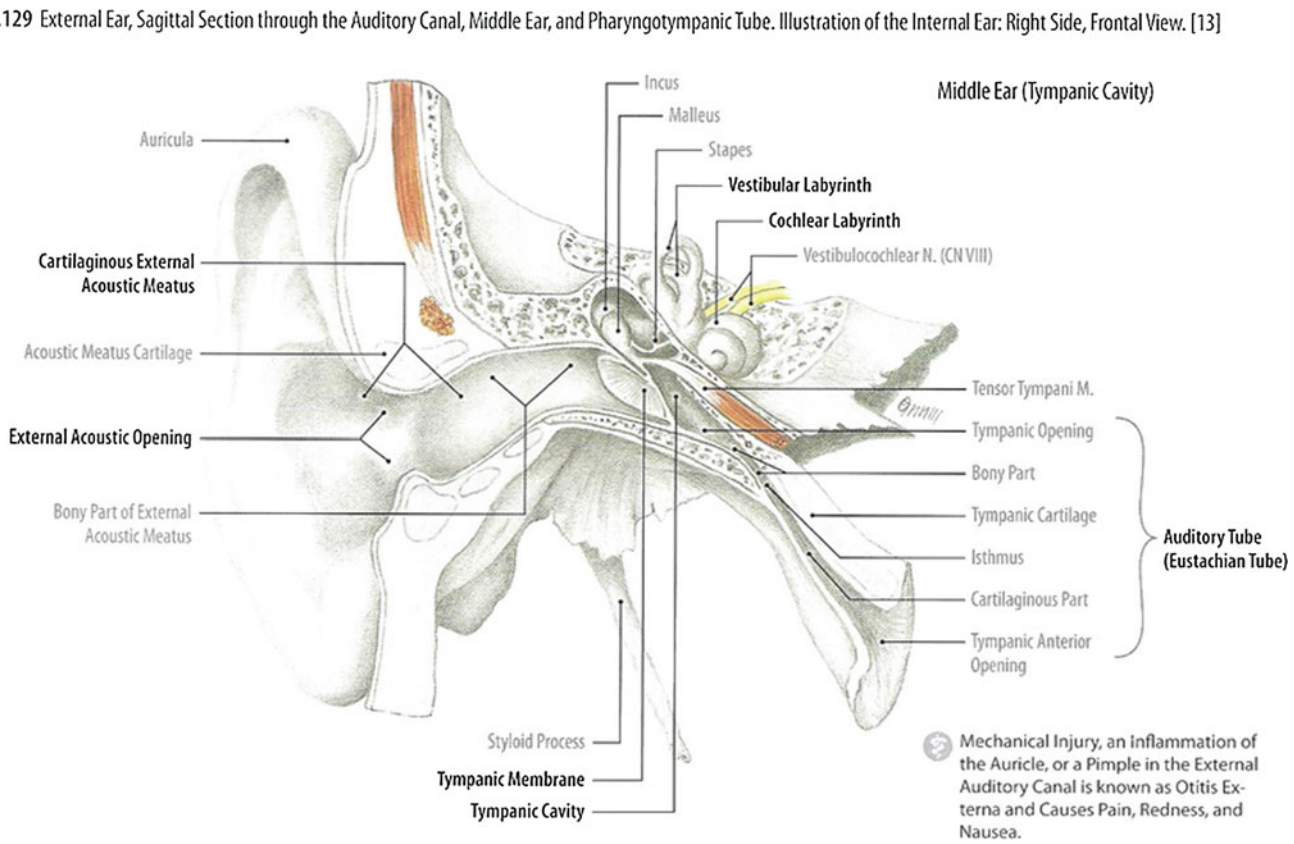

Fig. 2 External ear, sagittal section through the auditory canal, middle ear, and pharyngotympanic tube. Illustration of the internal ear: *Right* Side, Frontal View (with permissions from Tillman 2007)

2.2 Histology

The cochlea is the portion of the boney labyrinth that contains the organ. It is a spiral boney canal about 35 mm in length, which spirals for two 3-quarter turns around a conical pillar of spongy bone, the modiolus, and forming a conical spiral shape contour (Fig. 3a). The cochlear canal is an enlargement of one cross-section of the cochlea. It consists of three parts, scala vestibuli, and scala tympani, are lined by a simple squamous epithelium, and supported by the connective tissue, blending with the periosteum. These are perilymphatic spaces filled with perilymph. The scalae are in communication with the helicotrema at the apex of the cochlea. The perilymph of the scala vestibule is continuous with that in the perilymphatic space of the vestibule, and thus reaches the inner ear of the oval window, which is occluded by the base plate of the stapes. The organ of the Corti, the auditory sensory organ, is supported on a basilar membrane, while the tectorial membrane is formed on the surface of the spiral limbus. Bundles of afferent nerve fibers arise from the base of the organ of Corti, and converge toward the spiral ganglion, which is located in the bone of modiolus (Fig. 3a, b).

The organ of Corti is an epithelial auditory receptor composed of supporting and hair cells, resting on the basilar membrane of the cochlear duct. Two rows of pillar cells, the inner and outer pillar cells, form a triangular canal, the internal tunnel, which is an important landmark of the organ of Corti. At the inner side of the organ of Corti, neighboring inner hair cells and inner phalangeal cells surround the internal spiral tunnel. The basilar membrane, supporting the organ of Corti, contains radial range auditory strings. Vibrations of the auditory strings are transmitted to the hair cells by displacement of the tectorial membrane over the hair cells, and then converted into adequate bioelectrical impulses, which result in auditory sensations (Fig. 3b).

3 Physiology

Sound waves are collected and transmitted from the external ear to the middle ear, where they are converted into mechanical vibrations. The mechanical vibrations are then converted at the oval window into fluid vibrations within the internal ear. Fluid vibrations cause displacement of the basilar membrane on which rest the auditory sensory hair cells. Such displacement leads to stimulation of the hair cells and a discharge of neural impulses from them. The cochlear duct is shown here as if straightened (Fig. 4).

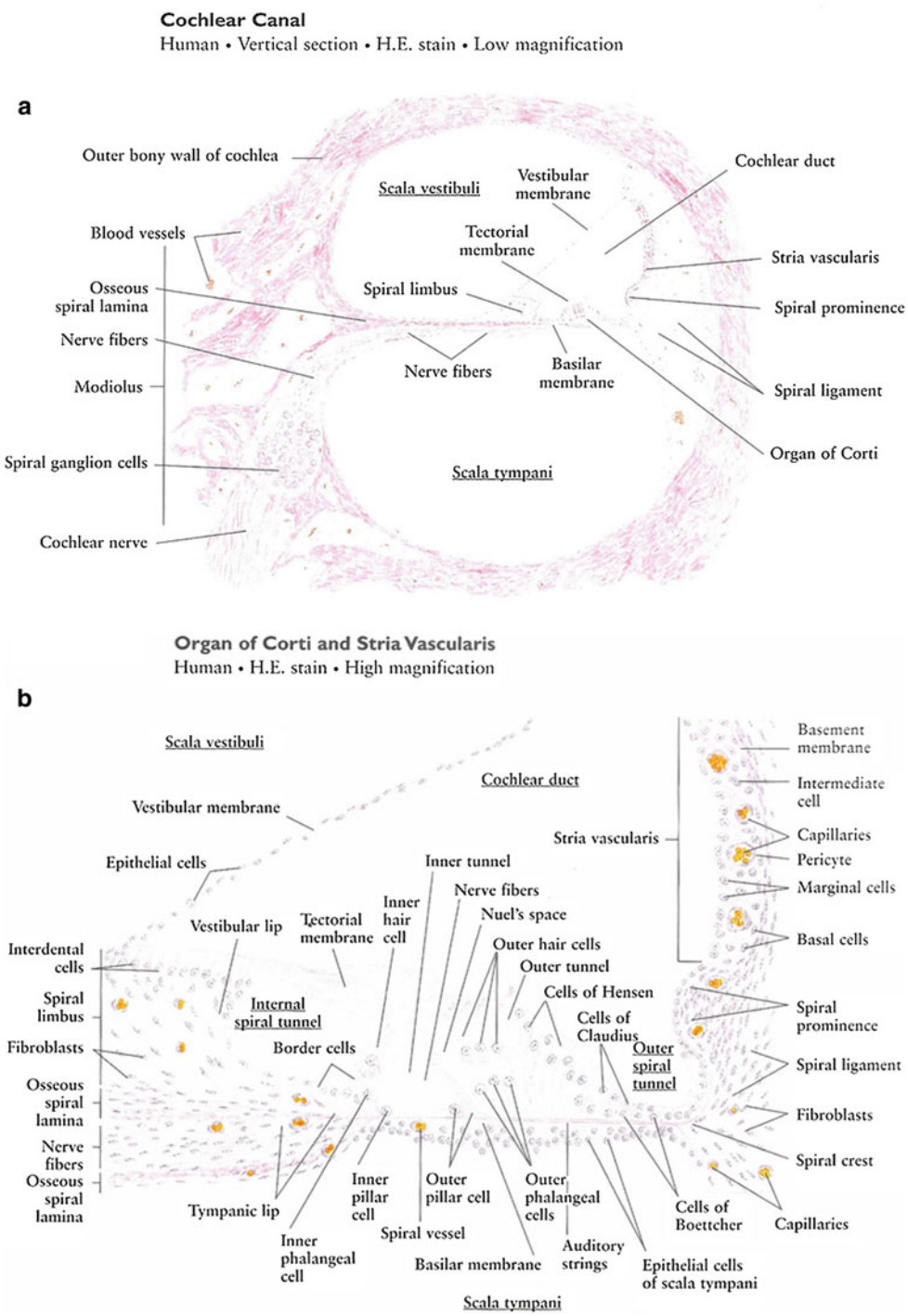

Fig. 3 **a** Cochlear canal: vertical section low magnification. **b** Organ of corti and stria Vascularis: high magnification (with permissions from Zhang 1999)

4 Pathophysiology

4.1 External Ear

Many inherent defense mechanisms are associated with the external ear, including hair follicles that help prevent gross contamination. The acidic ear canal environment inhibits bacterial and fungal growth. Cerumen is relatively hydrophobic and contains antimicrobial products. The first step in the pathogenesis of otitis externa is the breakdown of the skin-cerumen barrier. Radiation leads to progressive obliteration of vascular channels, inflammation and scaling of ear canal skin, and loss of adnexal structures, including the cerumen-producing glands. Resulting pruritus leads patients to clean their ears (e.g., with cotton swabs), which may

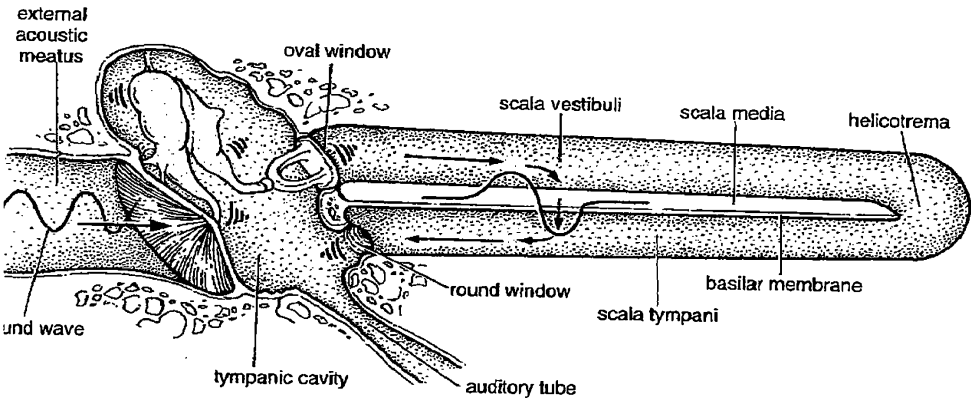

Fig. 4 Physiology Schematic diagram illustrating the dynamics of the three divisions of the ear (with permissions from Karmody 1983)

further breach the natural barriers. The dark, warm, and moist ear canal offers favorable conditions for microbial growth (Fig. 5 and Tables 1, 2, 3).

Radiation-induced acute external ear reactions involve skin reactions including erythema and dry or moist desquamation (Table 1). Occasionally, it leads to otorrhea and pain, occasionally combined with skin ulceration (Carls et al. 2002). Microbial overgrowth may lead to acute otitis externa. Late reactions include atrophy, deep ulceration, thickening of the epithelium of the canal, and subepithelial fibrosis. Chronic otitis externa is often followed by pain with otorrhea and otalgia. Radiation may induce osteitis, vasculitis of surrounding soft tissue of the external auditory canal, deep ulceration of the external auditory canal, cartilage necrosis of the external canal, and osteonecrosis. Underlying osteonecrosis of the temporal bone may manifest as otitis externa refractory to treatment, including necrotizing otitis externa (a.k.a., skull base osteomyelitis). Occasionally, RT injury may lead to canal stenosis (Carls et al. 2002). Chronic otitis externa and canal stenosis have been linked in patients receiving high doses of radiation to the external auditory canal (Carls et al. 2002; Bhandare et al. 2007).

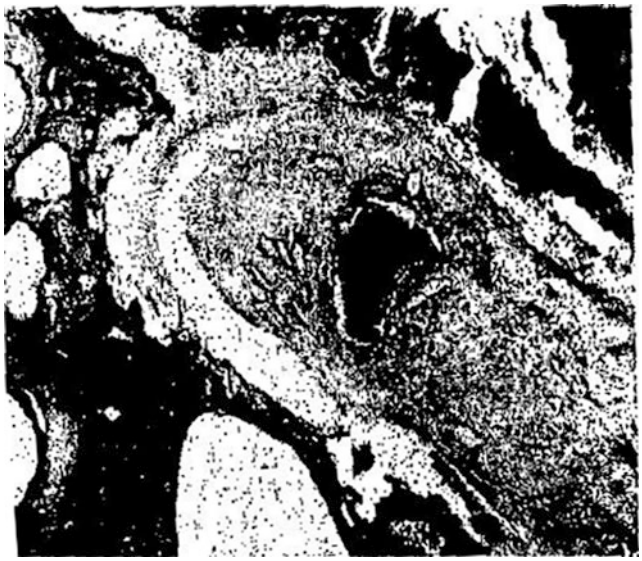

Fig. 5 Fibrosis of the middle ear with old hemorrhage at the center, hollow spaces where cholesterol crystals have dissolved and aseptic osteitis in bone walls with lacunar absorption (with permission from Rubin and Casarett 1968)

4.2 Middle Ear

Middle ear mucosa consists of ciliated and nonciliated cells (squamous, cuboidal, and columnar), secretory cells, and support cells. The cilia usually covers the anteroinferior one-third to two-thirds of the middle ear mucosa and are important components of the mucociliary transport system of the middle ear. The eustachian tube lumen contains ciliated epithelium and secretory cells over the hyaline cartilage framework (Table 2).

4.2.1 Animal Studies

The early effects of radiation on the ear are typical of any inflammatory reaction. This includes vascular dilation with pyknotic changes in the endothelium and necrosis of damaged cells (Klemm 1967), swelling of endothelial cells, extravasation of blood cells, stasis, perivascular edema, sticking of platelets, and leukocyte migration leading to subendothelial proliferation (Berg and Lindergren 1961). Fibrosis and other related changes in the middle ear mucosa in rabbits exposed to 3,000–10,500 Roentgen have been reported (Berg and Lindergren 1961). In mild cases, the mucosa was thickened and fibrotic. The epithelium subsequently showed atrophy with some inflammatory cells and hemorrhagic exudates in a few cases. More severe cases exhibited destruction of the epithelium, involvement of the ossicles, evidence of lacunar absorption in the bony walls, and often purulent exudates with both plasma cells and lymphocytes. An example of middle ear fibrosis is shown in Fig. 5.

Table 1 Post-radiation noninfectious otologic histopathologic findings in human and animal studies: External ear

Edema, hemorrhage, epithelial hyperemia, hyperplasia, and atrophy
Atrophy of ceruminous glands and hair follicles
Vasculitis of soft tissue surrounding the external auditory canal
Subepithelial fibrosis
Leucocytic infiltration
Chondromalacia
Canal cartilage necrosis
Canal stenosis
Canal osteonecrosis

Table 2 Post-radiation noninfectious otologic histopathologic findings in human and animal studies: Middle ear

Mucosal hyperemia, stasis, hemorrhages, edema, and fibrosis
Diminution of epithelial cytoplasmic mass, ciliary loss, widening intercellular spaces, changes in the number of goblet cells
Tympanic membrane sclerosis and perforation
Osteonecrosis of temporal bone
Necrosis of ossicular chain
Petrous bone necrosis
Eustachian tube fibrosis, stenosis/occlusion
Atrophy of pharyngeal orifice of eustachian tube
Serous otitis media
Secondary cholesteatoma

4.2.2 Human Studies

The radiation-induced changes (i.e., ciliary, vascular, and stromal) in the middle ear mucosa of patients treated with RT for head-and-neck tumors have been observed under transmission and scanning electron microscopes (Elwany 1985) (Table 2). The epithelial changes have included diminution of the cytoplasmic mass, variable degrees of ciliary loss, widening of the intercellular spaces, and reduction in the number of goblet cells in some cases while increases in others. Middle ear mucosa usually only has a few goblet cells (Tos 1979). The density of goblet cells typically increases significantly with chronic tubal occlusion, OME, and active chronic suppurative otitis media. Few tubular seromucous glands may be present in the anterior part of the normal mesotympanic mucosa (Gristwood and Beaumont 1979). The new-gland formation may occur through the invagination of surface epithelium or the division of basal cells. The number and activity of the newly formed glands depends on the nature of the pathologic process in the middle ear, as the glands are highly active in secretory otitis. Normal cilia should beat in the same direction and in a synchronized fashion (metachronal beating). The abnormal ciliary motility is indicative of early ciliary damage. Ciliary loss represents the end stage (Dudley et al. 1982). The reduced cytoplasmic mass could be directly due to cell damage from RT, or it could be secondary to the obliterative vascular changes. The changes in lamina propria include decreased activity of the seromucous glands, depleted secretory granules in acinar cells, and moderate swelling of mitochondria.

Table 3 Post-radiation noninfectious otologic histopathologic findings in human and animal studies: Inner ear

Cochlea and spiral ganglion
Hemorrhage
Leucocytic infiltration
Organ of Corti destruction
Damage and loss of sensory hair cells
Stria vascularis atrophy, disruption/disintegration
Vascular fibrosis
Papilla disruption/disintegration
Edema of Dieter cells and Henson cells
Basilar membrane disruption
Elevation of tectorial membrane
Spiral membrane disruption
Destruction of cochlear duct
Spiral ganglion atrophy and nerve fibre loss
Degeneration of cochlear nerve
Vestibular labyrinth and ganglion
Hemorrhage
Leucocytic infiltration
Degeneration and atrophy of sensory epithelium of crista ampullaris
Endolymph/perilymph system
Hemorrhage into perilymph
Distension of pelymphatic spaces
Distension of endolymphatic spaces (Endolymphatic hydrops)
Facial Nerve
Facial nerve edema, hyperemia, and demyelination

Modified from Linskey and Johnstone (2003)

Similar to radiation-induced vascular changes in the other parts of the body (Rubin and Cassarett 1968), the capillaries of the middle ear mucosa show endothelial swelling, duplicated basement membrane, and fibrosis and thickening of the vessel walls with replacement by a cord of fibrous tissue, thereby altogether occluding the lumen. The vascular changes are representative of successive stages in the obliterative disease process and are also related to the amount of radiation received by the vessel. Another important factor contributing to vessel damage is injury to surrounding soft tissue with the release of different breakdown products, such as free radicals and peroxides (Baker et al. 1978).

The post-RT connective tissue stroma shows increased production of collagenous fibrous tissue and an increase in synthetically active fibroblasts in the tunica propria. These fibroblasts are characterized by abundant, irregular cytoplasmic processes, numerous mitochondria, and a well-developed granular endoplasmic reticulum.

Morbidity associated with the tympanic membrane involves thickening, sclerosis and perforation without, or after removal or extrusion of tympanostomy tubes (Bhandare et al. 2007). Fibrovascular granulation tissue formation may lead to the growth of inflammatory polyps through a tympanic membrane perforation and persistent otorrhea (Jereczek-Fossa et al. 2003). However, thickening of the tympanic membrane may persist several months after RT and permanent changes are uncommon (van Hasselt and Gibb 1999). Tympanic membrane perforations have been reported to develop long after RT (Carls et al. 2002).

Chronic otitis media (COM) and OME are frequently encountered in patients with head-and-neck cancers (particularly nasopharyngeal cancer) after RT. The development of COM and OME in post-RT patients is attributed to both impaired tubal function and middle ear inflammation (Sato et al. 1988; Young and Hsieh 1992; Young et al. 1995; Ho et al. 2002). Radiation-induced OME occurs in patients with no pre-RT tubal pathology and may have no bearing to the patency of the eustachian tube (Anteunis et al. 1994). The likelihood of an ear with pre-RT OME to have long-term post-RT OME was observed to be much higher compared to an ear without pre-RT OME (Low and Fong 1998).

The effects of radiation on middle ear mucosa in the acute phase include mucositis, sloughing, and edema (Borsanyi and Blanchard 1962), Moss (1959) coined the term "radiation otitis media" for this process. In the chronic phase, it includes epithelial atrophy and fibrosis (Berg and Lindergren 1961).

Acute otitis media most commonly occurs during or within a few weeks after completing RT. Swelling, puffiness, and transient edema of middle ear mucosa caused by the acute inflammatory reaction lead to functional impairment of the tube. Mucosal sloughing exposes binding sites for pathogens and impairs the normal mucociliary clearance mechanism.

OME may develop as a result of dilated capillaries and fluid transduction resulting in edema from further reduction in middle ear pressure. If the eustachian tube is impaired, the subsequent resorption of middle ear gas may create a negative pressure, which promotes further transudation (i.e., "hydrops ex vacuuo"). Inflammatory components of the middle ear effusion may then perpetuate the inflammation, creating a "vicious cycle". Subsequent to high doses of radiation to the middle ear, two types of chronic otitis media may be observed. The presence of post-RT middle ear effusion without signs of acute inflammation indicates chronic OME (COME), whereas persistence of the suppurative process through a perforation or a tympanostomy tube indicates chronic suppurative otitis media (CSOM).

4.2.3 Eustachian Tube

The eustachian tube connects the middle ear cavity and the nasopharynx. The eustachian tube framework is cartilage. It is lined with respiratory mucosa. Between the cartilage and mucosa is Ostmann's fat pad, which generally occludes the tube lumen at rest (Aoki et al. 1994). The tensor veli palatini and levator veli palatini muscles arise from the tubal cleft before inserting on the palate. In its resting state, the eustachian tube is closed. Movements of the palate lead to a transient tubal opening.

Differences between pre- and post-RT eustachian tube dysfunction have been reported and are usually observed in nasopharyngeal carcinoma. Pre-RT eustachian tube dysfunction in nasopharyngeal carcinoma patients is caused by tumor invasion of the tensor veli palatini muscle, extrinsic compression, or inflammation (Young and Hsieh 1992; Young and Sheen 1998. Post-RT eustachian tube dysfunction in nasopharyngeal carcinoma patients is caused by both tumor obstruction and functional impairment of the tube (Young et al. 1994; Bhide et al. 2007. The tubal patency and clearance function are affected by radiation, but dynamic function is preserved after radiation (Young and Hsieh 1992).

Post-RT COME has been attributed to obstruction of the eustachian tube opening and fibrosis of the fascial space around the levator veli and tensor palatini muscle (Lederman 1962). Edema and fibrosis resulting from RT can interfere with muscle function and lead to eustachian tube dysfunction (Dias 1966). Abnormalities of the mucosa of middle ear affect the production of mucous and its transportation down the eustachian tube (Fischer et al. 1978). RT has been shown to affect the mucosal cells in the middle ear (Gyorkey and Pollock 1960). The altered nature of mucous production both in quality and quantity after RT can contribute to serous otitis media in these patients.

The blockage of the pharyngeal orifice of the eustachian tube due to radiation-induced inflammatory reactions and the resorption of gas from the middle ear results in negative pressure, retraction of the tympanic membrane, and decreased mobility of the ossicular chain. The end result is pressure, pain, and hearing loss.

The supporting structures surrounding the eustachian tube were seen to be replaced by fibrous tissue in one study on the histopathology of the human eustachian tube (Takasaki et al. 2000). In some cases, the recovery of its functional impairment during the 5-year period post-RT has been observed and attributed to a subsiding inflammatory reaction (Young et al. 1994). Further delayed fibrosis and atrophy of the pharyngeal orifice of the eustachian tube, its

mucosal lining, and Ostmann's fat pad may contribute to the development of a pathologically patent, "patulous," tube 5–10 years after RT (Takasaki et al. 2000). This may lead to a constant sensation of aural fullness and the patient hearing his or her own breathing or voice (known as autophony).

4.2.4 Osteonecrosis of the Temporal Bone and Ossicular Chain

Osteoradionecrosis of the temporal bone is a well recognized, pathological entity that manifests with symptoms of refractory otitis externa, otalgia, otorrhea, and hearing loss (Leach 1965; Schuknecht and Karmody 1966; Thornley et al. 1979; Wurster et al. 1982). The basic reactions in the temporal bone to radiation involve vasculitis leading to obliterative endarteritis and aseptic necrosis of bone with compensatory reparative fibrosis enhancing the susceptibility of bone to injury, infection, and fracture. The effects of radiation have been divided into effects on soft-tissue damage and effects on bone (Leach 1965; Schuknecht and Karmody 1966; Fajardo and Berthrong 1988). The soft-tissue damage includes dermatitis of the external auditory canal, middle ear mucosal inflammation, otitis media, and aseptic labyrinthitis. The histologic observations on bone include destruction of osteoblasts from trabecular margins, loss of osteocytes (empty lacunae), progressive replacement of hematopoietic elements by loose connective tissue, thickening of vascular walls, narrowing of lumen with a concomitant decrease in the number of capillaries and sinusoids, and the absence of osteocytes followed by a lack of new osteoid deposits. The ischemic changes make the bone susceptible to infection.

Osteonecrosis of the temporal bone has been separated into two distinct patterns, localized and diffuse (Ramsden et al. 1975). The most common finding in the localized pattern was an area of exposed dead bone in the external acoustic meatus (EAM), usually in the floor of the tympanic ring, and occasionally in the anterior wall. These cases presented with mild otalgia and severe otorrhea. Although the bony dehiscence may heal when the bone sequestrum forms and gradually separates, the process may take years. In diffuse osteonecrosis of the temporal bone, there can be extensive ischemic necrosis of a large part or all of the temporal bone (van Hasselt and Gibb 1999). With diffuse osteoradionecrosis of the temporal bone, multiple bony sequestra form, and the patient may experience more serious problems such as cerebrospinal fluid leak, labyrinthine fistula, facial palsy, chronic mastoiditis, meningitis, sinus thrombosis, brain abscess, and death (van Hasselt and Gibb 1999; Leonetti et al. 1997; Sikand and Longridge 1991; Ito et al. 2000; Horan et al. 2007). Radiographs of the temporal bone may reveal a widespread moth-eaten radiolucency. The clinical manifestations in these cases often include pain, refractory otorrhea, CHL, SNHL, or mixed hearing loss. Associated diffuse white matter injury may lead to progressive cognitive neurological impairment with simultaneous vestibular or gait disorders (Jereczek-Fossa et al. 2003). A study on the incidence of radiation otomastoiditis using T2-weighted MRI reported significant increases above RT doses of 50 Gy, but decreases over time (Nishimura et al. 1997).

Delayed persistent CHL without OME is considered to be secondary to osteoradionecrosis of the ossicular chain with or without damage to the auditory end organ. Destruction of the incudostapedial joint after high-dose RT has been described in a case report (Thornley et al. 1979). Cases of osteoradionecrosis of the temporal bone along with CHL have been presented with speculation of radionecrosis of the ossicular chain (Kristensen and Jorgensen 1967). Surgical exploration in a case of CHL consistent with interruption of the ossicular chain or stapes fixation after high-dose RT revealed that the long process of the incus was replaced by a fibrous band (Kristensen and Jorgensen 1967). Another report on five patients with post-RT temporal-bone necrosis with mixed hearing loss (MHL) years after RT without symptoms of OME speculated the cause to be ossicular chain necrosis (Bhandare et al. 2007). Extensive osteonecrosis of the ossicular chain after resection of extensive osteonecrosis of the temporal bone has been documented (Gyorkey and Pollock 1960).

4.3 Inner Ear

Radiation-induced inner ear morbidity may include damage to the labyrinth (cochlea, otolithic organs, and semicircular canals), cochlear or vestibular nerves, and central auditory and vestibular pathways. Most of the information on the pathogenesis of radiation-induced inner ear damage and dysfunction comes from animal experiments (Novotny 1951; Berg and Lindergren 1961; Kelemen 1963; Winther 1969; Bohne et al. 1985) with a few human autopsy studies (Gyorkey and Pollock 1960; Hoistad et al. 1998; Leach 1965). Despite the animal studies and other patient data, a relationship among pathogenesis, pathophysiology of the radiation lesion, and subsequent clinical manifestations has not been established (Table 3).

4.3.1 Vestibular Damage

4.3.1.1 Animal Studies

There is limited experimental data on radiation damage to the vestibular labyrinth. Gross clinical vestibular findings without detailed pathologic studies of the vestibular structure in guinea pigs have been reported 2 months after single-dose X-ray RT (Gamble et al. 1968). These observations included constant turning in one direction and a tendency to

fall to the affected side. In a study of guinea pigs radiated to single-fraction high doses of 7,000 Roentgen, impaired balance function with positional nystagmus was correlated with radiation-induced degenerative changes in vestibular sensory epithelia on electron-microscopic examination. The vestibular apparatus was felt to be more resistant than the cochlea to the effects of radiation (Winther 1969). Another study (Nadol 1988) reported disturbed equilibrium in animals after a single-fraction RT to doses greater than 50 Gy.

4.3.1.2 Human Studies

In early human studies, a number of patients treated to doses between 30 and 120 Gy were reported by Leach (1965) to exhibit episodic, occasional, intermittent vertigo and moderate to severe balance problems, and no caloric response. An autopsy of a patient treated to high-dose RT demonstrated the absence of the organ of Corti, macula of utricle, and cristae of semicircular canals, as well as atrophic spiral ganglions and nerves (Leach 1965).

Imbalance and vertigo are the predominant symptoms of vestibular dysfunction. Gradual development of vestibular dysfunction will be offset by central nervous system compensation and varying degrees of imbalance. Acute onset of vestibular dysfunction will be manifest by vertigo. If mild, this may be noted only with movement. If more severe, it may be spontaneous, violent, and accompanied by nausea and vomiting. Acute onset of vertigo reported as lasting more than a day and accompanied by SNHL is often classified as labyrinthitis. In diagnostic evaluation of post-RT vertigo, the differential diagnosis of the peripheral etiology due to vestibular dysfunction from the central etiology caused by dysfunction of central vestibular structures in the brainstem or cerebellum is essential. Though a number of studies have reported vestibular dysfunction (Bhandare et al. 2007; Young et al. 2004; Zabel et al. 2004), data on the mechanism and pathophysiology of radiation-induced vestibular damage and subsequent clinical manifestations remain sparse.

4.3.2 Cochlear Damage

Table 3 lists the post-radiation noninfectious otologic histopathologic findings in human and animal studies.

4.3.2.1 Animal Studies

Subsequent to experimental fractionated RT (2 Gy per fraction, 5 days per week, 40–90 Gy) to chinchillas, Bohne et al. (1985) reported damage to the organ of Corti in 31 % of animals treated with 30–40 Gy and 62 % of animals treated with 60–90 Gy. The observations included loss of myelinated nerve fibers in the osseous spiral lamina, loss of peripheral processes of the spiral ganglion cells indicating degeneration of the ganglion cell bodies, scattered cell loss throughout the organ of Corti, significant losses of the inner and outer hair cells, and supporting cell losses in the inner and outer pillars.

Winther (1969) subjected guinea pigs to single-fraction RT ranging from 1,000 to 7,000 Roentgens. During their short follow-up, they did not notice any changes in hair cells with doses less than or equal to 2,000 Roentgens. The earliest post-RT changes with lower doses were observed in the stria vascularis, and increases in dose caused apoptosis of hair cells and distention of Reissner's membrane, consistent with endolymphatic hydrops, which may impair function of remaining hair cells (Gamble et al. 1968). The stria vascularis has been suggested to be more sensitive to radiation than the organ of Corti or spiral ganglion in both animal and human temporal bone studies (Gamble et al. 1968; Schuknecht and Karmody 1966). The vestibular apparatus is suggested to be more resistant to the effects of radiation than the cochlea (Gamble et al. 1968). A study in guinea pigs suggested that hair cell damage and compound action potential changes (i.e., hearing loss) occur secondary to stria vascularis degeneration (Ocho et al. 2000).

Auditory neurons in humans and animals differ (Nadol 1988; Felix 2002). The general pattern of neural degeneration is evident in the human cochlea, but at a significantly slower rate than in animals (Felix et al. 1990; Nadol 1990; Felder et al. 1997). The effects of radiation observed on stria vascularis and the organ of Corti in animal experiments have been reported to be similar to those found in the temporal bone of a patient who received radiation to his or her ear (Gamble et al. 1968; Schuknecht and Karmody 1966).

4.3.2.2 Human Studies

Histologic changes in connective tissue as well as vascular insufficiency have been suggested to result in cochlear anoxia and manifest as SNHL (Borsanyi and Blanchard 1962). Autopsy studies of nine temporal bones in post-RT patients with head-and-neck tumors showed a loss of inner and outer hair cells and spiral ganglion cells in the basal turn, atrophy of the stria vascularis, and changes in the vessels of the facial nerves (Hoistad et al. 1998). The loss of hair cells in mammalian cochlea leads to permanent SNHL and initiates a number of pathological changes to the primary auditory neurons that normally project to the organ of Corti (Schuknecht and Karmody 1966). The pathological changes start with a rapid and extensive loss of the unmyelinated peripheral processes within the organ of Corti that normally innervate the inner hair cells (Terayama et al. 1977), followed by a more gradual degeneration of the myelinated portion of the peripheral processes and ultimately cell death (Spoendlin 1984; Leake and Hradek 1988; Shepherd and Javel 1999; Hardie and Shepherd 1999). One histological study supports the theory that the greatest damage to the labyrinth is the result of injury to the vessels

of the stria vascularis and perhaps the cells of stria, which appear to be more easily affected than other nonvascular structures in the cochlea (Leach 1965).

Acute hearing loss after RT has been suggested to be partly due to transient alterations in the endolymph and perilymph physiology caused by disturbances in the stria vascularis (Linskey and Johnstone 2003). The mechanisms responsible for transient SNHL remain unknown. Radiation damage to the organ of Corti with loss of inner and outer hair cells and pillar cells (Winther 1969; Bohne et al. 1985; Hoistad et al. 1998; Schuknecht and Karmody 1966, degeneration of endothelial cells in vessels with a reduction in the number of capillaries (Borsanyi and Blanchard 1962; Berg and Lindergren 1961; Schuknecht and Karmody 1966; Sikand and Longridge 1991; Nadol 1990), and atrophy and degeneration of the basilar membrane, spiral ligament, stria vascularis (Hoistad et al. 1998; Schuknecht and Karmody 1966), spiral ganglion cells, and cochlear nerve (Bohne et al. 1985; Hoistad et al. 1998; Schuknecht and Karmody 1966) have been reported in histopathological studies in both animals and humans (Winther 1969; Bohne et al. 1985; Gamble et al. 1968; Leach 1965; Hoistad et al. 1998). Linskey and Johnston (2003) have reported that cochlear hair cells and the stria vascularis are suggested to be the two major sites of damage after high-dose RT. The basal turn of the cochlea, responsible for detecting higher frequencies, shows greater susceptibility to radiation damage. Delayed SNHL most commonly shows a chronic, progressive, and irreversible evolution (Pollock et al. 1995).

Radiation-induced vascular insult, subsequent inflammatory process resulting in progressive microvascular endothelial reactions that lead to slow degeneration and atrophy of the inner ear sensory structures, has been suggested as a process involved in delayed inner-ear damage (Honore et al. 2002). Contrary to this, Gibb and Loh (2000) presented a post-mortem histological examination of the temporal bone in a case of post-RT SNHL with a well-preserved organ of Corti and the presence of a normal number of inner hair cells, scattered losses of outer hair cells, and severe patchy atrophy of the stria vascularis after high-dose radiation. They concluded that degeneration of cochlear nerve and central auditory pathway was possible, instead of damage to the sensory end organ, as an etiology. Other causes of damage, such as free oxygen radicals and resulting apoptosis, needed to be excluded.

5 Clinical Syndromes

RT-induced morbidities show significant variation throughout the auditory system. To objectively compare studies, the criteria for diagnosis of any radiation-induced morbidity must be specified in the study. While identifying and diagnosing some post-RT morbidities and dysfunctions is based solely on clinical manifestations, others cannot be diagnosed without subjecting the patients to specific tests, and outcomes cannot be evaluated without an objective criteria. Table 4 summarizes the RTOG scoring criteria. The SOMA LENT system provides a means to categorize and grade late effects (Tables 4, 5).

Table 4 Acute radiation ear morbidity according to the RTOG scoring criteria

Score	Criteria
0	No change over baseline
1	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline
2	Moderate external otitis requiring topical medication, serous otitis media, and hypoacusis on testing only
3	Severe external otitis with discharge or moist desquamation, symptomatic hypoacusis, tinnitus, and not drug related
4	Deafness

5.1 Detection and Diagnosis

5.1.1 External Ear

Several conditions and their associated presentation include the following (some with overlap with the middle ear):

(a) *Necrosis of the pinna*. Necrosis of the pinna exhibits both temporary and persistent ulceration of soft tissue and/or chondritis.

(b) *Acute otitis externa*. Acute otitis externa is indicated by acute onset of pain, drainage, and swelling of the ear canal with extreme tenderness to traction on the pinna.

(c) *Chronic otitis externa*. Chronic otitis externa includes pruritus, otorrhea, scaling, edema, and erythema of the external auditory canal or auricle.

(d) *Canal stenosis*. Although more stringent criteria, such as 50 % constriction of bony lumen on radiographic examinations, can be used to define canal stenosis, post-RT stenosis of the external acoustic canal can be identified on clinical examination by otoscopy of the external acoustic canal and/or supported by radiography.

(e) *Osteonecrosis of the external auditory canal*. This condition is diagnosed by the exposure of the bone in the ear canal or radiographic evidence of bony sequestra (Tables 6, 7).

5.1.2 Middle Ear

Several conditions and their associated presentation include the following:

(a) *Acute otitis media*. Acute otitis media during or after RT is diagnosed by the abrupt onset of symptoms due to

Table 5 LENT SOMA Scoring System of the Ear

EAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Tinnitus	Occasional	Intermittent	Persistent	Refractory
Hearing	Minor loss, no impairment in daily activities	Frequent difficulties with faint speech	Frequent difficulties with loud speech	Complete deafness
Objective				
Skin	Dry desquamation	Otitis externa	Superficial ulceration	Deep ulceration, necrosis, and osteochondritis
Hearing	<10 decibel loss in one or more frequencies	10–15 decibel loss in one or more frequencies	>15–20 decibel loss in one or more frequencies	>20 decibel loss in one or more frequencies
Management				
Pain	Occasional non-narcotic	Regular nonnarcotic	Regular narcotic	Parenteral narcotics
Skin	Occasional lubrication/ ointments	Regular eardrops or antibiotics	Eardrums	Surgical intervention
Hearing loss			Hearing aid	
Analytic				
Pure tone audiometry	Assessment of characteristics of sensorineural perception			
Speech audiometry	Assessment of characteristics of speech perception			

Table 6 Criteria used to report hearing status after SRS or FSRT (stereotactic radiosurgery or fractionated stereotactic radiotherapy)

Score	Criteria
1	Preservation of pretreatment hearing level
2	Useful/serviceable hearing (corresponds to Gardener-Robertson Hearing Grade[GRHG] I-II), with commonly used criteria to define serviceable hearing as PTA $\leq$ 50 % and SDS $\geq$ 50 %
3	Measurable hearing; any hearing with detectable PTA
4	Preservation of the pretreatment hearing level corresponds to (a) GRHG I–IV hearing as preservation of preradiation GRHG, (b) for GRHG V patients with no speech discrimination but testable PTA as preservation of PTA scores
5	Improvement as well as loss in hearing expressed as change in GRHG

Table 7 Gardner-Robertson scale

Grade	PTA or SRT	SDS (%)
1	0–30	70–100
2	31–50	69–50
3	51–90	49–5
4	91(ML)	4–1
5	NR	NR

PTA pure tone average, *SRT* speech reception threshold, *SDS*: speech discrimination score, *NR* no response, *ML* maximum loss

middle ear inflammation (i.e., otalgia and CHL) accompanied by effusion, bulging, opacification, and erythema of the tympanic membrane. Spontaneous tympanic membrane perforation may occur.

(b) *Chronic otitis media*. Chronic otitis media after radiation is divided into two categories: chronic otitis media with effusion (COME) and chronic suppurative otitis media (CSOM). The criteria for COME include the presence of middle ear effusion without overt signs or symptoms of infection. Patients typically note aural fullness and hearing loss. CSOM is diagnosed when the suppurative process persists despite treatment and is nearly universally accompanied by otorrhea through a perforation or a tympanostomy tube.

(c) *Mastoiditis*. The diagnosis is derived from a clinical judgment based on the spread of otitis media across the mastoid with swelling, erythema, and occasionally fluctuance behind the pinna. If severe, the underlying bone may become demineralized, which is known as coalescent mastoiditis. Post-RT patients with acute mastoiditis receive intravenous antibiotics, a mastoidectomy, or both. These patients should be coded as having true mastoiditis.

(d) *Eustatchian tube*. A functional, patent eustachian tube is necessary for ideal middle ear mechanics. Unfortunately, testing of eustachian tube patency and function after RT can be difficult to perform, so it is not usually directly measured. Eustachian tube function is most commonly

assessed using tympanometry. Evaluation of eustachian tube function may be performed using four parameters: opening pressure, which tests for the passive opening function of the eustachian tube; positive and negative pressure tests, which indicate the dynamic functions of the tube; and clearance time, which indicates the clearance function of the tube. Pneumatic otoscopy, for retraction and stiffness secondary to effusion, indirectly assesses the tubal patency and function. Valsalva, Politzer, and Toynbee tests may yield gross information on tubal patency, but they are not routinely done by otologists.

5.1.3 Inner Ear

Tinnitus, the perception of a sound without acoustic stimulation, has been associated with cochlear damage, hearing loss due to pathologically increased spontaneous firing rates, or hyperactivity of neurons in the auditory pathway. Hypoxia/ischemia may play an important role in the pathogenesis of tinnitus secondary to SNHL, although the exact pathophysiologic processes involved in post-RT tinnitus is unknown (Mazurek and Haupt 2005).

The availability of a baseline evaluation is necessary for accurate diagnosis. Before beginning RT with high doses to the hearing apparatus, patients should be considered for a basic otologic evaluation including morphological evaluation by otoscopy, tympanometry, and other basic functional audiometric tests including pure-tone audiometry, speech audiometry (for speech-reception threshold and speech discrimination), and stapedial reflexes. Tympanometry objectively measures the middle ear acoustic impedance as well offers information on middle ear aeration, ossicular chain mobility, and eustachian tube function. Tympanometry may be followed by pure-tone audiometry to exclude otitis media and ossicular fixation as the cause of hearing loss (Raaijmakers and Engelen 2002). The audiologic assessment should be followed by repeated biannual evaluations for a period of at least 5 years after RT. Tuning-fork tests (e.g., Rinne and Weber) may be done with a 512 Hz tuning fork and yield relatively crude insights into the nature of the hearing loss (i.e., CHL vs. SNHL).

Pure-tone audiometry, including air and bone conduction, can subjectively assess patients' hearing thresholds and detect sensorineural, conductive, or mixed hearing loss. Transient CHL secondary to middle ear effusion is evaluated by pure-tone audiometry (air-bone-gap measurement), tympanometry, and otoscopy.

SNHL can be detected with audiometric assessment by measuring speech understanding and pure-tone thresholds with bone conduction at 0.5, 1, 2, 4, and 6 kHz. Pure-tone stimuli are presented via a bone oscillator placed on the mastoid of the ear to be tested, thus by passing the conductive mechanism. "Masking" of the contralateral ear is often necessary to avoid inadvertent detection of sound by the contralateral ear. There remains significant variation in the criteria used for coding of post-RT SNHL in the literature in terms of frequencies and the thresholds (Bhandare et al. 2007; Pan et al. 2005; Chen et al. 1999; Kwong et al. 1996) making the comparison between the studies difficult. To standardize reporting following criteria has been suggested (Bhandare et al. 2010).

- The effect should be determined through pre- and post-RT audiometry evaluations of same ear (i.e., the contralateral ear should not be used).
- To avoid transient post-RT hearing fluctuations, hearing should be tested starting 6 months post-RT and at least biannually thereafter.
- Speech discrimination (SD) and 4-frequency (0.5, 1, 2, and 3 kHz) bone-conduction pure-tone average should be used, as endorsed by the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium (Committee on Hearing and Equilibrium 1995).
- Additionally, 6 kHz bone conduction thresholds should be measured, because (1) the basal turn of the cochlea (i.e., highest frequencies) is the first to be affected, (2) 6 kHz is highest frequency bone conduction threshold measured with standard bone conducting transducers, (3) bone conduction thresholds minimize the influence of concomitant middle and external ear pathology. Above 6 kHz, measurements are performed using air-conduction thresholds alone, because bone conducting transducers generally cannot produce stimuli above 6 kHz.

An air-bone gap, assessed by the difference in the air-bone-conduction thresholds, is consistent with CHL. Persistent CHL, without symptoms of OME, is an attenuation of signals stimulating the cochlea without damage to the auditory end organ. It is attributed to fixation and/or osteoradionecrosis of the ossicular chain. Variation in the hearing thresholds over consecutive evaluations should be used to determine if SNHL is transient or persistent. Note that bone-conduction thresholds may also, to a much lesser extent, be altered by the presence of middle ear pathology in addition to the usual test-retest variabilities (Anteunis 1996). In addition to these, in patients with age-adjusted normal values, additional tests may provide useful information. Auditory brainstem response (ABR) testing may be used to assess retrocochlear pathology, such as radiation damage to the auditory nerve. An intra-neural latency response difference of at least 0.30 ms for wave V of the auditory brainstem indicates neural involvement.

In post-RT audiometric evaluations, a recovery from a higher bone-conduction threshold to a threshold of less than 10 dB in consecutive tests may indicate transient SNHL (Kwong et al. 1996). An increase in the bone-conduction threshold exceeding 10 dB in two consecutive tests performed at least 6 months apart may be considered persistent SNHL.

5.1.3.1 Additional Function Tests

Speech audiometry tests include a speech reception threshold and word discrimination scores (WDS). The speech reception threshold serves as a cross-reference for pure-tone air-conduction thresholds, whereas poor WDS may indicate radiation-induced neural damage and may help determine candidacy or ineligibility for hearing aids.

The stapedial-reflex examination evaluates the contraction of the stapedial muscle in reaction to loud sounds, is mediated by neural network with afferent input from auditory nerves and efferent input from the auditory nerve. It provides additional information on the status of neural loop and complements tympanometric measurements (Jereczek-Fossa et al. 2003; Jereczek-Fossa and Orecchia 2002).

- *Vestibular dysfunction*. Spontaneous and induced nystagmus can be recorded and quantified with electronystagmography (ENG) using electrodes placed around the eyes and videonystagmography (VSG) using infrared video cameras over the eyes. These tools record eye movement and can be used to evaluate the vestibule-ocular reflexes for assessment and follow up of vestibular dysfunctions.
- *Caloric response*. Loss of horizontal semicircular canal function is called canal paresis. The caloric test can evaluate vestibular function by irrigating the ear canal with 30 °C (cold) and 44 °C (warm) water or air for 1 min and measuring the resulting eye movement slow-phase velocities (Jongkees and Philipszoon 1964). An interaural difference of more than 20 % is considered abnormal. In patients with unilateral RT, a significantly reduced response to caloric stimulation of the irradiated side compared to the nonirradiated side indicates canal paresis of the irradiated side.
- *Otolith dysfunction*. RT-induced otolith dysfunction can be evaluated using vestibular evoked myogenic potentials, or VEMPs, by recording the muscular activity in the ipsilateral sternocleidomastoid muscle after delivering a loud sound or electrical stimulus to the ear. This test is subject to numerous confounding factors. Absent responses do not necessarily imply absent vestibular function.
- *Cochlear and auditory pathway*. Brainstem auditory evoked response (BAER), brainstem auditory evoked potentials (BAEP), or ABR detect electrical activity in the cochlea and auditory pathway in the brain by measuring the electrical waves from the brainstem in response to clicks or tone bursts in the ear. Neural waves result from synchronized neural discharge along the auditory neural pathway. Outcomes can be affected by pathology anywhere along the auditory pathway, thus abnormal results are nonspecific.

Transient-evoked otoacoustic emissions (TEOAE), which record an acoustic signal generated by the contracting outer hair cells of the inner ear, may reveal radiation damage to the outer hair cells in the organ of Corti. It is only detectable when the external, middle, and inner ear functions normal or close to normal. The emission strength (dB SPL) in the TEOAE reflects the number of active outer hair cells. This method has been used to study the ototoxic side effects of cisplatin, but has not been widely used in evaluating patients after RT (Allen et al. 1998; Biro et al. 1997). However, one study reported accurate identification of patients with a hearing level better than 25 dB for frequencies between 1 and 4 kHz. Also, a TEOAE correctly indentified all cases with a hearing threshold worse than 25 dB HL for all frequencies between 1 and 4 kHz (Johannesen et al. 2002).

5.1.3.2 End-Point Criteria After RT for Vestibular Schwannoma

The end-point criteria for evaluating and reporting hearing status after SRS or stereotactic radiotherapy (SRT) for VS differ from the criteria for standard fractionation RT (examples Tables 6 and 7). The Gardner-Robertson scale is commonly used (Table 7).

5.1.4 Radiologic Imaging

Radiology studies such as CT, positron emission tomography (PET), MRI, and nuclear medicine (bone scans) studies can help reveal the development and extent of delayed radionecrosis of the brain or osteoradionecrosis of the temporal bone (Nishimura et al. 1997).

Post-RT morbidities, including hemorrhage into the inner ear, labyrinthitis, and neuronitis, can be revealed by MRI. MRI has been used to visualize the eustachian tube and to assess its anatomy and pathology in patients with nasopharyngeal carcinoma. MRI has been a powerful tool in evaluating endocochlear diseases that cause sudden SNHL (Hegarty et al. 2002). Findings of high labyrinthine signal on unenhanced T1-weighted MRI of the internal acoustic canal in patients who presented with a sudden onset of SNHL 5–20 years following head and neck RT have been reported by Poh and Tan (2007). They posited that these findings are due to labyrinthine hemorrhage as a rare, delayed complication of head-and-neck RT seen in T1-weighted signal changes in the labyrinths of patients who experienced sudden SNHL. Further patency of inner ear fluid spaces as well as occlusion of inner ear fluid spaces by a fibrotic process can be revealed by MRI along with CT (Jereczek-Fossa et al. 2003).

5.1.4.1 Anatomical Definition of the Middle and Inner Ear for Treatment Planning

The maximum dimensions of the middle ear, vestibular apparatus, and cochlea are known to vary from 1 to 2.2, 1.4 to 1.8, and 0.5 to 1 cm, respectively (Pacholke et al. 2005). A 5-mm slice thickness for the computed tomography (CT)

scans is insufficient to accurately delineate and evaluate the volume of the middle and inner ear structures. Slice thickness less than or equal to 1 mm through the temporal bone is optimal. Proper treatment planning would include magnetic resonance imaging (MRI) fused with CT and selecting the appropriate window width and level settings (e.g., bone window setting on CT).

The tympanic membrane is often difficult to visualize on CT. Superiorly inferiorly, it extends between two bony projections. The middle ear is defined laterally by the tympanic membrane, annulus, and handle of malleus, medially by the promontory of the cochlea, superiorly by the tegmen tympani, and inferiorly by the bony wall covering the jugular bulb. These landmarks assist with defining and delineating the middle ear cavity on CT during treatment planning.

The eustachian tube is over 3 cm long and has bony and cartilaginous parts. The bony part is over 1 cm long and tapers down from the anterior wall of the middle ear to its orifice. This narrowest part of the tube is the isthmus, which has been related to the pathogenesis of OME (Wang et al. 2007). The cartilaginous part is over 2 cm long and joins the bony orifice at the isthmus. It is located in the groove between the greater wing of the sphenoid and the apex of the petrous apex of the temporal bone. To reduce the dose to these parts, the middle ear cavity and isthmus must be localized by identifying these landmarks for accurate delineation on the CT scans before optimizing a treatment plan.

The inner ear can be well demonstrated on CT scans. The base of the cochlea abuts the anterior aspect of the internal auditory canal fundus. The cochlea is a snail shell-shaped structure that lies anteriorly with its apex pointed anteriorly, inferiorly, and laterally. The vestibule is located posterior to the cochlea and medially adjacent to the internal auditory canal with three semicircular canals emanating at right angles. The internal auditory canal is a landmark that is significant for identifying, localizing, and delineating the cochlea and vestibule.

6 Radiation Tolerance of Otologic Organs

6.1 External Ear

Earlier studies suggested tolerance dose for 50 % complication for acute radiation otitis to be 40 Gy and for chronic otitis, it was 65–70 Gy (Burman et al. 1991; Emami et al. 1991). In a single-institution study of radiation for head-and-neck cancers, external-ear toxicity occurred in 33 % of the patients receiving doses above 50 Gy for megavoltage X-ray radiation (Bhandare et al. 2007). Both acute and chronic otitis externa increased significantly (above 5 % in each dose bin of 5 Gy) as the dose received by the external ear increased above 50 Gy. The incidence of atrophy and canal stenosis was reported to increase significantly above 55 Gy to the external auditory canal. Incidence of both acute and chronic otitis externa as well as atrophy and canal stenosis increased with increases in the radiation dose received by the external auditory canal. A correlation between the incidence of chronic otitis externa, atrophy, and canal stenosis was reported in patients receiving high doses of radiation (>55 Gy) to the external auditory canal (Bhandare et al. 2007). In patients treated with hypofractionated orthovoltage X-ray and electrons for epithelial tumors of the pinna, the incidence of skin necrosis was reported to be 13 % (Ashamalla et al. 1996; Lim 1992; Silva et al. 2000) (Fig. 6a–c, Table 8).

6.2 Middle Ear

Patients with pre-RT middle-ear effusion have been shown to be seven times more likely to have long-term post-RT middle ear effusion than an ear without pre-RT middle ear effusion (Low et al. 2006). Incidence of tympanic membrane perforation and otitis media has been observed to increase (above 5 % in each dose bin of 5 Gy) above a total dose of 50 Gy to the middle ear. The incidences of chorda tympani dysfunction, middle ear fibrosis, and mastoiditis increase above the dose of 60 Gy to the middle ear, indicating an increase in the incidence of otitis media with increases in the dose received by the middle ear (Bhandare et al. 2007).

A study of the factors controlling radiation-induced OME observed a relationship to the dose over the middle ear cavity (Wang et al. 2007). The radiation dose has been related to deterioration of the passive opening function of the eustachian tube. A dose to the isthmus of the eustachian tube below 52 Gy and a dose over the middle ear cavity below 46 Gy is reported to decrease the incidence of OME. Worsened middle ear function was observed in the first year after RT. Other studies (Wang et al. 2006, 2007) reported decreased OME with a dose to the middle ear cavity and isthmus of the eustachian tube below 47 Gy and concluded that limiting the dose over the bony part of the eustachian tube and middle ear to less than 47 Gy may significantly decrease middle ear morbidity. Because the anatomic location of the isthmus is closer to the nasopharynx than the middle ear cavity and the isthmus is the narrowest part of the eustachian tube, the dose to the isthmus will influence the incidence of eustachian tube dysfunction significantly, particularly for nasopharyngeal RT.

Both functional impairment and organic obstruction of the tube has been observed in patients receiving doses between 70 and 80 Gy, with tubal-function recovery in

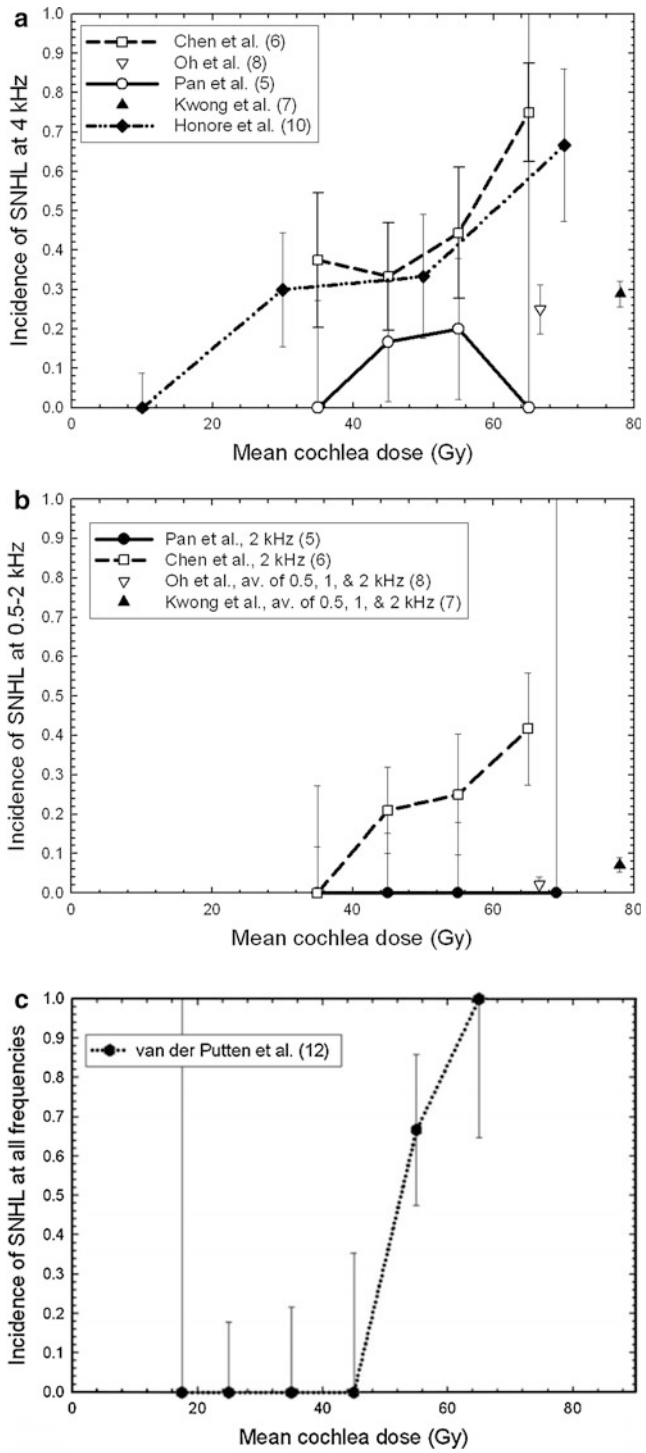

Fig. 6 The rate of SNHL versus mean dose to the cochlea at **a** 4 kHz, **b** 0.5–2 kHz, and **c** all frequencies (with permissions from Bhandare et al. 2010)

some ears that received doses less than 70 Gy (Young and Hsieh 1992; Young et al. 1995). For doses higher than 70 Gy, both tubal patency and clearance function of the eustachian tube deteriorated, but the dynamic function of the tube was preserved (Young and Sheen 1998). The risk of otomastoiditis is increased if the treatment involves a field that is both anterior and posterior to the clival line (Nishimura et al. 1997). While some datasets have generally supported these observations (Chen et al. 1999; Schot et al. 1992; Grau et al. 1991; Strohm et al. 1985), others have not reported a conclusive relationship between radiation dose and specific morbidity (Young et al. 1997; Miettinen et al. 1997).

6.3 Inner Ear

The incidence of post-RT SNHL has been reported to vary from 0 to 54 % in various studies (Dias 1966; Moretti 1976; Anteunis et al. 1994; Raaijmakers and Engelen 2002; Kwong et al. 1996; Grau et al. 1991) Most studies (Kwong et al. 1996; Honore et al. 2002) that have reported significant hearing loss at high frequencies (4 kHz and above), which may be outside the primary range of human speech (1–3 kHz), are still relevant since normal hearing in young people extends to 20 K; above the age of 50, it is typically limited to 10 kHz. In a review of nine studies, when averaged over all frequencies (0.5, 1, 2, and 4 kHz), the incidence of SNHL was 18 ± 2 %. About one-third of patients receiving a dose of 70 Gy in 2 Gy per fraction in close proximity to the internal ear developed hearing loss of at least 10 dB or more in the high-frequency region of 4 kHz (Bhandare et al. 2007). The pooled incidence of post-RT SNHL was reported to be 44 and 36 % for the nasopharynx and parotid, respectively (Bhide et al. 2007).

6.3.1 Total Dose to the Inner Ear

The dose response relationship for the inner ear has been evaluated in a number of prospective and retrospective studies (Honore et al. 2002; Pan et al. 2005; Oh et al. 2004; Chen et al. 2006; van der Putten et al. 2006). At a total dose as low as 30 Gy for fractionated RT to the head-and-neck region (Raaijmakers and Engelen 2002), SNHL, CHL, or mixed hearing loss (Leach 1965) has been occasionally reported in the literature. Other clinical studies have reported a limiting total dose received by the inner ear from fractionated RT above which SNHL increases. These include 40 Gy (at 2 Gy per fraction) (Honore et al. 2002), 45 Gy (fractionation not specified) (Pan et al. 2005), a mean cochlear dose of 48 Gy delivered by either conventional RT or IMRT followed by a twice-daily boost (Chen et al. 1999), and 50 Gy delivered at 1.8–3 Gy per fraction (van der Putten et al. 2006). A number of studies have reported hearing loss (sensorineural, conductive, and mixed) in patients receiving doses greater than 50 Gy (Linskey and Johnstone 2003). Taking into account variations in the criteria used to define SNHL and other parameters used in the designs of these studies, the incidence of SNHL rises

Table 8 Selected studies on the treatment of vestibular schwannomas

Author and year	Number of patients in study	Marginal tumor dose (Gy)[a]	Follow-up	Tumor control (%)	Hearing status (%)
SRS					
Hirsch et al. 1988 (34)	126	18–25	Mean 4.7 year	86	HP: 26
Noren et al. 1993 (35)	Total: 254	18–20	1–17 year	Unilateral: 94	HP: 22
	NF2: 61	10–15		NF2: 84	Moderate HD: 55 Severe HD: 23
Foote el al. 1995	36	16–20	2.5–36 months	100	HP (SH): 10 at 1 year 42 ± 17 at 2 year
Flickinger et al. 1996	273 CT: 118 MRI: 155	12–20	–	96.48 CT: 44 MRI: 32	HL, MRI: 32 ± 7 at 3 year HL, CT: 61 ± 7 at 3 year
Kondziolka et al. 1998	162	12–20 Mean: 16.6	6–102 month (60 % > 5 year)	94	HP (SH): 47 HP (MH): 51
Lunsford et al. 1998 (39)	402	Earlier in series: 17 Later in the series: 12–14	Mean: 36 month	93	HP: 39 at 5 year HP: 68 at last 5 year
Flickinger et al. 2001 (40)	190	11–18 Median: 13	Median: 30 month Max: 80 month	91 at 5 year	HP: 74 HI:7
FSRT/HP-FSRT					
Andrews et al. 2001	GK-SRS: 64	GK-SRS:12	GK-SRS: 119 ± 67 weeks	GK-SRS: 98	HP, GK: 33
	(NF2: 5) FSRT: 46 (NF2: 10)	SRT: 50 (2 Gy/fx)	SRT: 115 ± 96 weeks	SRT: 97	HP, SRT: 81
Williams et al. 2002	125	Tumors <3 cm: 25/5 fx Tumors >3 cm: 30/10 fx	1.0–5.7 year Median: 1.8 year	100	HP: 46 HL: 36 HI: 18
Meijer et al. 2003	Total: 37 SRS: 12 HPFSRT: 25	SRS: 10–12 HPFSRT: 20–25	12–61 month Mean: 25 month	–	HP: 91
Combs et al. 2005	106	FSRT: 57.6 (1.8 Gy/fx)	3–172 month	94.3 at 3 year, 93 at 5 year	HP: 94 at 5 year

SRS stereotactic radiosurgery, *HL* hearing loss, *MRI* magnetic resonance imaging, *BCT* bone conduction threshold, *CT* computed tomography, *SRT* stereotactic radiotherapy, *NF2* neurofibromatosis type 2, *FSRT* fractionated SRT, *HPFSRT* hypofractionated SRT, *HPRT* hypofractionation trial, *GRHG* Gardener-Robertson Hearing Grade, *HG* hearing grade, *HP* hearing preservation corresponding either to serviceable hearing (SH; GRHG-I, II) or measurable hearing (MH; GRHG: III, IV), *HD* hearing deterioration, *HI* hearing improvement, *NR* not reported, *UH* useful hearing, *GK* gamma knife, *fx* fraction.

[a] Single fraction unless otherwise stated

significantly between 40 and 47 Gy to the inner ear delivered by standard fractionation (Jereczek-Fossa and Orecchia 2002; Ashamalla et al. 1996). Based on the currently available information, a total dose of 30 Gy may be considered as the most conservative limit to the inner ear when delivering fractionated RT by standard fractionation, either for radical treatment, or radiation with chemotherapy (van der Putten et al. 2006).

Although linear and logistic regression analyses to evaluate the dose–response relationship for SNHL observed a general increase in the level of hearing loss with an increased dose to the inner ear, a definitive linear relationship of hearing loss as a function of dose received by the inner ear has not been established (Honore et al. 2002). Also, a statistically significant dose–response relationship has not been observed for lower frequencies (0.5, 1, 2 kHz). A statistically significant relationship was observed only at a frequency of 4 kHz, but the 95 % confidence interval was quite wide.

In addition to an increase in the severity of hearing loss, an increase in the incidence (fraction of patients with SNHL) with an increase in the total dose received by the inner ear has been reported in a number of studies (Chen et al. 1999).

In one SRS study, patients who received 11 Gy exhibited a decline in hearing, while patients who received a mean dose of 6.9 Gy to the cochlea were observed to retain useful hearing (Paek et al. 2005). In another study, serviceable hearing dropped to 20 % in those receiving >14 Gy, but was preserved in 100 % of the patients receiving ≤14 Gy (Niranjan et al. 1999). A study of patients treated for VS (secondary to NF2) with gamma knife SRS (Fong et al. 1995) concluded that reducing the dose from 25 to between 10 and 16 Gy increased hearing preservation ($p = 0.05$). A significant increase in hearing preservation in a group of patients treated between 12 and 14 Gy compared to those treated to 16–20 Gy was observed in other studies (Combs et al. 2005; Williams 2000). A summary of tumor and auditory outcomes for patients treated with single or multiple fraction radiosurgery/radiotherapy for acoustic tumors is provided in Table 8.

6.3.2 Dose per Fraction and Fractionation for Head-and-Neck Tumors

In addition to total dose, dose per fraction plays a significant role in the incidence of delayed toxicities. The effect of dose per fraction on post-RT SNHL has not been sufficiently evaluated in the present literature. While the incidence of SNHL in studies on dose per fraction greater than 2 Gy (Kwong et al. 1996; Grau et al. 1991) did not exhibit significant variations compared to studies involving standard fraction sizes (Bhandare et al. 2007), the effect of dose per fraction on the incidence of SNHL has not been evaluated in a two-arm study. In a single-institution study (Bhandare et al. 2007), twice-daily fractionation was significant in univariate analysis in reducing chronic otitis externa ($p < 0.01$), but not chronic otitis media ($p = 0.1$) or SNHL ($p = 0.79$). In multivariate analysis, twice-daily fractionation was not significant in reducing any of these long-term morbidities.

6.4 Dose Volume

6.4.1 Dose-volume Data

The doses received by the organs of the auditory system vary depending on the treatment site (e.g., parotid, nasopharynx) and the patient-specific treatment plan. Organs associated with the middle and inner ear (e.g., tympanic membrane, vestibular apparatus, semicircular canals, and cochlea) are small. The estimated volume of the middle ear is 0.56 cc (range, 0.40–0.77) (Pacholke et al. 2005) and the cochlear volume has been estimated to be 0.56 cc (range, 0.15–0.91 cc) (Pacholke et al. 2005; Pan et al. 2005). The enclosure of these structures within the temporal bone and their small size may contribute a significant level of uncertainty when delineating them on treatment planning CT. That uncertainty when confounded with the small volume of the individual structures will contribute significant uncertainty in dose-volume histograms and their interpretation.

6.4.2 Dose-volume Data for External-Beam RT

A limitation of the dose-volume analysis is that it does not account for the physical location nor the functional anatomy of the organ receiving a certain dose level and its corresponding volume (Table 9). The dose-volume effect for the observed damage is particularly difficult to interpret in a small organ like the organ of Corti or stria vascularis, as the location of a certain dose and its corresponding volume (maximum, minimum, or dose to 5 % of the cochlea) may not correspond with the lesion site. The dose gradient may vary depending on the specific treatment plan. Some studies have tried to associate the minimum dose (D_{min}), maximum dose (D_{max}), mean dose (D_{mean}), median dose (D_{med}), the highest 5 % of dose to the cochlea (D_{05}), and dose to 95 % of the cochlear volume (D_{95}) with SNHL (Chen et al. 1999; Herrmann et al. 2006). The difference between the mean and the median dose to the cochlea has been reported to be insignificant (Honore et al. 2002). A number of studies (Bhandare et al. 2007; Pan et al. 2005; Chen et al. 1999; Honore et al. 2002) have utilized the mean dose received by the organ of interest for calculations and have indicated that, at present, the mean dose to the organ should adequately estimate the dose to the middle ear or cochlea and vestibule.

The values suggested by Emami et al. (1991) of TD5/5 60 Gy, TD50/5 = 70 Gy for post RT SNHL are not supported in the present literature. Nevertheless, the information on dose response modeling for post RT SNHL remains limited. Among these studies is a linear model by Pan et al. (2005). Demonstrating the differences between pre-RT and post-RT BCTs (corresponding to frequencies varying from 0.25 to 8 kHz) for the ipsilateral and contralateral ears and their association with relative dose scale, age, test frequency, and baseline (i.e., pre-RT) bone-conduction threshold presented in the form of nomograms. Honore et al. (2002) presented a logistic model of the probability of post-RT hearing loss ≥15 dB at 4 kHz, including only dose, which indicated that $D_{50} = 48$ Gy (95 % confidence interval not reported) and $\gamma_{50} = 0.70$ (range, 0.22–1.18). Adjusting for patient age and pre-treatment hearing level revealed a steeper dose–response curve with $\gamma_{50} = 3.4$ (95 % confidence interval: 0.3–6.5). Multivariate logistic and linear regression for dose pre-RT and observation time after RT are presented in the study. Multivariate linear model for RT dose, number cycles of cisplatin, and post-RT observation time at frequencies between 0.5 and 4 kHz are presented by Chen et al. (2006). Van der Putten et al. (2006) fitted an NTCP model to the incidence of asymmetrical SNHL (averaged over 4

Table 9 Selected studies for SNHL after head-and-neck radiation therapy

Author	Number of patients in study	Mean cochlear dose (Gy)/Rx dose (Gy)	Dose per fraction (Gy)	Chemoradiation (cisplatin based)	Influence of variables on the outcome						Standard used for comparison	Endpoint for SNHL (shift in BCT)/ frequencies (kHz) tested
					Chemoradiation	Age	Post-RT SOM	Gender	Time to hearing test	Pre-RT hearing level		
Prospective												
Grau et al. 1991	22	NS/60–68	2–2.81	No, RT alone	–	No[a]	–	–	No	No	Same ear	Nominal shifts in BCT (in dB) reported/0.5, 1.0, 2.0, 4.0
Kwong et al. 1996	132	NS/71.3–85	2–3.5/2[b]	Yes[c], neoadjuvant	No	Yes[d]	Yes	Yes[e]	Yes	No	Same ear	15/avg of 0.5, 1, 2 15;4
Ho et al. 1999	294	70–91[b]/ 59.9–70	2–3.5/2[b]	Yes[c], neoadjuvant	No	Yes	–	–	Yes	No	Same ear	10/avg. of (0.5, 1, 2) 10;4[f]
Oh et al. 2004	32	54.3–81.4/70	2	Yes[c], neoadjuvant	No	Yes[g]	Yes	Yes[e]	Yes	No	Same ear	
Pan et al. 2005	22	Ipsi:[c] 14.1–68.8 Contract:[c] 0.5–31.3/ 40–70	NS	RT alone (18) Concurrent chemo. (4)	–	Yes	–	No	No	Yes[h]	Contralateral	20/0.25, 0.5, 2[f], 4[f], 8
Low et al. 2006	115	NS/70	2	Yes[c], concurrent and adjuvant	Yes (4 kHz)	–	–	–	–	–	Same ear	Nominal shifts in BCT (in dB) reported/ 4, avg. of (0.5, 1.0, 2.0)
Retrospective												
Honoré et al. 2002	20	7.1–68/50–68	2–4.3	No, RT alone	–	Yes	–	–	No	Yes[h]	Same ear	15/0.5, 1, 2, 4 20; 4[f]
Chen et al. 2006	22	28.4–70	1.6–2.34	Yes, concurrent and adjuvant	Yes (4 kHz)	No	No	–	Yes	No	Same ear	20/0.5, 1, 2[f], 3, 4[f]
Van der Putten al. 2006	52	29.2–77.3/ 50–70	1.8–3.0	No, RT alone	–	–	–	–	–	–	Contralateral	15/0.25–12 for ≥3 of these frequencies

NS not specified, *AS* absolute shift in the hearing threshold reported, *SOM* serous otitis media, *RT* radiation therapy, *CT* bone conduction threshold, *db* decibels, *SNHL* sensorineural hearing loss, *Rx* prescription

[a] Dose and age component of HL separated

[b] Total doses calculated as BED in 2 Gy fractions, with $\alpha/\beta = 3$ Gy

[c] The primary endpoint of a prospective clinical trial

[d] Older age found significant

[e] Rate of HL male > female

[f] Data for these endpoints reconstructed from figures for this paper

[g] Younger age found significant

[h] Better pre-RT hearing associated with worse post RT HL

frequencies) as a function of mean dose to the ipsilateral inner ear and found that $D_{50} = 53.2$ Gy with γ_{50} of ~ 2.74 and $D_{10} = 42$ Gy.

The incidence of hearing loss at 4 and 0.5, 1, and 2 kHz as reported by Chen et al. (2006), Oh et al. (2004), Pan et al. (2005), Kwong et al. (1996), and Honore et al. (2002) is shown in Fig. 6a, b. Table 9 presents selected studies for SNHL after head-and-neck radiation therapy.

6.4.3 Dose−Volume Data for the Treatment of Acoustic Schwannoma

The dose-volume data on SRS and SRT for acoustic schwannomas involve irradiated nerve length and serviceable hearing. RT dose received by the cochlear nerve is determined by the location and length of the cochlear nerve in the radiation field with respect to the tumor. The radiation-induced damage to the nerve was hypothesized to be related to the irradiated length of the cranial nerve (Linskey and Johnstone 2003). The most radiosensitive part of the cochlear nerve was considered to be the Obersteiner-Redlich zone of the cochlear nerve (Linskey and Johnstone 2003). Data on the length of the nerve irradiated and hearing status remain contradictory. SRS has been observed to be effective in hearing preservation in the treatment of small acoustic schwannomas (<3 mm) compared with larger lesions (Pollock et al. 1995). Another study compared the length of the 8th nerve irradiated in Gamma Knife SRS for intracanalicular acoustic schwannomas. It divided patients into two groups, one with tumors occupying only part of the canal (4–7 mm) and the other with tumors extending the entire length of the canal (8–12 mm), and concluded that neither the position of the tumor in the canal (lateral versus medial) nor the length of the nerve irradiated correlated with hearing preservation ($p = 0.1$). While tumor diameter was significant on univariate analysis ($p = 0.025$), only marginal tumor dose was significantly associated with long-term hearing preservation on multivariate analysis ($p = 0.0009$). The marginal tumor dose as well the dose extending beyond the tumor volume inside the canal were the most important factors responsible for cochlear nerve injury (Niranjan et al. 1999). Intracanalicular tumor volume (<100 mm^3 vs. >100 mm^3) and intracanalicular integral dose (dose × volume) are also suggested to influence hearing loss (Massager et al. 2006). The effects of minimum tumor diameter and transverse tumor diameter for the risk of acoustic neuropathy (defined as any variation in either PTA or SD resulting in decline in GRHG for patients with at least class IV hearing) in patients treated with SRS for VS in two datasets were modeled by Flickenger et al. (1996) with multivariate multiple regression analysis. Table 8 shows selected studies on the treatment of VS.

7 Chemo Tolerance

7.1 Cisplatin

Ototoxicity of cisplatin has been well studied and cisplatin-induced apoptosis of cochlear hair cells has been found to play a key role in SNHL (Cheng et al. 2005). Post-RT dose-dependent, apoptosis-associated reactive oxygen species was observed in the cochlear cell line OC-K3 (derived from the organ of Corti of transgenic mice) by flow cytometry and TUNEL assay in one study. Microarray analysis showed dose-dependent apoptotic-gene-regulation changes, while western blotting revealed p-53 up-regulation and intensive phosphorylation of p-53 at Ser18 h after RT. The increase in phosphorylation is related to transcriptional up-regulation of several p-53-regulated genes associated with cell-cycle regulation and arrest, and corresponds with marked cellular apoptosis (Low et al. 2006). Dose-dependent radiation-induced apoptosis has already been reported in noncochlear cell systems and is generally accepted as an important mechanism of cell death in vivo (Verheij and Bartelink 2000). The reactive oxygen species-based apoptotic model could explain the dose dependence of radiation-induced SNHL and the preferential damage at high-frequency hearing. However, it needs to be acknowledged that actual cochlear hair cells are far more complex than the experimental cell lines. Miller et al. (2009) studied hearing outcomes over 3 months following cisplatin, fractionated RT, or combined therapy designed to replicate human treatment protocols in guinea pigs. Hearing loss was common in the animals treated with RT and combined therapy, but not in the cisplatin-treated animals (Table 9).

7.2 ChemoRadiation

Chemoradiation is a commonly used modality for head-and-neck cancers. The combined effect of chemotherapy and radiation may depend on the chemo agent, the dose, and the sequence in which chemotherapy and radiation is delivered. Cisplatin, one of the commonly used chemo agents, has been reported to be ototoxic (Department of Veterans Affairs Laryngeal Cancer Study Group 1991; Skinner et al. 1990). The ototoxicity of cisplatin may be dose and sequence dependent (Skinner et al. 1990), with an increase in toxicity if given after radiation compared to pre-RT (neoadjuvent) administration (Walker et al. 1989). Both radiation and cisplatin may individually cause ototoxicity (Department of Veterans Affairs Laryngeal Cancer Study Group 1991). In patients who received cisplatin, RT, or a

combination of the two, atrophy of the stria vascularis and loss of its inner and outer hair cells with a reduction in spiral ganglion cells have been reported (Hoistad et al. 1998). Although the effects of chemo radiation on SNHL have been reported in the pediatric patient population (Hoistad et al. 1998), the data on synergistic effects of chemotherapy and RT in the adult patient population remain limited. The possible synergistic toxicity of chemotherapy combined with RT has been studied prospectively (Ashamalla et al. 1996; Silva et al. 2000; Skinner et al. 1990; Shirato et al. 2000; Hayter et al. 1996), and retrospectively (Klemm 1967; Kwong et al. 1996; Walker et al. 1989; Butler and Van Der Voort 2002). A significant increase in bone conduction threshold at 4 kHz and PTA over 0.5, 1 and 2 kHz was reported 1 and 2 years after RT delivered with concurrent and adjuvant Cisplatin (Low et al. 2006). Conversely, no such increase has been seen in patients treated with neoadjuvant cisplatin (Kwong et al. 1996; Oh et al. 2004; Ho et al. 1999) (Table 9).

Though the synergistic effects of cisplatin-based chemotherapy and RT remain debatable, to reduce toxicity restricting the total dose received by the inner ear to a minimal level when delivered with cisplatin-based chemotherapy has been suggested (Combs et al. 2006), as has reducing the radiation dose to components of the auditory system to less than 45 Gy (30 Gy more conservatively) (Bhandare et al. 2010), and substituting a less ototoxic agent such as carboplatin (Jacobs et al. 1989). Antioxidants have been promoted as a means of limiting ototoxicity, but their value has yet to be established in clinical trials (Fouladi et al. 2008; Gallegos-Castorena et al. 2007).

The use of a less ototoxic chemotherapy agent like carboplatin has been suggested as a substitute for cisplatin (Jacobs et al. 1989). Although carboplatin may be less ototoxic, its efficacy in treatment should be studied further before substituting it for cisplatin. In a recent meta analysis (Budach et al. 2006), the average survival benefit varied from 16.2 months for cisplatin to 6.2 months for carboplatin in the patients treated concurrently with either conventionally fractioned or hyperfractionated/accelerated RT.

The survival benefit to using platinum-based chemotherapy with RT compared with RT alone has been supported in multiple studies (Browman et al. 2001). Cisplatin has been used to treat cancer for over two decades. The ototoxic effects of cisplatin have been well recognized and are associated with the dose of cisplatin (Skinner et al. 1990). An incidence of hearing loss ranging from 20 to 90 % has been associated with cisplatin-based regimens. The ototoxicity of cisplatin is manifested as irreversible, high-frequency hearing loss. One histologic study shows that the outer hair cells are the most susceptible to cisplatin toxicity (Low et al. 2008). Despite the information on the synergistic effects of combining chemotherapy and RT, data on its effects on hearing remain limited. When delivered with RT, the effects may depend on both cisplatin and RT dose as well as the chemotherapy regimen (neoadjuvant, adjuvant, or concurrent). Low doses of neoadjuvant cisplatin have not been associated with increasing the incidence of SNHL (Kwong et al. 1996; Oh et al. 2004; Ho et al. 1999). Increased toxicity has been observed in patients treated with both adjuvant and concurrent cisplatin-RT (Bhandare et al. 2007; Low et al. 2006; Chen et al. 2006). Low et al. (2006) reported results at 1 and 2 years after RT delivered with concurrent and adjuvant cisplatin, and found significant increases both in BCT at 4 kHz, and in BCTs averaged over 0.5, 1, and 2 kHz.

8 Special Topics

8.1 Patient-Related Factors

- The incidence of post-RT SNHL has been observed to increase with age (>50) (Bhandare et al. 2007; Pan et al. 2005; Kwong et al. 1996). Grau et al. (1991) found a significant relationship between higher patient age and increased risk of hearing loss, but, when corrected for radiation dose, the correlation disappeared. While higher rates of post-RT SNHL have been reported in males compared to females (Kwong et al. 1996; Ho et al. 1999) other studies have not observed any difference in the incidence of SNHL between sexes or races (Bhandare et al. 2007).
- Pre-RT hearing level has been observed to be statistically associated with the incidence of SNHL (Pan et al. 2005; Honore et al. 2002). In some studies, patients with better hearing before receiving RT were more likely to have substantial hearing loss after high-dose radiation (Pan et al. 2005; Honore et al. 2002; Ho et al. 1999). The patients with poor pre-RT hearing were not observed to experience worse hearing losses in another study (Gristwood and Beaumont 1979).
- A number of studies have associated post-RT otitis media with the incidence of SNHL in a number of studies (Bhandare et al. 2007; Kwong et al. 1996; Ho et al. 1999).
- The transient and persistent hearing loss after shunt placement has been documented (van Veelen-Vincent et al. 2001; Stoeckli and Bohmer 1999). CSF shunt has been suggested to increase risk of HL after RT in pediatric patients and may enhance the risk of HL in adults (Merchant et al. 2004).
- *Latency*. The onset of hearing deterioration has been reported to occur as early as 3 months after fractionated RT (Wang et al. 2007). In one prospective study, SNHL occurred 1.5–2 years after fractionated RT (Ho et al. 1999). The progression of SNHL has been reported to

plateau within 2 years after fractionated RT (Wang et al. 2007; Kwong et al. 1996). Other studies concur with these observations (Bhandare et al. 2007). The stability of post latency SNHL after fractionated RT has been followed for 13 years (Honore et al. 2002). Though the cumulative risk of persistent SNHL (>15 dB) was noted to stabilize at 2 years, severe SNHL (>30 db) was observed to increase through the fourth year after fractionated RT (Grau et al. 1991).

8.2 Stereotactic Radiation Surgery (SRS) or Therapy (SRT) to Treat Acoustic Schwannoma

FSRT offers the advantages of both SRS and conventional RT and has the potential to spare normal tissues while killing tumor cells (Hall and Brenner 1993; Steel 2001). In two studies, the same investigators observed a 5-year local control rate of 93 % with serviceable hearing in 94 % of patients treated with FSRT to a total dose of 57.6 Gy delivered by standard fractionation (Combs et al. 2005). They observed a local control rate of 91 % and serviceable hearing in 55 % of patients treated with SRS to a median total dose of 13 Gy (range, 11–20 Gy) (Combs et al. 2006). Another study compared serviceable hearing after comparable follow-up in cases of sporadic tumors and observed that the probability of maintaining serviceable hearing remained significantly higher at 81 % in the FSRT group versus 33 % for the SRS group ($p = 0.0228$) (Andrews et al. 2001), concluding that SRT patients with pretreatment GRHC I exhibit a significantly greater probability of maintaining serviceable hearing than SRS patients. The class hearing preservation did not differ between cystic or solid tumors when delivered by FSRT (Shirato et al. 2000). The data in the literature are promising, but the advantage of FSRT over SRS in hearing preservation requires further investigation (Table 8).

Hypofractionation schedules deliver total doses in the range of 21–30 Gy in a short period of time (3–10 days) and a higher dose per fraction than the standard fraction sizes used in FSRT. But hypofractionation delivers fewer doses per fraction than the single high-dose fractions of 3–7 Gy used in SRS. A comparative two arm study with patients treated with SRS to a total dose of 10–12 Gy and hypofractionated SRT (HP-FSRT) regimen of either 5 fractions of 4 Gy or 5 fractions of 5 Gy did not show any difference in local control between the two groups. However, 5-year hearing preservation favored the hypofractionated group (75 vs. 61 %) (Meijer et al. 2003). In another study, (Williams 2002) delivering 5 Gy per fraction for 5 treatment days for smaller tumors (<3-cm diameter) and 3 Gy per fraction for 10 treatment days for larger tumors (≥3-cm diameter) led to 46 % hearing preservation and 36 % hearing deterioration at a median follow-up of 1.8 years. It is still unclear from the present literature if there is any advantage of using hypofractionation to optimize both local control and hearing preservation.

The recent QUANTEC review (194) concluded that:

a. For conventionally fractionated RT, to minimize the risk for SNHL, the mean dose to the cochlea should be limited to <45 Gy (or more conservatively <35 Gy). Because a threshold for SNHL cannot be determined from the present data, to prevent SNHL the dose to the cochlea should be kept as low as possible.
b. For SRS for schwannoma, the prescription dose should be limited to 12–14 Gy for hearing preservation.
c. A suggested hypofractionation schedule for schwannoma, to provide likely tumor control and preserve hearing, is a total prescription dose of 21–30 Gy in 3–7 Gy per fraction over 3–10 days, though data on this schedule are limited.

8.2.1 Timeline of Hearing Loss After SRS and FSRT

Post-SRS immediate hearing loss has been sparsely reported (Pollack et al. 2005). After SRS, early hearing loss within 3 months may occasionally result from neural edema or demyelination. Hearing impairment has been noted to occur within 3–24 months after SRS (Niranjan et al. 1999; Subach et al. 1999; Foote et al. 1995). The median time for hearing loss in post-SRS patients with NF-2-associated acoustic schwannomas does not differ from that among the sporadic tumors, and has been observed to be 4 months (Linskey and Johnstone 2003; Subach et al. 1999).

8.3 Acoustic Schwannoma Secondary to NF2

Acoustic schwannomas secondary to Neurofibromatosis type 2 (NF2) are often bilateral and tend to affect younger patients (Baldwin et al. 1991). A number of studies (Linskey and Johnstone 2003; Andrews et al. 2001; Mathieu et al. 2007; Rowe et al. 2003; Roche et al. 2000; Kida et al. 2000; Subach et al. 1999) have evaluated the outcomes after SRS, both local control and hearing status, in patients with acoustic schwannoma secondary to NF2. There is significant variation in tumor control, ranging from 100 (Kida et al. 2000) to 50 % (Rowe et al. 2003) and in hearing preservation from 57 (Roche and Regis 2000) to 0 % in the group of patients who received a total dose greater than 14 Gy (Mathieu et al. 2007). Hearing preservation in patients with acoustic schwannomas secondary to NF2 is comparatively lower than that in patients with sporadic tumors. Patients with acoustic schwannomas secondary to NF2, the group treated with SRS to a mean dose of 12 Gy experienced 80 % tumor control and

those treated to a total dose of 50 Gy with 2 Gy per fraction was 67 %, but this was not statistically significant ($p = 0.6$). However, hearing preservation was 0 and 67 %, respectively (Cook and Hawkins 2006). Whether fractionation can improve tumor control and hearing preservation in patients with acoustic schwannomas secondary to NF2 still needs further investigation.

8.3.1 VS Secondary to NF2

The response of VS secondary to NF2 varies significantly when compared to that of sporadic tumors after SRS or FSRT. The data for hearing response after SRS or FSRT for sporadic tumors may not apply to patients with VS secondary to NF2. Data on outcomes for VS secondary to NF2 remain scarce in the present literature.

8.4 Vestibular Dysfunction

A single-institution study reported a correlation between average dose received by the inner ear and vestibular dysfunction, canal paresis, and labyrinthitis in both univariate and multivariate analysis. Incidence of these dysfunctions increased above doses of 55 Gy to the inner ear (Bhandare et al. 2007).

Data on the relationship between incidence of vestibular dysfunction, including imbalance and vertigo, as well as dose response remain sparse and inconclusive (Young et al. 2004; Johannesen et al. 2002). Though cases of vestibular dysfunction after fractionated RT have been reported, the number of such cases remains too limited to draw any conclusions regarding a dose-response relationship. Hearing loss is sometimes accompanied by tinnitus and hyperacusis. Tinnitus is most commonly associated with SNHL, but it may occur subsequent to CHL (Jereczek-Fossa et al. 2003). Endolymphatic hydrops, indicated by an elevated summating potential, relative to the action potential on an electrocochleogram after treatment to a total fractionated dose around 50 and 54 Gy (Fong et al. 1995), is rare and so is facial paresis (Smouha and Karmody 1995).

9 Prevention and Management

9.1 Prevention

9.1.1 Middle Ear

The preventative role of inserting a ventilation tube (grommets) into the middle ear has been studied. While a grommet was an effective management strategy for OME induced by a bacterial infection, pre-RT grommet insertion was not observed to be beneficial. Otorrhea and persistent tympanic membrane perforation as well as recurrent effusion after grommet extrusion, in patients subjected to grommet insertion before RT, has been reported (Ho et al. 1999). That study concluded that the complications undermine the beneficial effects of the procedure. A prospective randomized controlled trial comparing two groups of patients, one with nasopharyngeal carcinoma with middle ear effusion subjected to pre-treatment ventilation tube insertion and the other with observation alone, did not exhibit significant differences in hearing benefits between the two groups (Ho et al. 2002). Serial CT/MRI examinations are recommended for post-RT nasopharyngeal carcinoma patients with intractable OME (Young and Sheen 1998).

9.1.2 Inner Ear

Cisplatin and gentamicin are both known to be ototoxic and have been shown to induce dose-dependent cochlear-cell apoptosis with its associated increase in reactive oxygen species production (Bertolaso et al. 2001). There is compelling evidence implicating reactive oxygen species in damage associated with cisplatin ototoxicity (Seidman and Vivek 2004).

Based on the apoptotic model involving post-RT reactive species, a potential use of antioxidants and antiapoptotic factors to prevent radiation-induced SNHL has been suggested (Leake and Hradek 1988; Seidman and Vivek 2004). Since these medications can be delivered topically through the middle ear, their systemic side effects could be minimized. RT-induced apoptosis has been prevented with antioxidants in cochlear cell culture (Low et al. 2008). At present, there is no clinical data to evaluate the suggested potential benefits of antioxidants or antiapoptotic factors.

In a small group of patients subjected to cisplatin with WR-2721 (amifostine), Rubin et al. (1995) observed some protective effects against ototoxicity. WR-2721 was suggested to have a protective effect on the neuro-epithelium of ears in the patients treated with cisplatin. Other clinical studies have not demonstrated significant oto-protection (Glover et al. 1989; Gandara et al. 1991); however, WR-2721 was reported to protect against neurotoxicity and nephrotoxicity without diminishing the antitumor effect (Glover et al. 1987; Mollman et al. 1988). The possible protective effects of WR-2721 against ototoxicity in patients treated with RT and cisplatin needs further investigation.

9.2 Management

9.2.1 External Ear

A basic approach for managing post-RT external otitis involves the following (Table 5):

- Thoroughly cleaning the ear canal with removal of excess cerumen, desquamated skin, and any exudate facilitates healing and helps ear topical preparations penetrate the

infected site. When wax production is impaired, moisturizing the canal with mineral oil can be helpful.

- Treatment of inflammation or infection generally involves topical application of corticosteroids and antimicrobials directly to the ear canal. Mild to moderate otitis externa can be treated with the combination of aural toilet and topical therapy including acidifying agents, antiseptics, steroids, and antibiotics. If the otitis externa develops into osteomyelitis, system antibiotics are required.
- Pain from otitis externa may be controlled with topical therapy and nonsteroidal anti-inflammatory agents, if necessary. Surgical procedures are rarely necessary (Hayter et al. 1996; Mazeron et al. 1986).

9.2.2 Middle Ear

Vasoconstricting agents (i.e., nasal spray) may be used episodically to manage complications due to eustachian tube dysfunction and its resultant negative middle ear pressure (Jereczek-Fossa et al. 2003). Nasal administration of corticosteroids may be beneficial in chronic cases, particularly if upper respiratory allergies are present. Though antibiotics and corticosteroids have been suggested for treating OME, no long-term benefits have been reported (Butler and Van Der Voort 2002; Williams et al. 1993; Rosenfeld and Post 1992). Surgical placement of a tympanostomy tube was once thought to be a treatment method for post-RT OME (Wei et al. 1987), but chronically discharging ears resulted in a high incidence of post-RT OME for those who underwent grommet insertion (Young and Sheen 1998). One study evaluated the efficacy of tympanostomy tube insertion versus myringotomy alone and the incidence of post-RT OME and concluded that post-RT OME tube insertion is not beneficial in post-RT OME. To decrease inflammation, middle ear effusion may be drained by repeated myringotomies instead of grommet insertion, and sinusitis should be evaluated and treated, because sinusitis can aggravate OME (Young and Sheen 1998). If the only complaint relative to OME is hearing loss, hearing aids may be sufficient.

9.2.3 Inner Ear

While antibiotics, hyperbaric oxygen (HBO), and surgery have been used to treat post-RT osteonecrosis, corticosteroids, HBO, and occasionally surgery have been used to manage brain necrosis (Jereczek-Fossa and Orecchia 2002; Ashamalla et al. 1996; David et al. 2001; Yuen and Wei 1994; Shaha et al. 1997). The approach to post-RT sudden or progressive SNHL while similar shows significant variation and parallels the approach for idiopathic sudden or progressive SNHL.

- *Corticosteroids*. Corticosteroids have been shown to improve inflammation and edema in the inner ear after noise-induced damage (Lamm and Arnold 1998). Improved hearing loss after corticosteroid intake may lessen the inflammation and edema in the inner ear after RT-induced damage. Factors associated with conservative treatment, including corticosteroid intake with recuperated hearing deterioration after fractionated SRT, include young age, immediate delivery after hearing loss, and pretreatment hearing at a useful level. On the other hand, some studies have not observed improved hearing impairment after corticosteroid use after either fractionated SRT or sudden hearing loss (Chang et al. 1998; Minoda et al. 2000). The benefit of this treatment for hearing loss after single-fraction SRS for acoustic neuroma is unclear (Lamm and Arnold 1998; Kondziolka et al. 1998). More data are needed to evaluate if there is any benefit to using corticosteroids for hearing impairment after RT.
- *Hyperbaric oxygen (HBO)*. Fibroatrophic changes, local hypoxia, impaired cellular proliferation, and decreased vascularity are the commonly exhibited characteristics of tissue subjected to high doses of radiation. While using HBO to treat or prevent hearing loss may elicit potential benefits in theory, there have not been any randomized trials conducted. The actual benefit of this approach remains questionable. Cochrane's collaborated review suggested that although HBO may benefit patients with late-radiation tissue injury to the head, neck, rectum, and other parts, there was no benefit for neural tissue (Bennett et al. 2005).
- *Air conduction hearing aids*. Moderate SNHL is managed well with classical air conduction hearing aids for hearing amplification. Binaural fitting may provide the most benefit, including balanced hearing, sound localization, directional hearing, and better speech understanding, particularly in the presence of background noise. Hearing aids, specifically designed for patients with high frequency hearing loss, are available that do not have the occlusive effect of conventional hearing aids. Besides hearing aids, other devices such as amplified telephones and portable amplification systems are available to amplify the sounds for patients with hearing loss. The efficacy of these devices in patients with post-RT SNHL has not been evaluated.
- *Cochlear implantation*. A cochlear implant provides direct electrical stimulation to the auditory nerve, bypassing the normal sound-transducing mechanism. Cochlear implants are effective when the auditory nerve is functionally intact. When treating nasopharyngeal carcinoma with RT, it has been reported that the retrocochlear pathway could remain intact despite the cochlea receiving greater than 60 Gy (Marangos et al. 2000; Formanek et al. 1998). Due to the risk of significant retrocochlear pathology after radiation damage, patients

who receive high doses of radiation may be worse off than other deaf patients (Jereczek-Fossa et al. 2003).

- *Auditory brainstem implants (ABI)*: The ABI functions by stimulation of ascending auditory pathways with minimal nonauditory effects through electrode placement in the vicinity of the ventral and dorsal cochlear nuclei (Brackman et al. 1993). ABI is indicated for bilaterally deaf patients with dysfunctional acoustic nerves (Kalamarides et al. 2001). Multi-electrode arrays allow different pitch perceptions and global use of the tonotopic organization of the cochlear nucleus complex. Speech discrimination can be achieved by optimizing the number of electrodes and correctly placing the ABI on the brainstem surface. Promising long-term results with ABI have been reported (Marangos et al. 2000). Hearing restoration with ABI after radiosurgery for NF2 has been reported after implantation at the time of tumor removal that progressed after radiosurgery (Kestler et al. 2001). The degenerative effect of radiation on the cochlear nuclei may reduce electrical induction of auditory sensation and may lead to an absence in auditory response after placement of ABI, thereby limiting its efficacy (Kalamarides et al. 2001; Slattery et al. 2003). More data are needed to evaluate ABI in patients subjected to either radiosurgery or fractionated RT.

10 Future Directions

10.1 The Chemoradiation Modification

The effect of chemoradiation needs further systematic investigation, although the limited data on cisplatin-radiation in the present literature suggest that radiation doses to the cochlea should be strictly limited when delivered with cisplatin (Bhandare et al. 2007; Chen et al. 1999).

While the use of alternative chemotherapy agents (e.g., carboplatin, oxaliplatin) may possibly reduce ototoxicity, their cytotoxicity to tumor cells and treatment efficacy in terms of the local control and survival benefit should be compared with that of cisplatin.

10.2 Dose-Reduction Methods

All ototoxicities of the outer, middle, and inner ear have been observed to be dose dependent (Bhandare et al. 2007; Jereczek-Fossa et al. 2003). The most important preventive measure is dose reduction. Dose reduction to all parts of the ear will reduce the incidence of morbidity.

Radiation-induced SNHL is dose dependent (Sataloff and Rosen 1994). Advanced, complex treatment modalities, such as intensity-modulated radiation therapy (IMRT) and proton beam therapy, may offer an advantage over conventional 3-dimentional or conformal RT in optimizing the dose to auditory systems. Early reports indicate a significant reduction in grade 3 and 4 ototoxicities after IMRT for head-and-neck tumors (Huang et al. 2002; Wolden et al. 2006). Studies using IMRT and inverse planning have shown that SNHL can be minimized or avoided altogether (Wolden et al. 2006; Park et al. 2004; Lin et al. 2000). Accurate delineation and identification of the components of the auditory system in CT-based treatment planning are necessary to protect the auditory apparatus from high doses of RT, particularly when dose escalation is desired and when the patients are subjected to concurrent or adjuvant chemotherapy.

10.3 The Effects of Fraction Size and Fractionation

Delayed radiation morbidities show a dependence to fraction size. An increase in fraction size above the standard fraction of 1.8–2 Gy has been associated with an increase in the incidence of delayed radiation complications. The effects of fraction size on the incidence of ototoxicities, particularly SNHL, have not been evaluated in the present literature. The information on the effects of fractionation (once daily or twice daily) remains limited (Bhandare et al. 2007). The effect of hyperfractionation on ototoxicity also needs further investigation.

10.4 Hypofractionation in SRS

Hypofractionation has been suggested to be promising, but its efficacy in SRS needs to be further studied. Further prospective investigation is needed into the effects of fractionation (SRS vs. FSRT with standard fractionation and hypofractionation), the location and length of the acoustic nerve relative to the tumor, and doses received by the acoustic nerve in the treatment of VS.

10.5 Grading of Ototoxicity

The assessment of ototoxicity in the current literature is qualitative and descriptive. Comparing results from the qualitative assessments is difficult. For a relative assessment, documentation and reporting of radiation-induced ear toxicity rely on a number of scoring systems that were developed in recent years. These systems have some limitations and modifications have been proposed for each of them. None of the systems have been widely used and validated in clinical practice. The Radiation Therapy

Oncology Group (RTOG) criteria (Table 4) can be applied for retrospective analysis. It is limited to acute complications but does not extend to late complications. Detailed late prospective assessment of delayed radiation-induced ototoxicity is addressed by the Late Management of Normal Tissue/Somatic Objective Management Analytic (LENT/SOMA) scoring system (Table 5). The limitations of this system include a lack of distinction among external, middle, and inner ear toxicity and a relatively narrow categorization of hearing loss (Jereczek-Fossa et al. 2003). While the National Cancer Institute Common Toxicity Criteria (NCI CTC) includes auditory side effects, the clinically significant but relatively smaller changes in hearing are not adequately addressed (Shotland et al. 2001). This system grades the post-RT changes to the external ear as radiation dermatitis (a dermatology and skin category) and earaches are categorized under the pain category (Jereczek-Fossa et al. 2003; Green and Weiss 1992). Changes to the NCI CTC scoring have been mainly applied to chemotherapy studies (Jereczek-Fossa et al. 2003; Shotland et al. 2001). Assessment and scoring of hearing status after SRS or SRT is carried out in terms of Gardner-Robertson grade (Table 7) and its variations (Table 6).

At present there is no comprehensive scoring system that sufficiently and adequately addresses outer, middle, and inner ear toxicities after RT. It is necessary that a comprehensive system be defined for evaluating, coding, and documenting ototoxicities that will facilitate uniformity in its estimation of an ototoxicity after RT.

11 Landmarks in History and Literature Review

11.1 Animal Research

Experimental Studies: The earliest experimental observations on the effect of ionizing radiation on the ear were in 1905 when Ewald (1905) exposed the ears of pigeons to radiation and reported its harmful effects on vestibular function, signs similar to extirpation of the labyrinth, with the severity of these signs varying with radiation exposure. Signs and symptoms of vestibular damage were also reported by Halbertstadter (1920) in 1920 after subjecting one side of the heads of mice to radiation. In 1933, Girden and Culler (Culler et al. 1933) were the first to investigate the effects of radiation on the hearing of dogs subjected to small doses of X-rays. They reported an increase in the hearing thresholds. Signs of vestibular and cerebellar damage after radiating rabbit heads were detailed by Russell et al. (1949). Gerstner et al. (1954) reported signs of RT destruction of the labyrinth and described it as labyrinthine syndrome. In 1957, Abdullin (1957) documented the delayed effects of single high-dose RT to the heads of pigeons and rabbits by marked postural disturbances such a opisthotonus, turning of the head to one side, and forced rotary movements. Kozlov (1958) in 1959 reported hearing impairment of 3.9–9.1 dB in frequency ranges of 0.5–8 kHz in guinea pigs. In 1965, McDonald et al. (1965) reported reduced post-rotatory nystagmus after local exposure of the inner ear of rabbits to alpha particle beams. The most common symptoms following RT of animals involve disturbances of equilibrium, which have been documented in a number of studies (Chilow 1927; Novotny 1951; Berg and Lindergren 1961; Levy and Quastler 1962).

In most experiments, animals were subjected to single large doses of radiation and their associated morbidity may be far removed from everyday fractionated clinical RT. Radiation delivered in a single dose has been estimated to be much more lethal than the equivalent amount administered over time using appropriate fractions (Dale 1985). Recently, Miller et al. (2009) compared the effects of RT (70.75 Gy over 25 fractions) against cisplatin and the combination of therapies using a model designed to mimic human treatment exposure. Five of six animals treated with RT alone developed severe SNHL in at least one ear. Animals that received only cisplatin showed no significant SNHL.

Among the earliest investigators who correlated experimental observations of RT to the ear with histology is Marx (1909) who, during his experiments, placed radium in pigeon middle ears and examined them over 12 months under microscope to find labyrinthine signs. He observed degenerative and atrophic changes in the sensory epithelium of the vestibule and crista ampullaris. Novotny (1951) reported a decrease in the hearing of guinea pigs, but did not observe changes in inner ear histology or labyrinthine pressure. Nylen et al. (1960) reported degenerative changes of the cochlear nerve, areas of bone necrosis, and soft-tissue damage of the middle ear of rats. Keleman (1963) reported extravasation of blood from the middle ear mucosa. Keleman (1963), Winther (1969), and Bohne et al. (1985) reported damage to the inner ear manifested by destruction to elements of the cochlear duct, organ of Corti, and their surroundings. Details of degenerative structural and pathologic changes in the cochlea affecting auditory function were described in numerous studies, including, Chilow (1927), Thielemann (1928), Berg and Lindgren (1961), Levy and Quastler (1962), and Gamble et al. (1968).

11.2 Human Studies

Moskovskaya (1960) reported the effects of radiation on vestibular function in patients. Borsanyi and Blanchard (1962) were the first to report SNHL following radiation in

14 patients who received doses in the range of 4,000–6,000 Roentgen for various head-and-neck cancers. Evaluation of pretreatment and immediate post-treatment audiograms noted small shifts in the threshold with the greatest change at 4 kHz and the least change at 2 kHz. One case of SNHL was reported, and a number of patients developed various degrees of recruitment during RT, most of which disappeared after RT was completed. None of the patients were followed-up for hearing evaluation after 1 year.

Leach (1965) in a survey of 56 head-and-neck cancer patients subjected to RT, reported that 20 (36 %) of the patients developed a hearing deficit. Dias (1966) reported a series of 29 patients treated with radiation of 1,000–18,000 Roentgen for a variety of head-and-neck tumors, with some patients showing various hearing disturbances and some showing serviceable hearing at a significant time interval after radiation. Moretti (1976) reported audiological data showing SNHL in 13 patients who received radical or post-surgery radiation and suggested that older subjects may be more susceptible to the effects of radiation.

Leach (1965) was the first to report the histology of a human temporal bone after radiation and deafness. Although Leach's report has been widely cited as an early example of radiation to the inner ear, there was gross infection throughout the middle ear, mastoid, and labyrinth, indicating that suppurative labyrinthitis was a possible cause. Gyorkey and Pollock (1960) reported avascular necrosis of the ossicular chain and CHL several years after RT. Hoistad et al. (1998) examined temporal bones from 5 patients who received a prescribed 50–70 Gy and observed loss of spiral ganglion cells and inner and outer hair cells, stria vascularis atrophy, and progressive vascular fibrosis.

These reports provide limited information on the differences in vulnerability between the sensory and supporting cells and on the individual sensory components (e.g., the saccule vs. the utricle vs. the cristae). Unfortunately, these studies have not established a consistent pattern of inner ear damage. This may be due to the different radiation exposures, time points of evaluation after exposure, methods of evaluation, and patient-related factors (e.g., age, genetics, and comorbidities).

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Late Oral Adverse Effects of Cancer Treatments

Sharon Elad and Cyril Meyerowitz

Contents

Abstract

This chapter describes the late adverse events of cancer therapy involving the oral tissues. A summary of the normal anatomy and physiology is followed by a review of the clinical presentation and management of the late oral adverse events in cancer patients. As the oral tissues involved are variable, the nature and quantity of late oral complications are extremely diverse. The impact of these oral complications can result in significantly debilitating basic oral functions, negatively affecting the quality of life. It is well recognized that surgery, chemotherapy and radiotherapy are associated with oral and maxillofacial morbidity. Furthermore, cancer therapy modalities have developed substantially over the years, resulting in newer types of radiotherapy, newer concept of hematopoietic stem cell transplantation, and emerging novel targeted therapy. These new modalities introduced a new set of oral complications, in addition to the classical oral complications attributed to surgery, chemotherapy and radiotherapy. Notably some of the essential supportive therapies (such as bisphosphonates) have oral complications as well. The clinical approach to these oral complications will be outlined.

1 Introduction

The oral cavity is composed of numerous structures each responding differently to cancer treatment (Fig. 1). The mucosa, salivary glands, taste buds, bone, teeth, periodontium, muscles, nerves, blood vessels, lymphatic tissue, connective tissue and cartilage together with the oral flora comprise what can be considered as a complex organ. The

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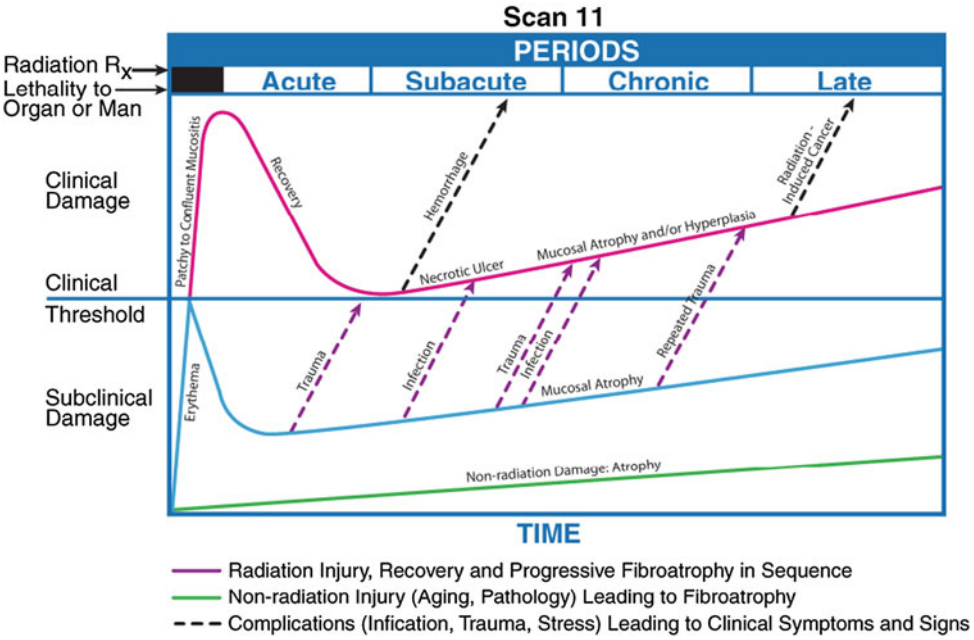


Fig. 1 Historic view on early and late mucosal effects related to radiotherapy (with permissions from Rubin and Casarett 1968)

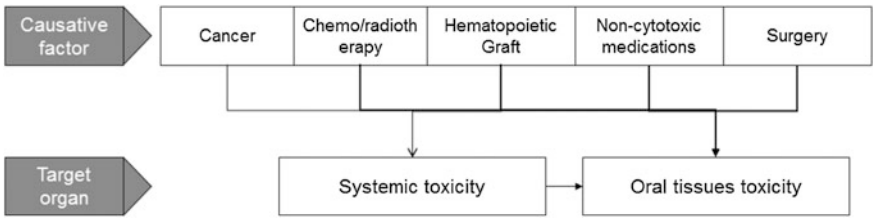


Fig. 2 Oral toxicities may be resulted from the cancer, treatment for the cancer, pharmacologic treatment for cancer complications or from systemic side-effects

simultaneous coordinated physiological activities of all these tissues enable essential oral functions. Impaired oral function has a tremendous negative impact on the well-being of patients.

Treatment for malignant disease produces unavoidable toxicities to normal cells. The oral tissues are highly susceptible to direct and indirect toxic effects of cancer chemotherapy and ionizing radiation. Some of the oral complications in cancer patients are related directly to the effects of chemo-radiotherapy on oral tissues and others are the indirect consequence of systemic toxicities (Fig. 2). Patients undergoing cancer treatment may develop oral complications associated with their modified immune status post hematopoietic stem cell transplantation (HSCT) or with the supportive care (e.g., bisphosphonate-related osteonecrosis). Surgical tumor removal may also cause oral and nutritional problems.

The tissue response depends on factors related to the form of cancer treatment and the patient. Treatment-related factors include: treatment modality (radiotherapy, chemotherapy, surgery, combination protocols, hematopoietic stem cell transplantation [HSCT]); the level of exposure to cytotoxic agents (e.g., intensity of protocol, field of radiation); and use of preventive measures. The patient-related factors include age, genetics, underlying malignant disease, immune status, co-morbidities, concurrent medications, nutritional status, history of previous cancer treatments, and compliance. Interaction of these elements governs the risk, course and severity of tissue injury.

With the emergence of new cancer treatments, the response is even more variable. For example, the introduction of reduced-intensity HSCT changed the profile of oral complications compared to those following myeloablative HSCT. Similarly, more advanced radiation technique may minimize some of the characteristic oral complications. Lastly, the introduction of targeted-therapy in oncology has caused a new series of oral complications.

Whereas the traditional bio-continuum of adverse effects (Fig. 1) was a linear progression from early acute oral complications to late chronic oral complications, the current understanding of the dynamics of the development of oral complications is multi-directional. Late complications may have an acute nature and vice versa. Tissue injury may be transient or permanent. The temporal behavior of each oral complication requires an appropriate clinical approach and patient education.

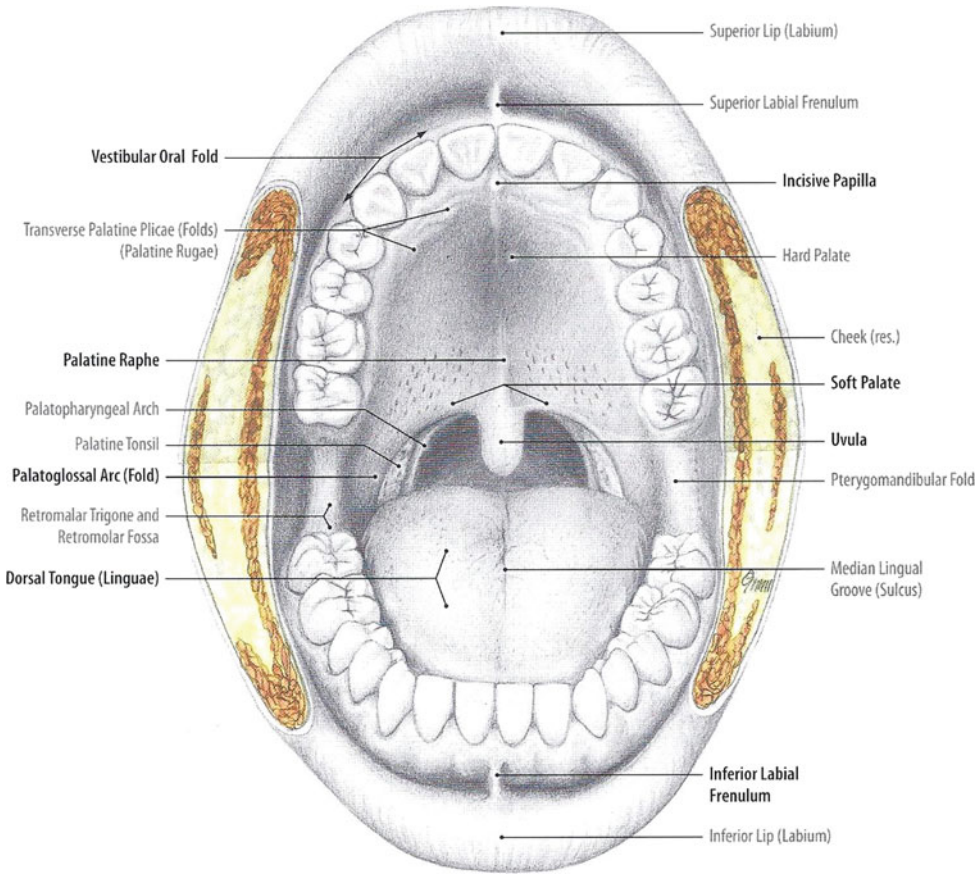


Fig. 3 Oral cavity: front view (With permission from Tillman and Elbermani 2007)

The late adverse oral effects, irrespective of their cause, are associated with loss of important oral functions such as eating, tasting, drinking, swallowing and speaking. Patients may also suffer dehydration, dysgeusia, ageusia, malnutrition and weight loss (Epstein et al. 2001, 2002). The patient's quality of life (QOL) can be severely affected, impacting their daily lives (Talmi 2002). When there are esthetic considerations such as mutilation or malformation, the impact on the psychological state of the patient can be profound (McMillan et al. 2004; Nordgren et al. 2008).

Details of the late oral complications in cancer patients are presented in this chapter, including their pathophysiology, clinical presentation, and potential treatment. According to the template of this textbook, a summary of the normal anatomy and physiology will provide the basis for understanding the pathology.

2 Anatomy and Histology

The oral cavity originates with the lips and extends posteriorly to the oropharynx (Fig. 3). It can be diagrammatically sketched as an elongated box with the cheeks contributing the side walls, the palate contributes the ceiling, and the floor of the mouth contributes the base. The supporting-frame for this three-dimensional box is composed of the dental arches positioned on the upper and lower jaw bones. Within this space lies the tongue. The oral mucosa covers the interior of the oral cavity, including the tongue, and merges into the gingival tissue covering the alveolar jaw bones. The major and minor salivary glands, the muscles, the blood vessels, the nerves, the lymphatic system and the taste buds are within the walls of the theoretic box structure of the oral cavity (Fig. 3).

Although the oral mucosa serves as a continuous coverage, the characteristic of the oral mucosal are not uniform through the oral cavity and are adjusted to the specific function of each oral surface. The mucous membranes of the oral cavity and pharynx are characterized as *masticatory, lining, or specialized*. The masticatory mucosa is bound down tightly by the lamina propria to the underlying bone. It covers the hard palate and gingiva and is characterized by keratinized epithelium that provides resistance to friction during mastication. The lining mucosa is characterized by non-keratinized epithelium, which provides flexibility and mobility that is needed during oral function. The specialized oral mucosa is found on the dorsum of the tongue and contains various types of papillae and taste buds (Fig. 4a).

The mucosal epithelium rests on a basement membrane. Below this, minor salivary glands and numerous small arteries, veins, and lymphatic vessels are found. Normal

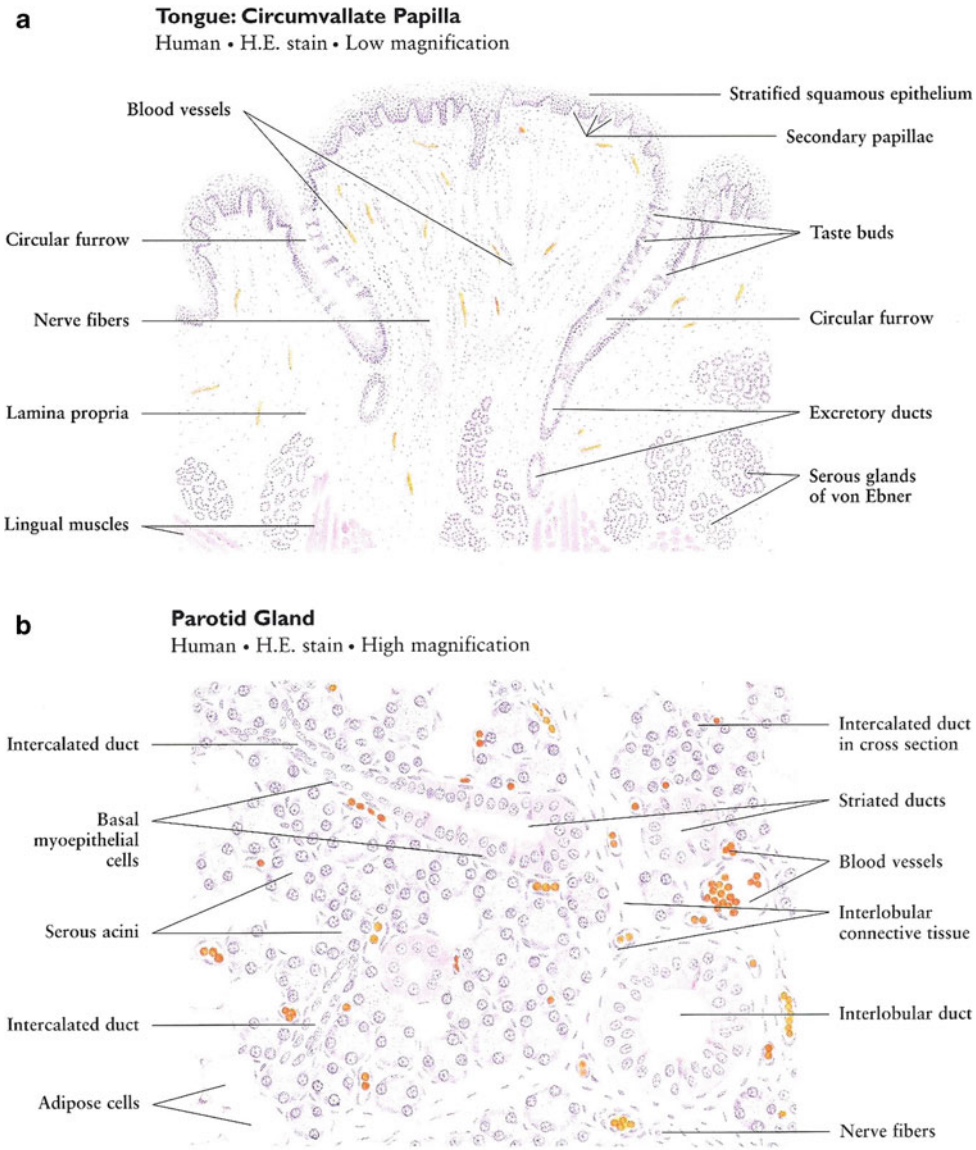


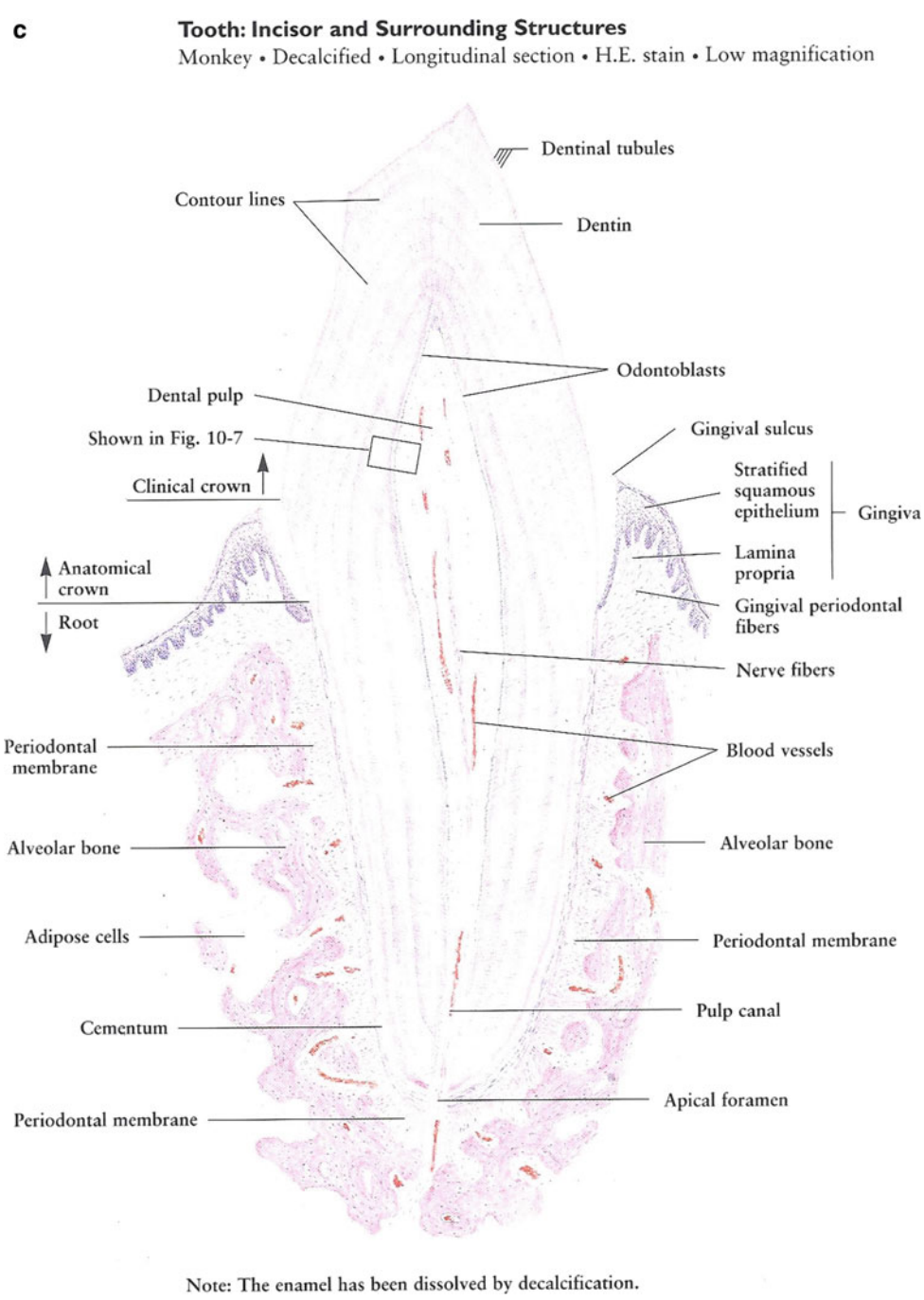
Fig. 4 **a** Tongue. **b** Parotid (With permission from Zhang 1999). **c** Tooth: Incisor and Surrounding Structures, decalcified, low magnification. (With permissions from Zhang 1999)

mucous membrane is pink to pale pink, depending on the thickness of the mucosal epithelium and amount of blood flowing through the underlying microvasculature.

There are three paired sets of major salivary glands—the parotid, submandibular, and sublingual glands—and hundreds of minor salivary glands scattered in the submucosa throughout the oral cavity, except the gingiva and anterior part of the maxilla. A typical salivary gland is a composite of numerous functional units: secretory end pieces known as acini, collecting ducts, and a framework of myoepithelial cells and connective tissue (Fig. 4b). There are two kinds of acinar cells, mucous and serous. Secretions from each of the acini pass through the intercalated ducts, then the striated (secretory) ducts and terminal lobar (excretory) ducts before traversing the major salivary duct into the oral cavity.

The main body of the tooth is made up of dentin (chemical composition of the calcium-phosphate-hydroxide apatite being 70 % inorganic and 30 % organic). Covering the crown portion of the tooth is the enamel (96 % inorganic, 4 % organic). The root portion is covered by cementum (50 % inorganic, 50 % organic), in which is imbedded protein fibrils that attach the tooth to the alveolar bone that surrounds the socket. The inner portion of the tooth—the pulp—is composed of blood vessels, lymphtics, nerves, and fibrous connective tissue (Fig. 4c). The tooth is embedded in alveolar bone. The compartment around the teeth is termed periodontium and the portion that supports the tooth in bone is the periodontal ligament. With aging and loss of teeth alveolar bone is physiologically resorbed.

Fig. 4 (continued)



The mandibular bone is characterized by cortical bone (lamellar bone and Haversian systems) that covers the spongy or marrow bone. The tooth sockets are lined by this compact bone. The posterior mandible (ramus) extends vertically ending in the condylar process that forms the temporomandibular joint, allowing opening and lateral movements for speech, mastication and expression.

The internal structure of mandibular bone responds to mechanical stresses by remodeling of marrow trabeculae, which are lined by osteoblasts and osteoclasts on the surface, and osteocytes in inner lacunae. The marrow itself contains blood vessels, fat, and fibrous connective tissue.

3 Physiology and Biology

The oral mucosa has an important role in protection as it creates a barrier between the oral environment and the circulation. Its capability to withstand friction allows food chewing and swallowing. Additionally, receptors in the oral

Table 1 Mucosa LENT SOMA

	Mucosa—oral and pharyngeal			
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Dysphagia	Difficulty eating solid food	Difficulty eating soft food	Can take liquids only	Totally unable to swallow
Taste alteration	Occasional, slight	Intermittent	Persistent	
Objective				
Mucosal integrity	Patchy atrophy or telangiectasia	Diffuse atrophy or telangiectasia, superficial ulcer	Deep ulcer no bone or cartilage exposure	Deep ulcer with bone or cartilage exposure
Weight	<5 % loss	>5–10 % loss	>10–15 % loss	>15 % loss
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Ulcer		Cleanse	Antibiotics or oxidants	Debridement + other surgical intervention
Dysphagia	Lubricants, diet modification	Non-narcotic	Narcotic	PEG tube and/or surgical intervention
Taste alteration	Minor diet changes (non-acidic)	Minor diet changes (semi-soft)	Major diet changes (soft)	Major diet changes (liquid)
Analytic				
Color photo	Assessment of changes in appearance			
Cytology, biopsy, imaging	Rule out persistent tumor			
Smear, culture, antifungal trial	Rule out candidiasis			

mucosa respond to temperature, touch and pain and the tongue has the unique capability of taste detection.

The salivary glands generate saliva which has important physiologic functions. It protects the oral cavity by providing a washing effect. This clearance of bacteria, debri and sugars, is important to prevent infection and the development of dental and periodontal diseases. Saliva lubricates the oral mucosal surfaces, allowing for tissue protection. Its flow, electrolytes composition and buffering effect, helps prevent demineralization of teeth. Saliva proteins, such as lysozyme, lactoferrin, peroxidase, and secretory immunoglobulin A, have an antimicrobial action. Other salivary molecules, such as mucins and agglutinins, aggregate microorganisms and prevent them from adhering to the oral tissues. Additionally, saliva is important for taste perception and for digestion of the food. Lastly, the moistening of the oral cavity allows for speech and breathing.

Both the teeth and jaw bones are essential for mastication, intelligible speech, swallowing, appearance, and expressions.

Within the complex structure of the mouth, the biofilm of saliva and oral flora is an invisible component that is integrated into the normal physiology of this entire organ. The oral flora is characterized by harmonious interaction between hundreds of bacteria and fungi. This co-existence may alter during changes due to an exogenous triggers (e.g., antibiotics) or endogenous change (e.g., immunosuppression). Some of the normal oral micro-organisms may turn into opportunistic micro-pathogens when the harmonious balance between various oral residents is interrupted.

4 Clinical Presentation

4.1 Overview

Previous editions of this book addressed the oral mucosa, the salivary glands and the teeth and mandible (i.e., jaw bone). This clinical approach is based on the LENT SOMA system that categorizes and grades various toxicities (Tables 1, 2, and 3), and does not differentiate between early and late adverse events. As evidence-based data on oral complications of cancer patients expanded, scales were published for specific oral complications. Several global scales are currently used. For example, the National Cancer Institute published an update for the Common Toxicity Criteria for Adverse Events (CTC-AE ver. 4.0) and a new

Table 2 Salivary gland LENT SOMA

	Salivary gland			
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Xerostomia	Occasional dryness	Partial but persistent dryness	Complete dryness, non-debilitating	Complete dryness, debilitating
Objective				
Saliva	Normal moisture	Scant saliva	Absence of moisture, sticky, viscous saliva	Absence of moisture, coated mucosa
Management				
Xerostomia		Occasional saliva substitute Sugarless candy or gum, Sialogogues	Frequent saliva substitute or water Sugarless candy or gum, Sialogogues	Needs saliva substitute or water in order to eat Sugarless candy or gum, Sialogogues
Analytic				
Salivary flow/quantity/ stimulation	76–95 % of pre-treatment	51–75 %of pre-treatment	26–50 % of pre-treatment	0–25 % of pre-treatment

Table 3 Mandible[a] LENT SOMA

	Mandible			
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Mastication		Difficulty with solids	Difficulty with soft foods	
Denture use		Loose dentures	Inability to use dentures	
Trismus	Noted but unmeasurable	Preventing normal eating	Difficulty eating	Inadequate oral intake
Objective				
Exposed bone		< 2 cm	> 2 cm or limited sequestration	Fracture
Trismus		1–2 cm opening	0.5–1 cm opening	<0.5 cm opening
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention or resection
Exposed bone		Antibiotics	Debridement, hbo2	Resection
Trismus and mastication		Soft diet	Liquid diet, Antibiotics, Muscle relaxant meds	NG tube, gastrostomy
Analytic				
Mandibular radiograph	Questionable changes or none	Osteoporosis (radiolucent)	Sequestra	Fracture
		Osteosclerosis (radiodense)		
Panograph X-rays/ CT	Assessment of necrosis progression			

[a] Refers to the dentition, both jaws and the masticatory system

version is expected in the near future. Selected items from the CTC-AE are presented in Table 4.

Additional scales are listed in the RTOC website.

In this edition, common oral complications will be presented, including oral mucosal alterations (late-mucosal injury and cGVHD), taste disorders, salivary gland dysfunctions, infections, neuropathy and chronic pain, complications of the dentition and periodontium, trismus and loss of elasticity, osteoradionecrosis and osteonecrosis, developmental abnormalities and secondary malignancies.

Table 4 Common Toxicity Criteria for Adverse Events (CTC-AE ver. 4.0)

Adverse event	1	2	3	4	5	Definition
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	–	–	Disorder characterized by inflammation of the lip
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	–	–	A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow > 0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1–0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva < 0.1 ml/min	–	–	A disorder characterized by reduced salivary flow in the oral cavity
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	Disorder characterized by difficulty in swallowing
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	–	–	Disorder characterized by a sensation of marked discomfort in the gingival region
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–	A disorder characterized by a sensation of marked discomfort of the lip
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the oral mucosal
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site

(continued)

Table 4 (continued)

Adverse event	1	2	3	4	5	Definition
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	–	–	A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	Disorder characterized by bleeding from the mouth
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	–	–	A disorder in the gingival tissue around the teeth
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death	Disorder characterized by inflammation of the salivary duct
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	Disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	–	–	A disorder characterized by a pathological process of the teeth occurring during tooth development
Tooth discoloration	Surface stains	–	–	–	–	A disorder characterized by a change in tooth hue or tint
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–	A disorder characterized by a sensation of marked discomfort in the tooth

Selected items relevant to late oral complications

Table 5 Late oral complications post radiotherapy

Tissue involved	Type of cancer treatment				Oral complications
	CT	RT	HSCT	Surgery	
Oral mucosa	X	X	X		Mucosal changes
	X		X		Secondary oral infections
			X		Mucosal GVHD (lichenoid/plaque type)
	X	X	X		Secondary malignancy
Taste buds	X	X	X		Taste disorders
Salivary glands	X	X	X		Dry mouth
	X	X	X		Sialoadenitis
			X		Multiple mucocele
	X	X	X		Secondary oral infections
	X	X	X		Secondary malignancy
Teeth	X	X	X		Rampant caries
	X	X	X		Dental malformations
	?	X	X		Cervical sensitivity
Periodontium		?	?		Advanced periodontitis
			X		Desquamative gingivitis
Connective tissue and musculature		X	X	X	Trismus
		X	X	X	Loss of elasticity
		X	X	X	Limited mouth opening
Bone (jaw)		X			Osteoradionecrosis
	X		X		Bisphosphonate-related osteonecrosis
	X	X	X	X	Developmental malformations
Nerve	X	X	X	X	Neuropathy and chronic pain

May concur at any time: dysphagia, oral dysfunction (eating, drinking, speech), dehydration
CT-chemotherapy, RT-radiotherapy, HSCT-hematopoietic stem cell transplantation

The association between the various toxicities and therapies is provided in Table 5.

4.2 Oral Mucosal Alterations

The prominent effects of cancer treatment on the oral mucosa are seen in the early period following treatment and results in oral mucositis. Once mucositis has developed, the oral mucosa is more susceptible to the toxic effects of a second cycle of RT or CT (Sonis 2007). This clinical observation is supported by histomorphological evaluations of oral mucosal specimens taken from patients 6 to 12 months after RT. A decreased number of blood vessels, different expression patterns of adhesion molecules and subpopulations of integrins and macrophages are found (Prott et al. 2002). Patients complaining of a burning sensation months after their acute mucositis has apparently healed support this observation.

Targeted therapy was associated with various oral complications. Recently drugs belong to the Mammalian Target of rapamycin (mTOR) inhibitors were associated with aphthous-like oral lesions, mostly sirolimus, everolimus and temsirolimus. Other oral symptoms, such as dysphagia, dry mouth and dysguesia were reported in relation to mTOR inhibitors as well. Furthermore, additional groups of targeted therapies, such as monoclonal antibodies (cetuximab, bevacizumab) and tyrosine kinase inhibitors (sunitinib, sorafenib, and imatinib) were suggested to have oral adverse events.

Patients post allogeneic HSCT may develop oral mucosal GVHD. GVHD is an allo-immune inflammatory process, which results from a donor-origin cellular response against host tissues. The chronic form of GVHD (cGVHD) occurs in 30–50 % of allogneic transplants and oral involvement is seen in up to 80 % of them (Schubert and Correa 2008). The clinical presentation includes lichenoiod, erythematous, or ulcerative lesions which may be occasionally asymptomatic, but more often is associated with pain, burning sensations, or a rough texture of the oral surfaces. Painful mucosal lesions may represent a significant impediment to nutritional intake and performing oral hygiene.

Clinical examination of the oral tissues can support the diagnosis of GVHD. Correlation of oral changes with systemic manifestations should be considered, although the

Table 6 NIH scale for oral cGVHD activity assessment

Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema Lichenhold Ulcers Mucoceles[a]	None	0	Mild enythema or moderate erythema (< 25 %)	1	Moderate (> 25 %) or Severe erythema (< 25 %)	2	Servere erythema (25 %)	3
	None	0	Hyperkeratotic changes (< 25 %)	1	Hyperkeratotic changes (25–20 %)	2	Hyperkeratotic changes (50 %)	3
	None	0	None	0	Uicers involving (20 %)	3	Servere ulcerations (20 %)	6
	None	0	1–5 mucoceles	1	6–10 scattered mucocel3es	2	Over 10 mucoceles	3
							Total score for all mucosa chages	

http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXAFormA.pdf

[a] Mucoceles scored for lower labial and soft palate only

oral cavity may be the only site affected. Histopathologic evaluation may be complementary to clinical evaluation (Bradley et al. 2003). Scoring of oral cGVHD was addressed by the NIH in 2006 (Pavletic et al. 2006) (Table 6). Other scales may be used for research (Piboonniyom et al. 2005; Elad et al. 2003).

Importantly, GVHD is one of the potential risk factors associated with the development of secondary solid cancers including those presenting in the head and neck area (see "Secondary Malignancy").

4.3 Taste Disorders

When the oral and pharyngeal mucosa is exposed to radiation, taste receptors are damaged and taste discrimination becomes increasingly compromised (National Cancer Institute 2008; Ruo Redda and Allis 2006; Gamper et al. 2012; Epstein et al. 2010). Loss of saliva flow (hyposalivation) impairs the transport and solubilization of gustatory stimulants to the taste buds, which leads to taste disorders. The outcome may be a reduction in taste sensitivity (hypogeusia), absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia). Studies in RT patients showed mixed results about the pattern of taste impairment. Some studies showed that sensitivity to sweet mainly decreases and that sensitivity to bitter increases. Others showed that sensitivity to bitter and salty simulants is mainly decreased (Ruo Redda and Allis 2006) and that umami was the only taste to be impaired (Shi et al. 2004).

After 3–4 weeks of radiation it is common for patients to complain of an absence of a sense of taste. It will generally take upwards of several months after the end of radiation therapy for taste receptors to recover and become functional, but it may require up to 2 years (Ruo Redda and Allis 2006).

Radioactive iodine in the form of (Paulino et al. 2000) I^{131} is used to treat thyroid cancer and reportedly causes taste alterations in approximately 10 % of patients (Rosenbluth et al. 2005, Lee JN et al. 2010).

Most commonly used cytotoxic agents have been linked to chemosensory disorders (Comeau et al. 2001; Bernhardson et al. 2007; Berteretche et al. 2004), and are known to damage chemosensory structures and disrupt saliva and mucus production, which indirectly affects the sense of taste (Schiffman and Zervakis 2002). Research into the side effects of cytotoxic chemotherapies indicates that 46–77 % of patients receiving chemotherapy report changes in taste (Lindley et al. 1999; Foltz et al. 1996; Rhodes et al. 1994; Wickham et al. 1999; Youngblood et al. 1994). However, most of these changes resolve within a few months after chemotherapy ends with little long-term impact (Bernhardson et al. 2007).

Approximately 20 % of patients 90–100 days post HSCT report moderate to severe levels of taste change (Epstein et al. 2002). More patients report reduced intensity of taste and abnormal tastes. However, it seems that these taste changes have a limited impact on QOL (Epstein et al. 2002). In patients 24–30 months post HSCT taste changes are also noted (Marinone et al. 1991). In patients that received allogeneic transplants, hypogeusia to salt and sour, but no difference in sweet or bitter are reported. In recipients of autologous transplants statistically significant taste changes are seen (Marinone et al. 1991). These finding are ambiguous as other studies show recovery in 80 % of patients 1 year-post HSCT (Mattsson et al. 1992). It is important to note that in pediatric patients undergoing HSCT taste changes may resolve faster (Cohen et al. 2012).

4.4 Salivary Gland Dysfunction

Long-term salivary gland dysfunction is a common complication of cancer treatment, predominantly in RT and in allogeneic HSCT patients. Salivary gland impairment is also well recognized following CT, and generally recovers within 6 months (Chaushu et al. 1995).

The RT-induced damage to the salivary gland results in a quantitative and qualitative change in saliva. Consequently, there is loss of salivary function, reduction in salivary flow and symptoms of dry mouth. The irradiated volume of salivary gland tissue correlates directly with the severity of oral complications (Cheng et al. 1981; Eisbruch et al. 1999; Roesink et al. 2001). The bottom range of the mean doses which have been found to cause significant salivary flow reduction is from 26 to 39 Gy (Roesink et al. 2001; Eisbruch et al. 2001). Changes in quantity of saliva occur shortly after radiotherapy. With cumulative RT dose of 60–70 Gy, more irreversible extensive damage to salivary flow rate is detected (Vissink et al. 2003). The implementation of alternative fractionation schedules, like hyper fractionation and accelerated fractionation has only a negligible positive effect on salivary gland function and morphology in animal models (Vissink et al. 2003; Price et al. 1995; Coppes et al. 2002). However, evidence in humans shows that xerostomia (a sensation of decreased saliva) is worse in accelerated fractionation compared to conventional fractionation (Awwad et al. 2002).

The introduction of IMRT allows more accurate delivery of a specific radiation dose to the tumor and spares the surrounding tissues, including major salivary glands. There is much encouraging data suggesting that salivary gland impairment is reduced by using IMRT compared to traditional radiotherapy techniques (Rathod et al. 2013). A systematic review concluded that the benefits of IMRT on salivary gland function, xerostomia, and xerostomia-related QOL are most pronounced late ($\geq$ 6 months) after radiotherapy and there are improvements in xerostomia-related QOL over time (Jensen et al. 2010).

It is unclear yet what the sparing effect of novel radiation techniques such as cyberknife, protons and carbon ions is (Thariat et al. 2011).

Dry mouth in HSCT patients is a multifactorial condition. The most common etiologies are the conditioning regimen, chronic GVHD (cGVHD) and chronic administration of medication. In addition altered oral intake may be associated with dehydration.

(1) *The conditioning regimen*: Salivary secretion is substantially reduced during the conditioning stage of HSCT (Chaushu et al. 1995). Gradual flow rate recovery typically begins a few days following HSCT. Patients conditioned with chemotherapy or chemotherapy and total lymph node irradiation display earlier and complete recovery of saliva secretions 2–5 months after engraftment. Recovery is delayed and incomplete when total body irradiation (TBI) is added to the conditioning regimen, suggesting that TBI induces irreversible damage to the parotid glands resulting in permanent hyposalivation (Chaushu et al. 1995).
(2) *GVHD*: 60 % of cGVHD patients experience hyposalivation and a direct correlation is observed between the degree of hyposalivation and the severity of GVHD (Nagler et al. 1996; Alborghetti et al. 2005).
(3) *Chronic medication use*: As the vast majority of HSCT patients remain under polypharmacy treatment, the added risk of drug-induced dry mouth, in addition to the impact of the cGVHD, exists.

Cancer treatment and cGVHD also result in a change of salivary composition. Clinically, saliva color becomes yellowish to brownish, mucoid, sticky and viscous. The qualitative changes in saliva include increased viscosity, reduced buffering capacity, altered salivary electrolyte concentrations, and increased levels of anti-bacterial proteins including sIgA, lysozyme and lactoferin (Vissink et al. 2003; Makkonen et al. 1986; Valdez et al. 1993; Izutsu et al. 1985; Hiroki et al. 1994; Nagler et al. 1996). When flow rates and buffer capacity is diminished, salivary pH is lowered. In the presence of food containing fermentable carbohydrates, plaque pH is decreased and the lack of clearance, due to decreased salivary flow, inhibits the rise of the plaque pH back to normal levels. The prolonged low pH environment impairs the balance between demineralization and remineralization predisposing to greater demineralization and results in dental caries. In the absence of preventive therapy, primarily fluoride, the dental caries progress very rapidly (see following paragraphs about "Dentition and Periodontium"). In addition, the acidic plaque pH provides optimal conditions for the shift of the oral flora to a cariogenic flora (Brown et al. 1975). Since the decrease in salivary flow rate is greater than the increase in immunoprotein and lysozyme levels, a significant immunoprotein deficit compromises saliva's protective role (Kielbassa et al. 2006).

Patients complaining about xerostomia often describe that the discomfort increases during night and that adhesion of the tongue to the palate necessitates repeated arousal to drink water during their night sleep. This polydypsia lead to nocturnal polyuria. Clinical evaluation will reveal a dry appearance of the oral mucosa. In extreme oral dryness the oral mucosa may be atrophic, erythematous and fissured. Some patients may describe episodic painful swelling of the salivary glands, which is usually caused by retrograde infection due to the absence of the washing effect of saliva in the salivary ducts. When such an acute sialoadentitis exists, the salivary gland region may be swollen, the

covering skin may be erythematous and tender, and salivary expression upon milking will be missing.

The typical manifestation of cGVHD involving the minor salivary glands is multiple mucoceles, with labial and soft-palate mucosa being the most frequently involved sites. Mucoceles often cause a disturbed sensation in the mouth but not pain (Schubert et al. 2004). In rare cases mucoceles may evolve into a large mucocele or ranule.

Hyposalivation has multiple additional consequences (Schubert and Correa 2008; Vissink et al. 2003). Oral function such as speech, chewing and swallowing, is negatively affected due to insufficient wetting and lubrication of the mucosal surfaces, as well as insufficient moistening of the food by saliva. These conditions lead to increased friction of the mucosal surfaces and a tendency to easily traumatize the oral mucosa. In edentulous patients hyposalivation causes intolerance to prosthetic appliances and reduced retentiveness of the prosthesis. Additionally lack of saliva predisposes the patients to oral infections, most commonly candidal infection.

Oral assessment of patients with xerostomia should include a thorough evaluation of oral tissues, salivary flow rate and, when necessary, imaging to rule out local salivary gland obliteration. However, the data on the radiation-induced severe drop in flow rate of both the parotid and submandibular glands does not correspond to the functional data derived from scintigraphic studies (Liem et al. 1996). Therefore, it is suggested that the combination of measurement of salivary flow rate and patient questionnaires is preferred for assessment of xerostomia over scintigraphic studies (Vissink et al. 2003).

4.5 Infections

Viral, bacterial and fungal infections are common in cancer patients and may manifest years after cancer therapy (Belazi et al. 2004; Redding et al. 1999).

Candidal infection is the most prevalent oral fungal infection in cancer patients, either post-RT or post-CT. The diminished amount of saliva, the lack of salivary immunoproteins and the lack of washing affect predisposes these patients to infections. The clinical presentations include pseudomembranous candidiasis (thrush), erythematous candidiasis (red appearance), hyperplastic candidiasis (white tissue overgrowth) and angular cheilitis (redness at the corners of the mouth).

Herpes Simplex Virus (HSV) reactivation, is common in CT and HSCT patients but rarely occurs during radiation therapy (Epstein et al. 2002). Most of the viral infections occur when the white blood count drops. Typically the lips and keratinized mucosa are affected, however, during periods of immunosuppression other oral mucosal surfaces also be affected. The clinical presentation ranges from single to numerous vesicles to isolated confluent extensive ulcerations.

Bacterial infections are common during immunosuppression, which can persist or recur in patients post chemotherapy or HSCT. The micropathogens isolated most frequently are Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae and Staphylococcus aureus. There is no characteristic clinical presentation; however, a non-specific ulceration should raise the index of suspicion for bacterial infection.

Infected and ulcerated periodontal pockets may be a niche for a wide variety of microorganisms, bacterial cell wall components and pro-inflammatory cytokines that may translocate into adjacent anatomical structures or the blood stream and induce systemic infectious complications (Raber-Durlacher et al. 2002; Benoliel et al. 2007; Epstein et al. 2007). However, this risk in patients treated with irradiation is probably not as large as in patients administered chemotherapy, due to the relatively minor systemic immunosuppression that RT induces.

4.6 Neuropathy and Chronic Pain

Chronic pain and specifically neuropathy are frequent in cancer management protocols (surgery, RT, CT and HSCT). In addition to the effect of cancer treatment, orofacial pain can be related to the recurrence of cancer (Benoliel et al. 2007).

Postradiation neuropathy (sensory or motor) is well documented following the treatment of head and neck cancers; the interval between treatment and onset ranges from 1 to 10 years, and radiation dosages from 62.5 to 100 Gy (Benoliel et al. 2007; Epstein et al. 2007; Mizobuchi and Kincaid 2003; King et al. 1999). The incidence of neuropathy varies with protocols used and areas irradiated (Chen et al. 2007; Kang et al. 2000; van Wilgen et al. 2004; LeCouteur et al. 1989).

Radiation induced peripheral nerve injury may occur by at least 4 mechanisms: Direct damage to neural tissues by high dose irradiation is one mechanism observed in experimental animal models; Electron microscopy findings are suggestive of axon damage and subsequent nerve fiber loss due to radiation induced hypoxia as a mechanism of late radiation injury to the peripheral nerve (Vujaskovic 1997), particularly large nerve fibers at doses higher than 20 Gy; Radiation is also known to suppress proliferation of Schwann cells (Love et al. 1986); and lastly, connective tissue fibrosis has been postulated to mediate neuropathy (Kang et al. 2000).

Surgically related pain involves inflammatory and neuropathic pain mechanisms and is dependent on the extent of surgery and its anatomic location. Functional consequences are often secondary to pain, but may involve wound

contractures and scarring (Epstein et al. 2007; Gellrich et al. 2002). In a series of patients that underwent neck dissection, with and without radiotherapy, for head and neck cancer, persistent neck pain and loss of sensation were commonly encountered (van Wilgen et al. 2004). Myofascial pain was most commonly detected (46 %), and correlated to the extent of dissection. Neuropathic pain of the neck was present in 32 % and correlated with radiotherapy and dissection level. Patients with neuropathic pain experienced symptoms (hyperpathia, allodynia) during everyday activities such as shaving, exposure to wind or low temperatures. Loss of sensation of the neck was present in 65 % and was also related to type of neck dissection and radiation therapy.

Surgery to orofacial structures increases the risk for neuropathy and chronic pain. Resection of the mandible for tumor excision will inevitably lead to sensory impairment (Chow and Teh 2000), with 50 % experiencing regional hyperalgesia or allodynia. It has been reported that at 2–5 years post maxillectomy 88–90 % of patients report persistent pain (Rogers et al. 2003). In an analysis of patients treated for laryngeal cancer, ablative surgery (with adjuvant chemo- and/or radiotherapy) was associated with more chronic pain and psychosocial morbidity than in patients treated by chemoradiation alone (Terrell et al. 1999), underscoring the negative effects of tissue loss on pain and psychosocial well-being. Fortunately there is a tendency for symptoms to improve with time (Hammerlid et al. 2001). At 54–60 months post-surgery, about 15 % have persistent pain in any of the above sites (Gellrich et al. 2002). Long term H&N cancer survivors (> 3 years) still suffer from significantly more pain and functional problems than matched control subjects, but with a relatively quicker return to normal general function and mental health (Hammerlid et al. 2001; Hammerlid and Taft 2001).

Some cytotoxic agents may cause jaw pain and neuropathy. Most of these drugs are administered for a limited duration and thus have no long-term effect (e.g., vincristine, vinblastine, platinum) (Hilkens et al. 1997). Additionally non-cytotoxic drugs often employed in cancer treatment (e.g., interferons, thalidomide) or in supportive protocols (e.g., amphotericin-B) also induce paresthesias and other sensory neuropathies (Benoliel et al. 2007). Significant oral neuropathies seem unusual (Elad et al. 1997; Zadik et al. 2010).

4.7 Dentition and Periodontium

In the absence of effective preventive regimens, advanced dental caries is observed in patients with dry mouth. This is mostly seen in patients post RT or in patients suffering from cGVHD of the salivary glands. This form of dental caries progress rapidly and is typically localized at the cervical aspects of the teeth. However, it has been noted that accelerated dental caries can be present in other cancer patient populations, including patients post CT, though to a lesser extent. For example, in a comparison of cancer pediatric patients to their siblings, the long-term survivors had a significantly higher number of decayed surfaces as compared with their siblings (Duggal et al. 1997).

As has been described before, dental-caries risk increases secondary to a number of factors including decreased clearance and prolonged plaque pH depressions, shifts to a cariogenic flora, reduced concentrations of salivary antimicrobial proteins, and loss of mineralizing components (Kielbassa et al. 2006; Silverman 2003). Tooth hypersensitivity which is observed in many of cancer patients may be due to the same mechanisms but occur before dental decay is clinically obvious (Kielbassa et al. 2006). There are no histological differences between initial radiation caries lesions and healthy incipient lesions and the demineralization and remineralization mechanisms appear to be the same for both (Kielbassa et al. 2006).

A number of studies show that periodontal attachment loss and tooth loss due to periodontal disease is greater in irradiated areas than in non-radiated areas. The periodontal impairment is manifested in increased probing depth, increased recession on the facial aspects and increased mobility of teeth (Epstein et al. 1998; Marques and Dib 2004). This periodontal response to RT is probably due to decreased vascularity and acellularity of the periodontal membrane with rupturing, thickening, and disorientation of Sharpey's fibers and widening of the periodontal space (Vissink et al. 2003).

The long-term effects of chemotherapy are of less concern than those associated with high dose radiation therapy, because chemotherapy effects are reversible. In neutropenic patients, acute exacerbations of chronic periodontal disease can be potentially life threatening requiring aggressive antimicrobial therapy (Epstein and Stevenson-Moore 2001).

Data are scarce about the risk of periodontal disease post HSCT. Pattni et al. did not find periodontal health to be decreased when patients were followed 6 months post allogeneic HSCT and no significant alterations in the prevalence of periodontal pathogens occurred during the study period (Pattni et al. 2000). However, this study included patients that were relatively periodontally healthy prior to HSCT and follow up time was short. A recent study reported that the risk of developing dental caries or periodontal attachment loss after transplant is associated with HLA type (Dobr et al. 2007). There is anecdotic evidence that periodontal infection may trigger GVHD and oral GVHD ameliorates when periodontal treatment is provided (Schubert and Correa 2008). While no clinical trial addressed the association of GVHD and periodontal disease fully, it is noteworthy that one of the typical presentations of oral cGVHD is desquamative gingivitis. The combination of chronic inflammation with long-

term steroid treatment may lead to gingival atrophy. The vulnerable atrophic gums may deteriorate and the patient may present with advanced gingival recession.

These findings emphasize the need for proper periodontal treatment. Mechanical oral hygiene procedures, such as brushing and flossing, to remove the etiologic factors of inflammatory periodontal disease are beneficial (Epstein and Stevenson-Moore 2001).

4.8 Trismus and Loss of Elasticity

Trismus may be caused by fibrosis of the muscles of mastication after high-dose RT to the oral cavity or oropharynx (Manon et al. 2008). A systematic review of trismus in head and neck oncology showed that radiotherapy (follow-up: 6–12 months), involving the structures of the temporomandibular joint and or pterygoid muscles, reduces mouth opening by 18 % (Dijkstra et al. 2004).

The underlying disease and the surgery may amplify tissue fibrosis. Perioral fibrosis may limit mouth opening, thus significantly impacting the quality of life of the patient. In addition to difficulty with oral intake, trismus may compromise speech, oral hygiene, tumor surveillance, the ability to safely secure an airway and may increase the risk of aspiration. Furthermore, in patients who use an obturator after maxillectomy, trismus may limit proper postoperative maintenance of the appliance (Bhrany et al. 2007).

Motor deficits following HSCT are not uncommon, and have two major etiologies, the most dominant being cGVHD of sclerodema-like type, which is less common than the lichenoid type. However, it may deteriorate into an inability to activate the mastication apparatus. Scleroderma-tous changes can result in perioral fibrosis that decreases oral opening and limited tongue movement, interfering with oral function (Schubert and Correa 2008). TBI administered during the conditioning regimen is a contributing factor for fibrosis and limitation of mouth opening. However, the effect of radiotherapy in the doses typically used in myeloablative HSCT (1,200 Gy), is not as pronounced compared to those typically used to treat head and neck cancers (4,500–7,000 Gy). The effect of TBI is most pronounced when administered at young age (Dahllof et al. 1994).

4.9 Osteoradionecrosis and Osteonecrosis of the Jaws

Osteoradionecrosis (ORN) is a relatively uncommon clinical entity related to hypocellularity, hypovascularity, and ischemia, with a higher incidence after cumulative radiation doses to the bone which exceed 65 Gy (Vissink et al. 2003). This process may be spontaneous, but it is usually related to trauma such as a tooth extraction and may progress to pathological fracture, infection of surrounding soft tissues, and severe pain. The risk of ORN does not diminish over time and may even increase.

Bisphosphonates are commonly prescribed for the treatment of hypercalcemia associated with breast and prostate cancers, osteolysis associated with metastatic bone disease, especially multiple myeloma, Paget's disease, and for the treatment and prevention of post-menopausal corticosteroid-induced osteoporosis (Lindsay 2001). Since late 2003, there have been reports a possible association between bisphosphonate use and the appearance of osteonecrosis of the jaw (ONJ) (Pogrel 2004; Wang et al. 2003). Clinical signs and symptoms of this pathological process are pain, erythema, bone exposure, fistula, purulent secretion, sensory abnormality or swelling (Khosla et al. 2007). These may deteriorate into pathological jaw fractures, oro-antral fistulae, and airway obstruction. The impact on the quality of life is extreme as all essential oral functions are affected.

ONJ probably results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiologic stress (mastication), iatrogenic trauma (tooth extraction or denture-induced local injury), or tooth infection in an environment that is both trauma-intense and bacteria-laden. Coexisting factors may include the use of other medications with anti-angiogenic properties such as glucocorticoids, diabetes mellitus, irradiation of the jawbone, peripheral vascular disease and hyperviscosity syndrome (Khamaisi et al. 2007).

The incidence of ONJ is higher if intravenous bisphosphonates are administered, compared to oral bisphosphonates and the risk increases with duration of exposure. The reported frequency of ONJ ranges from 0.6 to 6.2 % in breast cancer patients, from 0 to 18 % in prostate cancer patients, and from 1.7 to 15 % in patients with multiple myeloma (Hoff et al. 2011). The incidence of ONJ is 1.5 % among patients treated with these agents for 4–12 months, rising to 7.7 % after treatment for 37–48 months (Bamias et al. 2005).

The American Association of Oral and Maxillofacial Surgeons position paper outlined a staging system (Ruggiero 2009).

- At risk: No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates.
- Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms.
- Stage 1: Exposed and necrotic bone in asymptomatic patients without evidence of infection.
- Stage 2: Exposed and necrotic bone associated with infection and pain and erythema in the region of exposed bone with or without purulent discharge.
- Stage 3: Exposed and necrotic bone in patients with pain and infection and one or more of the following: exposed and necrotic bone extending beyond the region of

alveolar bone, (i.e., inferior border and ramus of the mandible, maxillary sinus and zygoma) resulting in pathological fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor.

Osteonecrosis may be associated to medications other than bisphosphonates, such as denozumab, bevacizumab and sunitinib is new (Hellstein et al. 2011; Sivolella et al. 2013). It seems that the overall incidence of denosumab-related ONJ is similar to that of bisphosphonate-related ONJ. The incidence of ONJ due to the anti-angiogenic drugs is lower. Although this complication is considered rare following bevacizumab or sunitinib, its seriousness requires taking a cautious approach and avoiding risk factors known in bisphosphonates-related ONJ.

4.10 Developmental Abnormalities

Skeletal and dental growth abnormalities may result in patients that are treated with irradiation during their childhood or adolescence. For this reason RT is nowadays avoided in this population. Several studies about the late effect in long-term survivors of children cancer have been reported (Paulino et al. 2000; Duggal et al. 1997; van der Pas-van Voskuilen et al. 2009; Otmani 2007; Duggal 2003; Oguz et al. 2004).

Disturbances in odontogenesis in irradiated pediatric patients result in microdontia, short or blunted roots, small crowns, incomplete calcification, enlarged pulp chambers, premature closure of apices and delayed, hypodontia or arrested development of teeth. These changes in the teeth can cause malocclusions (Otmani 2007; Duggal 2003).

Long term effects of HSCT on dental development in children are observed in nearly all patients examined, including agenesis, short roots, and arrested root development (van der Pas-van Voskuilen et al. 2009; Dahllof et al. 1989). In one study, children who were under 3 years of age at the start of cytotoxic treatment presented with the highest number of missing teeth (van der Pas-van Voskuilen et al. 2009). Another study identified 5 years of age at the start of cytotoxic treatment as the age in which most severe disturbances are found (Dahllof et al. 2001). The observation that the most severe disturbances takes place between the ages of 3–5 is compatible with the fact that calcification of permanent teeth starts approximately at the time of birth. Root formation is completed after the tooth has erupted into the oral cavity. During active growth teeth are susceptible to environmental disturbances; similar long-term effects on dental structures were reported in children with non-Hodgkin lymphoma, including enamel discoloration (Oguz et al. 2004).

The development of the craniofacial skeletal structures may be abnormal (Otmani 2007; Denys et al. 1998; Karsila-Tenovuo et al. 2001; Gevorgyan et al. 2007). These changes are secondary to the effects of radiation on cartilaginous growth centers located in condyles of the mandible and on the sutural growth centers of the maxilla. Such skeletal abnormalities include mandibular and maxillary hypoplasia (Paulino et al. 2000). Facial growth is affected by lower doses of RT, such as the doses given in the conditioning regimen to the HSCT. Significant reductions in length of both jaws and a decrease in the alveolar height have been observed (Dahllof et al. 1994). Craniofacial and dental abnormalities can cause severe cosmetic or functional sequelae, necessitating surgical or orthodontic intervention.

4.11 Secondary Malignancy

Secondary malignancies in the oral tissues have been reported, particularly in HSCT patients. Data are also available for patients post RT to the head and neck.

Patients undergoing allogeneic HSCT are at a high risk of developing secondary neoplasms. Studies assessing the risk of cancer among long-term survivors of HSCT have demonstrated a low but significant risk of secondary neoplasms, with the reported incidence being 4–7 fold that of the general population (Bhatia et al. 1996; Witherspoon et al. 1989). Malignancies occurring after HSCT may be of hematologic or lymphoproliferative origin, or may be solid tumors. The first category is relatively frequent and develops early in the post-transplant period, while secondary solid tumors are less common and the incidence appears to increase over time (Demarosi et al. 2005).

Post-transplantation lymphoproliferative disorder (PTLD) has been defined by the WHO as a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in a recipient of a solid organ or bone marrow allograft (Harris et al. 2001). PTLD is associated with compromised immune function and Epstein–Barr virus infection (Bhatia et al. 1996; Witherspoon et al. 1989). Manifestations of PTLD include lymphoma-related B-symptoms, compression of organs and anatomical structures by the malignant mass or a disease mimicking viral infection (Micallef et al. 1998; Loren et al. 2003). Oral involvement of PTLD is rare. Most oral presentations are reported for PTLD following solid organ transplantation (Elad et al. 2008; Ojha et al. 2008). PTLD manifesting as a gingival crater-like defect and an ulcerated dark-red mass has been reported post HSCT (Elad et al. 2008; Raut et al. 2000).

Since the oral cavity is one of the most prevalent sites for solid cancers post-HSCT, oral cancer is not as rare as oral PTLD (Curtis et al. 1997). The risk of new oral cancer post-HSCT is increased 11-fold in patients post allogeneic HSCT; however this increases 70-fold in over 10 year survivors; (Bhatia et al. 1996; Witherspoon et al. 1989;

Curtis et al. 1997) The vast majority of cases are oral squamous cell carcinoma (Demarosi et al. 2005). Salivary gland tumors are reported as well (Curtis et al. 1997).

The risk for any solid cancer following HSCT, including oral cancer, is higher for recipients who are younger at the time of transplantation than for those who are older and for patients treated with higher doses of TBI. Furthermore, specific risk factors for oral cancer has been identified, including cGVHD (Demarosi et al. 2005; Curtis et al. 1997). GVHD treatment may also be associated with the development of cancer (Deeg et al. 1996).

Additional risk factors have been suggested contributing to the development of post-transplant neoplasms, including being male (Demarosi et al. 2005), viral infection and antigenic stimulation by viral or donor-recipient histocompatibility differences, and genetic predisposition (Demarosi et al. 2005).

The nature of oral cancer in GVHD patients is aggressive, and tends to include repeating primary tumors and multifocality (Mawardi et al. 2011). Therefore, in cGVHD patients vigilant follow-up and coordination of care are critical.

Of special interest are patients with Fanconi Anemia (FA) who undergo HSCT. FA long-term survivors of HSCT have increased risk of solid tumors, particularly of the oral cavity, which is even higher than the already high "baseline" risk of neoplasia in untransplanted FA patients (Alter 2005). Most of these cancers are squamous cell carcinomas.

The carcinogenic effect of ionizing radiation has long been recognized. The latent interval between RT and the development of cancer varies from several to many years. Early studies concluded that moderate or high-dose RT did not produce any new squamous cell carcinomas of the oral mucosa (Loprinzi et al. 2004). A later study showed contrary trends with radiation becoming a risk factor after 10 years of follow-up for solid cancers of the oral cavity, pharynx, esophagus, lung (2.8, 5.9, 3.9, 1.5 times fold than in the healthy population, respectively), and after 1–5 years of follow-up for second primary leukemia (2.5 times fold than in the healthy population) (Hashibe et al. 2005).

An association has been noted between RT and thyroid tumors. The latent period is usually 10–30 years. Almost all reported cases have followed low doses of RT (Loprinzi et al. 2004). Not all thyroid neoplasms after RT are malignant, and many of the malignant neoplasms that do develop are curable with surgery.

5 Management

5.1 General Preventive Dental Care

Prior to the initiation of cancer treatment, especially head and neck RT and myelocytotoxic chemotherapy, a thorough oral and dental evaluation, including radiographic imaging, should be performed. The treatment plan should aim to remove or minimize potential sources of infection in order to prevent immediate infections and late complications (Bradley et al. 2003; Manon et al. 2008). Dental prophylaxis including scaling, root cleaning, and polishing reduces the number of potential sites of infections. Patient education in oral hygiene techniques is of utmost important. Patient should perform thorough oral hygiene measures, using a soft toothbrush and floss or an interproximal brush, and a fluoridated toothpaste. In addition they should use a topical fluoride rinse or gel daily (Bradley et al. 2003; Rankin 2008). Custom-made dental fluoride trays can be fabricated, and the daily application of a neutral 1.1 % sodium fluoride gel or a 0.4 % stannous fluoride gel should be recommended. Neutral pH fluoride products are designed to reduce irritation to the oral mucosa.

Several products may curb demineralization and enhancing remineralization (Papas et al. 2008). For example a supersaturated Ca–P rinse, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), or casein derivatives complexed with calcium phosphate (CD-CP). Human in situ studies have shown that casein products are buffered by saliva which stabilizes and localizes amorphous calcium phosphate in the plaque and maintains a state of supersaturation compared to enamel (Reynolds et al. 2008).

Restorative dental procedures including endodontic treatment should be performed for restorable teeth. Sharp dental cusps or anything that could cause intra-oral trauma should be eliminated in order to minimize mucosal injury during RT. Poor restorations with loose contact points should be repaired in order to prevent food impaction and papillitis. Alternatively, patients should be instructed to keep meticulous oral hygiene using interproximal dental hygiene aids.

Before RT, dentition in poor condition should be considered for extraction to minimize the subsequent risk of osteoradionecrosis. Such teeth include teeth in high-dose radiation areas that demonstrate significant periodontal disease, advanced caries, dentoalveolar abscess and apically involved teeth within the radiation field or teeth that are unrestorable. In addition, impacted teeth and teeth that have no antagonist to oppose should be considered for extraction. Poor oral hygiene is a factor supporting the extraction of teeth that are marginal. Gingival morphology resulting in an operculum, which creates a sanctuary for micropathogens, should be considered for operculectomy or extraction of the involved tooth. A similar approach is appropriate prior to initiation of therapy with bisphosphonate, denosumab and anti-angiogenic agents.

Timing of the dental treatment is a factor to consider. The optimum management for the patient receiving chemotherapy requires that the patient be seen by the dental

practitioner before chemotherapy begins. In general, oral care should be completed at least 1 week before chemotherapy starts. This will leave approximately 2 weeks before the patient will be at greatest risk of oral complications (Bradley et al. 2003). If an extraction is required, neutrophil count and platelet count will be critical. With neutrophil counts of $> 2{,}000/mm^3$ and platelet counts $> 75{,}000/mm^3$, no other preoperative interventions are necessary. However, if counts are lower, supplementation may be needed, such as prophylactic antibiotics, injection of granulocyte growth factor or platelet transfusion. It is advantageous to the patient to set this baseline before the initiation of CT.

After RT, patients should be monitored frequently. Dental routine procedures can be performed (Loprinzi et al. 2004). However, invasive periodontal or surgical procedures should be avoided. When the surgical procedure is necessary, atraumatic techniques should be utilized and primary closure should be obtained. Prophylactic antibiotics should be considered and hyperbaric oxygen may be an adjuvant according to well-known protocols (Bradley et al. 2003; Koga et al. 2008; Rankin 2008).

After chemotherapy the dental recall schedule should enable the implementation of optimal preventive measures (Bradley et al. 2003; Rankin 2008). Prior to any dental intervention hematologic status should be determined. Optimal oral health should be maintained, especially in light of the potential to have future myelosuppression episodes.

During the first 100 days after HSCT the patient is at increased risk for multiple complications. These complications are reduced after day 100 and decrease thereafter. Therefore, up to 100 days post-transplant, only emergency oral care should be delivered (Bradley et al. 2003). From 100 to 365 days post-transplant the spectrum of dental treatment can be extended. After 365 days post-transplant routine dental care can be provided with adjustments of the dental treatment plan, if manifestations of cGVHD are present.

5.2 Oral Mucosal Alterations

During late post-therapy period most CT- or RT-induced ulceration has resolved and chronic pain is managed using topical or systemic pharmacologic interventions. The first line of treatment is topical anesthetics (e.g., viscous xylocaine). However their efficacy for chronic pain is limited. The efficacy of mixtures of topical anesthetics with antihistamines, coating agents, anti-inflammatory or antibiotics to prevent secondary infections has been reported in the literature. Sometimes pain requires treatment with systemic analgesics or narcotics. Scrupulous hygiene is essential to prevent secondary infections.

Management of oral GVHD includes appropriate systemic therapy combined with proper oral hygiene and use of topical drugs (Schubert and Correa 2008; Imanguli et al. 2006). Because extensive cGVHD often involves multiple organs, systemic treatment is indicated. Systemic therapy starts with steroids and, if unsuccessful, other immunosuppressive agents or immunomodulators, such as azathioprine, mycophenolate mofetil and thalidomide, are used alone or in combination (Imanguli et al. 2006). Topical treatment is needed when the oral mucosa does not respond to high doses of systemic corticosteroids or when the only lesions are on the oral mucosa (Couriel et al. 2006). In general, topical steroid preparations, such as flucinonide and clobetasol gel, and steroid elixirs (dexamethasone or betamethasone), are used as local treatment for GVHD. Budesonide is a highly potent steroid and its very low bioavailability when absorbed through mucosal surfaces minimizes systemic side effects. (Elad et al. 2003; Sari et al. 2007; Elad et al. 2012) Additional approaches to the local management of oral GVHD may be considered, including topical anti-inflammatory and immunosuppressive agents such as azathioprine (Epstein et al. 2001). cyclosporine (Epstein and Truelove 1996; Eckardt et al. 2004), and oral psoralen plus ultraviolet A (PUVA) therapy (Redding et al. 1998). Other local modalities including CO_2 laser and ultraviolet B (UVB) have been employed with anecdotal reports of success (Elad et al. 1999).

5.3 Taste Disorders

Although sporadic studies suggest the benefits of certain interventions, two systematic reviews failed to demonstrate any significant improvement in dysgeusia (National Cancer Institute 2008; Ruo Redda and Allis 2006; Hovan et al. 2010; Gamper et al. 2012).

Amifostine, a cytoprotective agent, has been used during radio-chemotherapy to prevent the loss of taste (Loprinzi et al. 2004; Vissink et al. 2003; Buntzel et al. 2002), however the results are questionable because of the heterogeneity of the study populations.

Zinc sulfate supplements reportedly help with taste recovery (National Cancer Institute 2008), however others found this supplements ineffective (Halyard et al. 2007).

Dietary counseling helps adaptation to the loss of taste and serves to prevent reduced food intake which results in weight loss and nutritional deficiencies.

5.4 Salivary Gland Dysfunction

The most effective intervention for hyposalivation is its prevention. Prevention of RT damage to the salivary glands

is best achieved by limiting the areas exposed to radiation using three-dimensional treatment planning and conformal dose-delivery techniques (Hazuka et al. 1993; Nishioka et al. 1997; Henson et al. 2001). IMRT reduces the incidence of late salivary gland toxicity (Eisbruch et al. 2001; Wu et al. 2000; Saarilahti et al. 2005; Pacholke et al. 2005; Chambers et al. 2007). Of secondary importance, as a preventive strategy, is the pharmacological stimulation of salivary flow with sialogogues (Zimmerman et al. 1997). Continuous pilocarpine administration may protect the glands (Vissink et al. 2003). The benefits of pilocarpine may be due to stimulation of the minor salivary glands or parts of the major salivary glands (Vissink et al. 2003). According to the MASCC/ISOO systematic review, early use of pilocarpine to prevent the salivary gland damage is not supported by consistent evidence and therefore is not recommended (Jensen et al. 2010). Another strategy to spare the salivary glands is the use of a radioprotector such as amifostine (a free-radical scavenger) (Antonadou et al. 2002; McDonald et al. 1994). Unfortunately multiple side-effects of this drug, together with the potential protection of the tumor impede its acceptance. An unusual technique reported to prevent RT damage to the salivary glands is surgical transfer of the submandibular gland (out of the radiation field) prior to RT (Seikaly et al. 2001). The long-term outcomes of this technique showed prevention of xerostomia in 83 % of the patients 2 years post RT (Seikaly et al. 2004). Based on a systematic review it was suggested that the obtained level of sparing by submandibular salivary gland transfer might be of clinical significance (Jensen et al. 2010).

Once it occurs, treatment of chronic xerostomia essentially relies upon the use of saliva substitutes for palliation and/or mechanical, gustatory or chemical sialogogues to stimulate the flow rate.

Water and glycerin preparations, or commercially prepared "artificial saliva" are used. Newer artificial saliva solutions added electrolytes and enzymes to mimic the natural consistency of saliva.

Several pharmacologic sialogugous have been reviewed in the literature. (Vissink et al. 2003; Dirix et al. 2006) The use of several agents has been reported including bromhexine, anethole-trithione, bethanechol chloride, potassium iodide, neostigmine, and reserpine. However, the side effects of these agents led patients and clinicians to abandon them.

Pilocarpine has been widely used for the last three decades in RT and HSCT patients (Singhal et al. 1995). Pilocarpine is a cholinergic stimulant that acts on postganglionic cells that enervate smooth muscles and exocrine glands (e.g., the sweat and salivary glands). Best results were obtained with continuous treatment for 8–12 weeks with doses > 2.5 mg three times per day. There was no major drug-related toxicity. Residual functional salivary gland parenchyma is needed in order for any sialogogue to be effective.

In recent years cevimeline, a cholinergic stimulant, has gained recognition for its effectiveness and with fewer side effects (Petrone et al. 2002; Chambers et al. 2007; Carpenter et al. 2006). Cevimeline acts on M3 muscarinic receptors which are mainly found in the salivary and lacrimal glands, therefore it has minimal limited effects on the lungs and heart, which have M2 and M4 muscarinic receptors (Nieuw Amerongen and Veerman 2003). Gustatory stimuli with an acid-tasting substance and tactile stimuli with chewing gum can increase salivary secretion and may be an important component in the palliation of xerostomia (Dirix et al. 2006; Olsson et al. 1991). Another principal component of palliation is saliva substitute solutions, gels or sprays (Dirix et al. 2006; Momm et al. 2005). However, the moistening effect of saliva substitutes is of limited duration, and therefore patients often use water. Hypnosis, guided imagery and acupuncture may assist some patients (Braga et al. 2008). Gene transfer technology is currently being investigated and may open new therapeutic opportunities for these patients (Cotrim et al. 2006).

5.5 Infections

Oral infections can be prevented by good oral hygiene, routine rinsing and moistening of the oral cavity and, when indicated, anti-fungals, anti-virals or anti-bacterials. Various topical and systemic medications are available. There seems to be evidence supporting the use of systemic antifungal and anti-viral agents, but clearly these medications have side effects (Lalla et al. 2010; Elad et al. 2010.

5.6 Neuropathy and Chronic Pain

Treatment depends on the type of chronic pain as suggested by the American Headache Society (AHS) and International Association for the Study of Pain (IASP). It includes tricyclic-antidepressants, gabapentine and its derivatives (Benoliel et al. 2007; Merskey and Bogduk 1994). For drug-induced neuropathy, dose-adjustment of suspected drug is needed. Physiotherapy may relieve post-operative musculoskeletal pain (Benoliel et al. 2007; Epstein et al. 2007).

5.7 Dentition and Periodontium

Treatment strategies must be directed to each component of the caries process. The frequency of consumption of fermentable carbohydrates should be reduced. Optimal oral hygiene must be maintained. Xerostomia should be managed whenever possible via salivary substitutes or

stimulants. Caries resistance can be enhanced with use of topical fluorides and/or remineralizing agents (Meyerowitz and Watson 1998; Meyerowitz et al. 1991). Efficacy of topical products may be enhanced by increased contact time on the teeth by application using vinyl carriers (National Cancer Institute 2008; Chambers et al. 2007; Dirix et al. 2006; Hay and Thomson 2002). If carious lesions develop, removal and restoration should take place immediately.

Whenever possible, teeth should be retained to support tooth-borne appliances. Although tissue-borne prostheses are not contraindicated, mucosa that appears fibrosed, telangiectatic, and atrophic is at greater risk of subsequent damage from prostheses. The periodontium should be maintained in optimal condition by periodic routine periodontal care. There are no particular contraindications for endodontic procedures.

5.8 Trismus and Loss of Elasticity

Physical therapy interventions such as mandibular stretching exercises as well as prosthetic aids designed to reduce the severity of fibrosis are beneficial (Dijkstra et al. 2004; Bensadoun et al. 2010). This appears to be particularly useful in the prevention of trismus because once contraction occurs, such maneuvers are far less effective. Less expensive tongue blades may be inserted between the teeth to increase the interincisor distance until slight pain is encountered. The exercises should be performed for 30 s every few hours, and heating the muscle area before and after exercise may increase flexibility. Anti-inflammatory and muscle relaxant drugs may be prescribed in selected cases (Bradley et al. 2003). Microcurrent electrotherapy and pentoxifylline significantly increase mouth opening, but these modalities are rarely employed (Dijkstra et al. 2004). A recent paper describing a limited intra-oral surgical approach in an oral cGVHD patient reported success (Treister et al. 2012).

5.9 Osteoradionecrosis and Osteonecrosis of the Jaws

Often conservative treatment of ORN with antibiotics and surgical debridement is unsuccessful. Hyperbaric oxygen is highly effective in the treatment of ORN (National Cancer Institute 2008; Harding et al. 2008). The boost of oxygenation in the irradiated poorly healing wounds is probably the explanation for this. Hyperbaric oxygen stimulates angiogenesis, with increased neovascularization and optimization of cellular levels of oxygen for osteoblast and fibroblast proliferation, collagen formation, and support of ingrowing blood vessels. The hypoxic, acellular matrix in the postirradiated field is changed to a hypercellular, hyperoxic/normoxic situation (Myers and Marx 1990). Furthermore, hyperbaric oxygen –based preventive protocol are accepted as a standard of care before dental extraction and include 20 or more presurgical HBO treatments and 10 or more postsurgical HBO treatments. If ORN is diagnosed, protocol calls for 1 compression/decompression cycle per day for 5 days per week. Patients who meet the definition of ORN begin with staged treatment (Bradley et al. 2003):

- Stage I: If the wound shows definitive clinical improvement after 30 compression/decompression cycles, the patient is given a full course of 60 compression/decompression cycles. If there is no improvement after 30 compression/decompression cycles, the patient is advanced to stage II.
- Stage II: A transoral alveolar sequestrectomy with primary closure is done and the compression/decompression cycles are resumed. If healing progresses without complication, a total of 60 compression/decompression cycles are completed. If there is incomplete healing, the patient is advanced to stage III.
- Stage III: The patient undergoes a resection of the necrotic bone, the margins of which are determined by the presence of bleeding bone or by TCN fluorescence. Compression/decompression cycles are continued until healthy mucosal closure is obtained or a total of 60 compression/decompression cycles are given. The patient is then advanced to stage III-R. A patient can enter this stage directly if he/she presents with a pathologic fracture, orocutaneous fistula, or radiographic evidence of resorption to the inferior border. An initial course of 30 compression/decompression cycles are given in these cases.
- Stage III-R: Ten weeks after resection, 20 additional compression/decompression cycles are given and bone graft reconstruction is accomplished from a transcutaneous approach.

Several position papers on the presentation, predisposition, prevention and recommendations for treatment of osteonecrosis of the jaw in patients receiving bisphosphonates have recently been published (Khosla et al. 2007; Ruggiero 2009; Migliorati et al. 2005). The underlying principle is prevention of ONJ since no curative treatment is available. The main goal of treatment is palliation and infection control. Surgery other than the removal of loose bony sequestra, without exposing uninvolved bone, is to be avoided. Empiric antibiotic regimens have been implemented for various durations.

5.10 Developmental Abnormalities

Orthodontic treatment may be required in case of disturbed orofacial growth. A study in long-term survivors after pediatric HSCT showed that ideal treatment results were not

always achieved. The patients sample was too small to conclude the reason for this unsatisfactory result (Dahllof et al. 2001). Yet the orthodontic treatment did not produce any harmful side effects, even though most of the treated children exhibited severe preexisting disturbances in dental development (Dahllof et al. 2001).

5.11 Secondary Malignancy

Treatment for PTLD consists of anti-viral medication and reduction of immunosuppression, which may lead to complete resolution of PTLD. Treatment may include intervention with chemotherapy and/or radiotherapy, cytokines (interferon or Interleukin-6), intravenous immunoglobulins, anti-B cell antibodies or cellular immunotherapy (Loren et al. 2003). Surgery may be considered when the lesion is accessible.

Lifelong surveillance is imperative in cGVHD patients because of the increased cancer risk over time after transplantation. Frequency of recalls is higher when a dysplastic or malignant lesion is diagnosed. In addition, it is crucial that patients should avoid carcinogenic exposures, such as smoking. The treatment of oral cancer following HSCT generally follows the standards in non-HSCT patients. However, it is unclear if the use of RT in patients with GVHD will further increase the risk for secondary oral cancer.

6 Future Research

The field of oral medicine in oncology patients is broad and there are many topics of research. New frontiers include:

1. Validation of a predictive salivary function model that will enable the development of specific preventive measures. The extent of tissue sparing and preservation of salivary gland function by the new radiotherapy techniques is unknown.
2. Identification of markers that determine the risk for osteonecrosis of the jaws may facilitate the formulation of a protective algorithm that can be adjusted to meet the needs of specific sub-population. Genetics may be a key factor in this form of personalized medicine.
3. Considering the chronic nature of GVHD and its diffuse variable presentation, sophisticated microscopic imaging tools, such as confocal microscopy, may allow early detection of potentially malignant lesions. Development of targeted focal treatments such as photodynamic therapy may address the multi-focality and the recurrence of oral cancers.

7 Summary

Given early and more refine diagnosis of cancer patients and the efficacy of anti-cancer therapies, the number of long-term cancer survivors has increased. In addition, the number of patients undergoing HSCT has steadily increased. Improvement in survival rate following HSCT has resulted in a need to assess issues related to long-term complications. Cancer treatments lead to substantial oral and dental complications. Early and comprehensive dental treatment and oral care is essential and it requires a multidisciplinary health team. Attention to dental and oral health before and after cancer therapy can ensure that important oral functions, such as eating, talking, swallowing and speaking are maintained for the remainder of the cancer patient's life.

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Upper Respiratory and Digestive System: Pharynx, Larynx, and Xerostomia

Post-Radiation Dysphagia Toxicity After Irradiation of Larynx: Laryngeal Edema and Vocal Dysfunction Xerostomia After Irradiation of Head and Neck Cancer

Bharat Mittal, Yuhchyau Chen, and Avraham Eisbruch

Contents

Abstract

The head and neck includes multiple structures which play a role in deglutition, swallowing, saliva production, and senses. Many of these structures are highly sensitive to various treatment modalities and their damage following therapy leads frequently to functional abnormalities such as xerostomia, dysphagia, aspiration, hearing loss, and others, reducing substantially the quality of life of survivors. The anatomy of these organs, their tolerance levels to therapy, and recent efforts to reduce their dysfunction are detailed in this chapter.

1 Introduction

The anatomic separation of the upper respiratory systems from the upper digestive system is optimally designed at birth. The infant's ability to breast feed and drink in a supine position is possible because the epiglottis and larynx are elevated into the nasopharynx, so swallowing and breathing are separated. Four legged animals as the fox and wolf enjoy this separation of pharynx and larynx enabling them to simultaneously hold their prey in their mouths while running and respiring. When an infant becomes a child, then an adolescent, the assumption of vertical posture and becoming bipedal results in the separation and descent of the larynx. Thus, the admonition of not talking and eating at the same time since aspiration of food while swallowing is highly likely to occur. This is the basis for exploring the anatomy, histology, and physiology of each component: the pharynx and larynx together rather than separately. Furthermore, the cancers arising in one region invades the other as the malignancy advances and infiltrates. Combined modality

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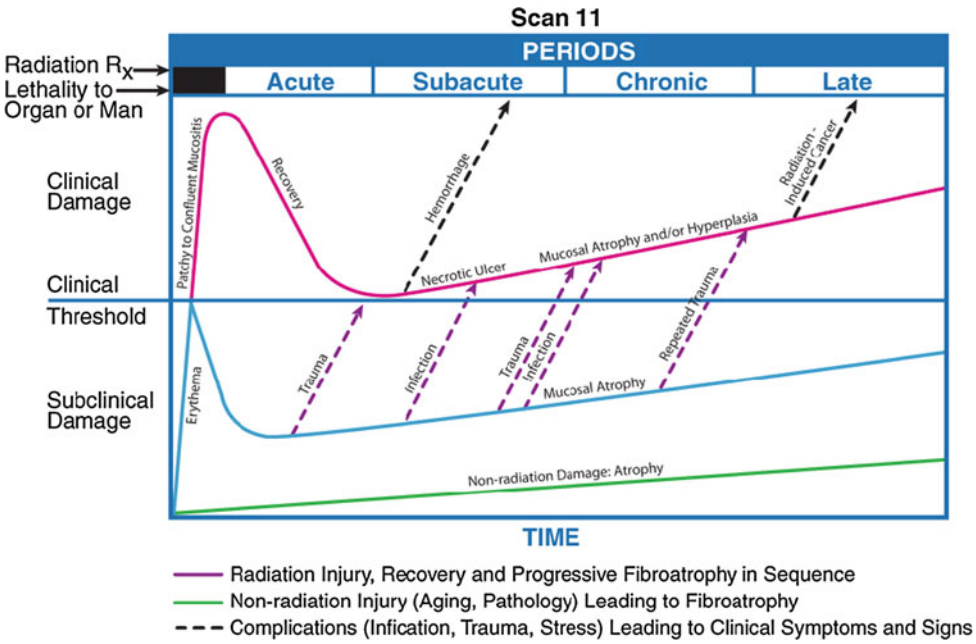

Fig. 1 Biocontinuum of adverse early and late effects of the upper digestive and respiratory system (with permission from Rubin and Casarett 1968)

treatment is designed to achieve normal tissue preservation since the process of savoring and swallowing food and wine and maintaining the ability to talk and converse are both essential and pleasurable to our well being. Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy of the Pharynx and Larynx

The pharynx is a fibromuscular tube extending from the base of the skull to the esophagus, regulating the flow of food and air in the upper aerodigestive passage (Fig. 2). The pharynx is composed of three sections: (i) the nasal, (ii) the oral, and (iii) the laryngeal pharynx.

In the coronal plane from a retropharyngeal view: There are four major sphincters in the pharynx that regulate the passage of air and food to their ultimate destinations. The sphincters, at the point of the entry, are the buccopharyngeal sphincters guarding the communication between the mouth and the pharynx (fauces). They are formed by the base of the tongue and the oropharyngeal bar, which is produced by a synchronized peristaltic contraction of the posterior oropharyngeal muscular wall.

The hypopharynx is the lower continuation of the pharyngeal tube and is anatomically defined laterally and posteriorly by the middle and inferior constrictor muscles and anteriorly by the hyoid bone, thyroid, and cricoid cartilage. If the larynx were postnasal, anatomy would be less complex and the oropharynx and hypopharynx functionally and structurally would be one. The descent of the larynx transforms the tube into a series of symmetrical gutters surrounding the larynx. In the coronal plane from a retropharyngeal view, the hypopharynx is best understood anatomically from a posterior coronal view, obtained by separating the inferior constrictor muscles at the midline. The hypopharyngeal sphincters and the piriform recesses circumvent the larynx to lead food into the esophagus. The recurrent laryngeal nerve enters the larynx and can be trapped by piriform sinus cancers (Rubib and Hansen 2007).

The larynx is divided into three parts: (i) supraglottis, (ii) glottis, and (iii) subglottis; these three parts are known as the vestibule, ventricle (glottis), and infraglottic cavity. The epiglottis is readily visualized at its vestibule. The opening of the larynx, referred to as the aditus larynges or the superior laryngeal aperture, can be traced from the epiglottis to the arytenoids. The aryepiglottic folds start at the free edge of the epiglottis and terminate at the corniculate and arytenoids cartilages. The false cords and the true cords are separated by the ventricle. The true cords act as a sphincter that closes off the airway (Rubin and Hansen 2007).

2.2 Histology of the Pharynx and Larynx

Pharynx: The pharyngeal mucosa consists of nonkeratinized stratified squamous epithelium. The epiglottis contrasts the transition from the pharyngeal to laryngeal mucosa. On the oral side, the epithelium is thick with connective tissue papillae beneath it. On the laryngeal side, however, the epithelium is much thinner and has no papillae. The laryngeal side is also characterized by taste buds scattered among the epithelial cells. At the base of the epiglottis on the laryngeal side, the stratified squamous epithelium undergoes a transition into ciliated pseudostratified columnar epithelium (Fig. 3).

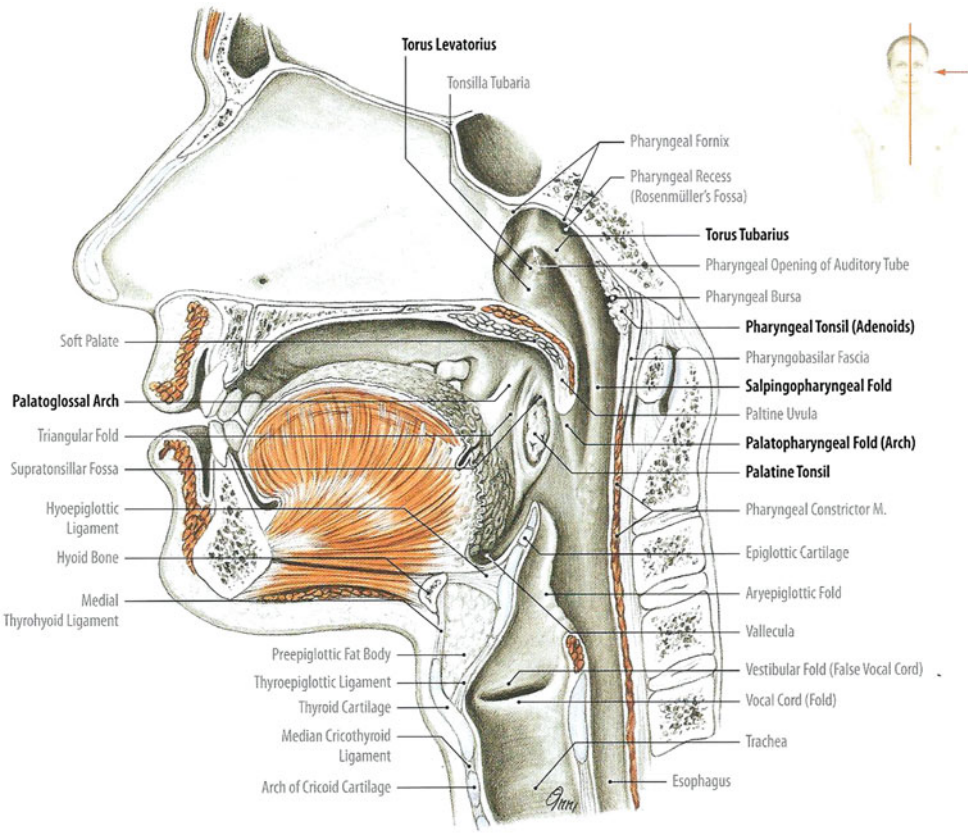

Fig. 2 Nasal and oral cavities, pharynx and larynx: median sagittal section through head and neck, medial view of the *right* half (with permission from Tillman and Elbermani 2007)

In the lamina propria, diffused lymphatic tissue (infiltration) may be found just beneath the epithelium. The lamina propria is a loose connective tissue with blood and lymphatic vessels, adipose cells, and nerve fibers. The epiglottis glands are of mixed type, and predominantly located on the laryngeal side. The core of the epiglottis is occupied by a large area of elastic cartilage with its perichondrium bound to the deepest layer of the lamina propria.

During swallowing, the epiglottis is pressed by the base of the tongue toward the posterior wall of the pharynx, thus closing the larynx. As a result, the bolus of food is pushed to slide through the oral surface of the epiglottis and to enter the esophagus, not the trachea (Robbins et al. 1992).

Larynx: The larynx is a complex hollow organ that connects the pharynx above and the trachea below. Its lumen is covered by a mucosa lined with ciliated pseudostratified columnar epithelium and stratified squamous epithelium (Fig. 3a, b). The wall of the larynx is supported by a group of cartilages and a group of skeletal muscles.

The mucosa of the larynx forms two pairs of folds: the upper are the vestibular folds (false vocal cords) and the lower are the vocal cords. Between these two pairs of folds is the laryngeal ventricle with its narrow pouchlike prolongation, the ventricular recess. The vocal cord and vestibular fold are covered by nonkeratinized stratified squamous epithelium, while the rest is lined by ciliated pseudostratified columnar epithelium with goblet cells. The beating direction of the cilia is toward the pharynx, moving foreign particles, bacteria, and mucus toward the exterior. The lamina propria is a loose connective tissue containing blood vessels and diffused lymphatic tissue. Within the lamina propria are numerous mixed glands, except where the vocal cords are present. The core of the vocal cord is composed of vocal ligaments with bundles of elastic fibers.

Besides the vocal cord ligament is the vocalis muscle, which controls the tension on the vocal cords and is therefore associated with phonation. The other skeletal muscles surrounding the larynx include the aryepiglottic muscle, thyroarytenoid muscles, and lateral cricoarytenoid muscle. These muscles are involved in breathing and swallowing. Between the bundles of muscles is a thin layer of loose connective tissue that contains blood vessels and adipose cells. The major cartilages supporting the wall of the larynx are the thyroid, the cricoid, and the arytenoids. These are all of the hyaline type. Additionally, there are several small elastic cartilages: the corniculates, cuneiforms, and the tips of the arytenoid. No cartilages are shown in this illustration; for details, see a relevant anatomy textbook or atlas. The larynx is designed to produce sound, to close the trachea during swallowing to prevent food and saliva from passing down the airways to the lungs, and to function as a part of the respiratory system (Zhang 1999).

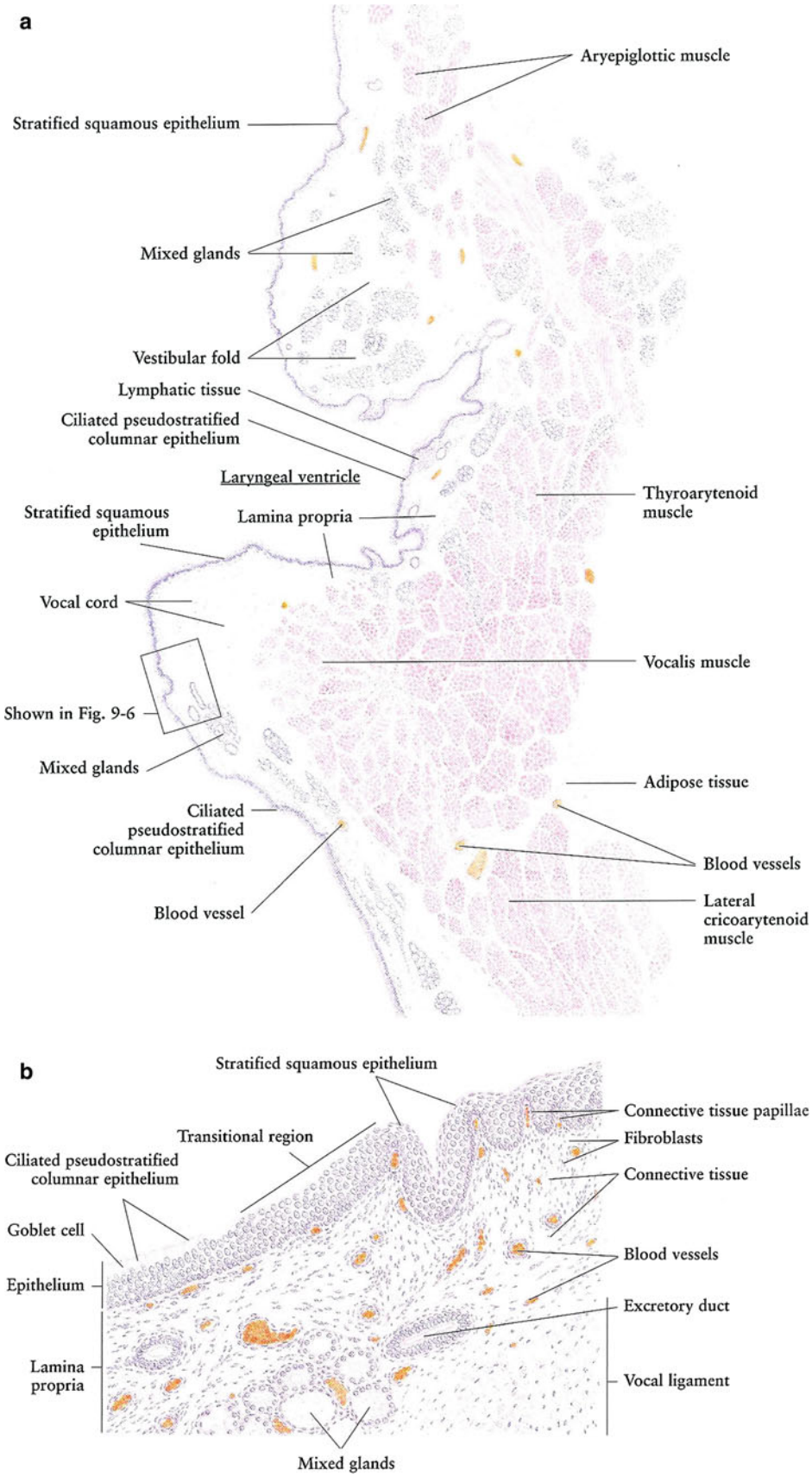

Fig. 3 **a** Larynx: frontal section, very low magnification. **b** Larynx: mucosa, high magnification (with permission from Zhang 1999)

3 Physiology and Biology

3.1 Pharynx

Swallowing is a complex process that begins with the placement of food in the mouth and ends when the food enters the stomach. It involves voluntary and involuntary stages which are coordinated through several cranial nerves and a multitude of muscles that control the function of the oral cavity, the pharynx (skull base to the lower border of the cricoid), the larynx, hyoid bone, and esophagus (Logemann 1998; Goldsmith 2003).

Swallowing is initiated by the stimulation of receptors in the oropharyngeal area. Sensory impulses reach the brain stem through cranial nerves VII, IX, and X, while motor control is exercised through cranial nerves IX, X, and XII. The cricopharyngeal sphincter (CPS) relaxes as the bolus reaches the posterior pharyngeal wall before it reaches the CPS. Cranial nerve V contains both sensory and motor fibers and is important to chewing.

Swallowing physiology consists of three phases (Logemann 2007):

1. Oral phase (1 s): The oral tongue and teeth reduce the food to a bolus. As the food is transported back toward the pharynx, receptors in the oropharyngeal mucosa trigger the pharyngeal phase.
2. Pharyngeal phase (1 s): During this stage, the velopharyngeal port closes to prevent food from entering the nose. The hyoid bone and larynx begin their forward and superior ascent, the epiglottis is folded down to an inverted position, the tongue base moves toward the posterior pharyngeal wall, and pressure is generated by the top-to-bottom contraction of the pharyngeal constrictor muscles, which push the bolus of food toward the esophagus. Lastly, through laryngeal and hyoid elevation and anterior movement, the cricopharyngeus muscle relaxes, resulting in the opening of the CPS.
3. Esophageal phase: When the CPS opens, the bolus of food enters the upper esophagus and is transported down to the stomach through peristalsis.

Patients with head and neck cancer tend to be elderly. With advanced age, swallowing physiology becomes compromised, resulting in increased bolus "holding", delayed onset of swallow, slower pharyngeal transit time, and reduced generation of pharyngeal pressure (Tracy et al. 1989; Robbins et al. 1992).

3.2 Larynx

The Larynx is the entry to the respiratory system and serves as the organ for speech (phonation). Expired air causes the true vocal cords to vibrate; the vibrations are modulated by varying the tension in the vocal cords and changing the degree of glottis opening. It is the alteration of vibrations that produces sounds of varying pitch. The false cords have no intrinsic musculature to modulate phonation. However, they and the ventricle that separate true and false cords create sound resonance.

Vocal function endpoints include objective measurements through instrumental assessment, subjective measurement related to patient-reported items, and observer-assessed scores on communicability.

Objective evaluation: Instrumental Assessment

a. *Videostroboscopy* patients are asked to produce standard vocal samples while videostroboscopy is performed. Images are obtained using a laryngoscope and a rhinolarynx stroboscope. Through this procedure, several parameters can be evaluated: supraglottic activity, vocal fold edge, amplitude, mucosal wave, phase symmetry, and glottic closure (Hirano 1981).
b. *Aerodynamic measurements* (Fung et al. 2001): a pressure flow device can be used to obtain and analyze the aerodynamic productions of each patient. Patients are asked to sustain a vowel or to repeat a syllable at a predetermined rate at a comfortable intensity level. Maximum phonation time, average airflow during sustained vowel production, vocal fold diadochokinetic (VFDDK) temporal rate, and the average airflow rate on VFDDK can be measured.
c. *Acoustic analyses* (Fung et al. 2001): analysis of some macro- and micro-analytical acoustic parameters such as fundamental frequency and phonational frequency range, measures of perturbation, and measures of noise.

Subjective evaluation: self-assessed questionnaire

a. *The Voice Handicap Index* (*VHI*) (Rosen et al. 2000; Jacobson et al. 1997): it is a 30-item validated questionnaire derived for patients with benign disorders and it includes a series of questions about patient's perceptions of their voice quality. Social-emotional and physical handicap are considered.
b. *The voice-Related Quality of Life* (*VR-QOL*) (Hogikyan and Sethuraman 1999): it is a 10-item self-administered validated questionnaire. Social-emotional and physical functioning are included.
c. *Head-and-neck cancer-specific functional outcome and QoL* (*HNCI*) (Funk et al. 2003, 2004): a 30-item validated self-report survey. Items address four separate quality of life domains: eating, speech, esthetics, and social disruption. Both functional and attitudinal outcomes are assessed.
d. *The Voice Symptom Score* (*VoiSS*) (Funk et al. 2004) is a rigorously evaluated and psychometrically robust measure for the self-assessment of voice quality. It comprises 44 items which assess voice impairment, emotional reaction, and related physical symptoms. It differs from

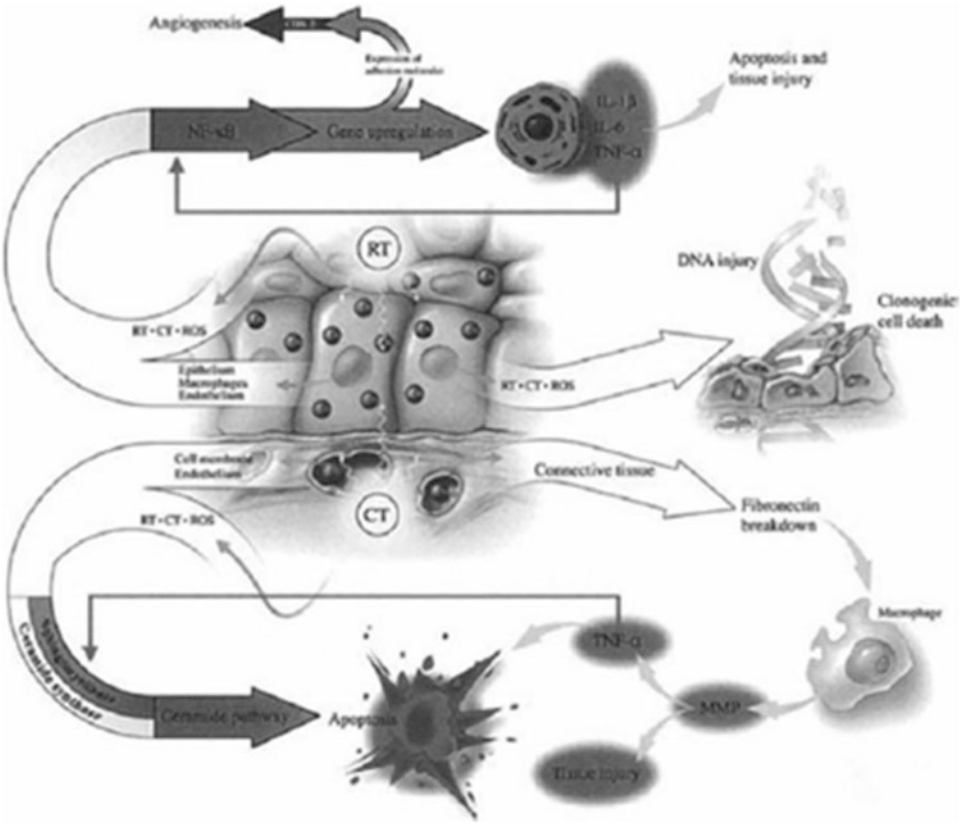

Fig. 4 Radiotherapy (RT) and chemotherapy (CT) generate ROS resulting in direct DNA injury as well as stimulation of secondary mediators leading to apoptosis. Other genes are also upregulated leading to angiogenesis. (Reprinted from Sonis et al. (2004), with permission.)

the other three questionnaires as it addresses other symptoms which may arise from the laryngopharynx.

Subjective evaluation: observer-assessed

a. *Communicative suitability* (Franken et al. 1997; van der Torn et al. 1997): a panel of untrained volunteers judge the voice samples on communicative suitability in three different, demanding speaking situations, ranging from low demanding (talking about everyday events with a friend), medium demanding (asking a passer-by for directions), and to highly demanding (giving a lecture).
b. *Vocal Profile Analysis Protocol* (Laver 1981): experts in rating of voice are asked to analyze voice samples (e.g. text read aloud). Breathiness, roughness, tension/strain, unsteadiness, asthenia, aphonia, falsetto, vocal fry, diplophonia, and tremor can be judged and scored (Hirano 1981).

3.2.1 Definition of Laryngeal Anatomical Structures

Vocalization is a complex process that involves multiple anatomical structures which act in coordination. Due to this complexity, the definition of the most important anatomic sites whose dose-volume parameters would have a major effect on vocal function has been studied only in recent years and it is still controversial.

Dornfeld et al. (2007) considered various structures in the head and neck to be related to vocal injury: the superior and inferior base of tongue, the epiglottis, the lateral pharyngeal walls at the level of the inferior base of tongue, the pre-epiglottic space, the aryepiglottic folds, the false vocal cords, the lateral pharyngeal walls at the level of the false vocal cords, and the upper esophageal sphincter.

Sanguineti et al. (2007) evaluated the correlation between dose-volume parameters and edema, and contoured the larynx from the tip of the epiglottis superiorly to the bottom of the cricoid inferiorly; the external cartilage framework was excluded from the laryngeal volume.

3.3 Biology

Sonis has described a five-phase oral mucositis pathogenesis model that includes initiation, message generation, signaling and amplification, ulceration, and healing. Initiation occurs after administration of cytotoxic CT as a result of DNA damage and the generation of reactive oxygen species (Fig. 4). The relatively acute inflammatory or vascular phase occurs shortly after CT or RT administration. Message generation involves the upregulation of transcription factors, including nuclear factor kD(NF-kB) and

activation of cytokines and stress response genes. Signaling and amplification involves the production of proinflammatory cytokines released from epithelial tissue, including TNF-α, which is related to tissue damage, and interleukin-1 (IL-1), which incites the inflammatory response and increases subepithelial vascularity that may lead to increased local CT levels (Devita et al. 2011) (Fig. 4).

4 Pathophysiology

4.1 Pharynx

Acute: the time course for expression of pharyngeal mucositis parallels those in the oral cavity. The intensity of the mucosal reaction is dose time dependent on fractionation schedules. With more aggressive schedules and combinations of chemoradiation interferes with feeding. Most pharyngeal cancers resolve and the mucosa regenerates. However, posterior wall cancers post-cricoid in location seldom heal and can persist.

Late: treatment with nasogastric feeding tube can result in scarring and structure at the cricopharyngeus sphincter at the esophageal inlet. The origin of the esophagus is vulnerable, because the posterior wall is deficient of muscular wall in V-shaped triangle of Laimer. Recent dose/volume analysis of proximal esophagus was equivocal (Eroschenko 2007).

4.2 Larynx

Acute: the early lesions are similar to the mucositis of the pharynx and larynx with the onset varying with the intensity of the radiation schedule as documented by early investigators and continuing with the investigation of numerous fractionation schedules: i.e., hypofractionation, hyperfractionation, split course, accelerated with concomitant boost, etc. The major concern is laryngeal edema which usually subsides within 6–8 weeks, if tolerance has not been exceeded. If edema persists or anticipated, a tracheostomy is performed.

Late: the later fibrogenic phase can lead to accumulation of collagen and webbing of the vocal cord, most often at the anterior commissure due to cord proximity. Atrophy of the mucosa appears as atrophic glands resembling small islands of tumor and requires careful evaluations due to varying degrees of atypia and pseudoepitheliomatous hyperplasia. The major concern is arterial neointimal proliferation, ischemia resulting in cartilage necrosis. Chondritis and perichondritis are due to loss of chondroblasts in cartilage growth zones. When frank necrosis occurs, infection is highly likely to set in accelerating the chondronecrosis. Since laryngeal cartilage ossifies, bone sequestra occur once the mucosa is ulcerated. Arytenoid cartilages (hyaline) were most commonly involved and epiglottis (elastic) cartilages are least affected.

5 Clinical Syndromes

5.1 Pharynx

5.1.1 Swallowing Disorders Induced by Radiation Alone

Radiation-induced late toxicities, including swallowing disorders, are unevenly distributed, with some patients exhibiting more cellular radiosensitivity. Conflicting data have emerged related to target-tissue sensitivity (fibroblast vs. DNA repair capacity vs. lymphocytic chromosomal damage) and late radiation damage (Rudat et al. 1999; Borgmann et al. 2002; Geara et al. 1992). Denham et al. (2001) have categorized radiation-induced normal tissue injury as direct, indirect, and functional, in addition to resulting from genetic susceptibility. A number of tumor and radiation variables (Mittal et al. 2001; Eisbruch et al. 2002; Ang et al. 1997; Maciejewski et al. 1983; Fu et al. 1995; Taylor et al. 1992) also influence the incidence of late damage. Several investigators have documented cervical and pharyngeal fibrosis and laryngeal dysfunction resulting in swallowing disorders following standard or accelerated radiation schemes (Delaney et al. 1995; Horiot et al. 1992; Nguyen et al. 1988; Olmi et al. 1990; Marks et al. 1982; Cooper et al. 1995). Therefore, it is essential to understand the biomechanics of swallowing disorders and to know the anatomical organs that are critical for swallowing and the radiation dose-volume relationship of these organs, in order to prevent and reduce the incidence of swallowing disorders and devise effective rehabilitation techniques (Mittal et al. 2003) (Table 1).

Acute dysphasia during, and soon after, RT may result from alterations in saliva, and/or short-term laryngopharyngeal edema, resulting in acute dysphagia. This is usually limited as the salivary function and edema usually resolve within a few weeks post-RT. If these issues persist, they can lead to persistent dysphagia: e.g. long-term xerostomia can hinder swallowing function.

Radiation-induced swallowing disorders can manifest months to years later as a result of extensive fibrosis and vascular and neural damage of the pharyngeal region (Dejaeger and Goethals 1995). The biomechanics of these disorders have been studied by Lazarus (1993) using VFG in a group of patients with dysphagia 10 years following radiation. These patients demonstrated a number of oropharyngeal motility disorders, including reduced tongue-base contact with the posterior pharyngeal wall, reduced

Table 1 LENT SOMA of the Upper Respiratory and Digestive System

Larynx				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Voice/ hoarseness	Occasional hoarseness on prolonged use	Intermittent hoarseness, voice unreliable, varies in day-to-day communication	Persistent hoarseness, incapable of normal communication	Complete loss of voice
Breathing	Occasional difficulty	Intermittent difficulty	Labored breathing	Stridor
Objective				
Edema	Arytenoids only	Arytenoids and aryepiglottic folds	Diffuse edema of supraglottis, airway adequate	Diffuse with significant narrowing of airway, <1/2 normal
Mucosal integrity	Patchy atrophy, telangiectasia	Complete atrophy, extensive telangiectasia	Ulcer, cartilage not exposed	Necrosis, cartilage exposed
Respiration		Dyspnea on exertion	Labored at rest	Stridor at rest
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Hoarseness		Rest voice, or whisper only	No talking or whispering	Laryngectomy
Respiration		Humidifier, steroids	Temporary tracheostomy	Permanent tracheostomy
Analytic				
Indirect laryngoscopy	Assessment of edema, mucosal integrity, vocal cord motion, ulcer, and necrosis			
Direct laryngoscopy	Assessment of edema, mucosal integrity, vocal cord motion, ulcer, and necrosis			
CT	Assessment of edema, necrosis, and asymmetry			
MRI	Assessment of edema, necrosis, and asymmetry			

laryngeal elevation, and compromised vestibule and true vocal cord closure. These disorders resulted in pharyngeal residue, which was aspirated after swallow. Despite different tumor sites, all patients exhibited similar altered biomechanics, which most likely resulted from the large radiation doses and volumes that encompassed the oral-aryngopharyngeal area during treatment. In 1995, a similar observation was made by Dejaeger and Goethals (1995) who used manofluorography in a patient 5 years following radiotherapy for a pharyngeal carcinoma. Kendall et al. (1998, 2000) used VFG to evaluate 20 patients with head and neck cancer previously treated with radiation. These patients were able to maintain nutrition and none complained of dysphagia. When compared with 60 normal subjects, all 20 patients demonstrated abnormal swallow mechanics and prolonged oropharyngeal time for all bolus sizes. The onset of aryepiglottic fold closure relative to the onset of swallow was delayed and there was a trend toward delayed hyoid elevation. In this study, there was a trend toward earlier opening of the upper esophageal sphincter relative to the arrival of the bolus, most likely as a compensatory mechanism. Patients with base of tongue cancer had worse swallow mechanics compared to patients with pharyngolaryngeal cancers.

To assess pharyngeal dysfunctions following radiation, Wu et al. (2000) used fiberoptic endoscopic examination in 31 patients with dysphagic nasopharyngeal cancer, with a mean follow-up of 8.5 years following radiation. They observed pharyngeal retention (93.5 %), post-swallow aspiration (77.4 %), atrophic changes in the tongue with or without fasciculation (54.8 %), vocal cord paralysis (29 %), velopharyngeal incompetence (58 %), delay or absence of swallow reflex (87.1 %), and poor pharyngeal constriction (80.6 %).

Jensen et al. (2007) made a similar observation using functional endoscopic evaluation of swallowing (FEES) and EORTC-QOL questionnaires in 25 patients with pharyngeal cancer treated with radiation alone and followed up for a minimum of 2.5 years (mean 5 years). Of these patients, 83 % had subjective swallowing complaints. The most frequent objective finding was reduced sensitivity in the oropharynx (94 %) and reduced range of motion at the

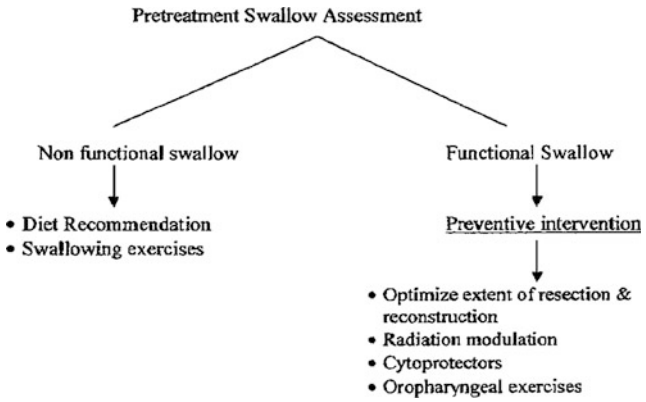

Fig. 5 Algorithm for evaluation and treatment of swallowing dysfunctions in patients with head and neck cancers

tongue base (79 %). Pharyngeal residue appeared in 88 % of these patients, 59 % experienced laryngeal penetration, and 18 % aspirated. Penetration and aspiration were observed primarily with thin liquids. All of the six patients with aspiration were smokers. Thus, based on these studies, it is generally considered that the structures are critical for the maintenance of swallowing.

5.2 Detection and Diagnosis

5.2.1 Evaluation of the Swallowing Mechanism

1. Objective Evaluation: Instrumental Assessment (Fig. 5)
   a. Videofluorography (VFG) is the most commonly used procedure to assess swallowing dysfunctions. VFG, including modified barium swallow and esophagogram, can visualize the oral, pharyngeal, and esophageal phases of swallowing. During VFG, the patient is given food in measured volumes and viscosities. Swallowing physiology is viewed in the lateral and anteroposterior planes and temporal measures are made. The duration of physiologic events during the entire swallow can be measured as they change during swallows of boluses of various volumes and viscosities. Oropharyngeal residue and aspiration can be quantified. Oropharyngeal swallow efficiency (OPSE), a global measure of the safety and speed of swallow, is calculated by measuring the total oral and pharyngeal transit time of the bolus divided by the percentage of the bolus swallowed (Hansen et al. 2007; Zhang 1999; Devita et al. 2011; Eroschenko 2007).
   b. Manometry, in which the patient swallows a soft tube containing pressure sensors, measures pressures generated in the mouth, pharynx, and esophagus during swallowing. Manometry is used primarily to measure pressure changes in the esophagus and has value for studying oropharyngeal swallowing dysfunctions. (Ergun et al. 1993; McConnel 1988).
   c. Functional endoscopic evaluation of swallowing (FEES) provides views of the laryngopharynx different from those seen with VFG. This procedure, which is easy to perform, uses fiberoptic endoscopy (FE) to view mucosal and anatomical integrity, pharyngeal residue, swallowing with sensory testing, and aspiration (Wu et al. 2000). Wu et al. (1997) have discussed the advantages and disadvantages of using the fiberoptic endoscope versus VFG to evaluate patients with swallowing disorders.
   d. Ultrasonography can be used to study tongue physiology during swallowing (Shawker et al. 1983). However, this procedure has no value for assessing other phases of deglutition.
2. Objective Evaluation: Observer-Assessed

Several tools are available to assess short- and long-term cancer treatment-induced swallowing dysfunctions. Common Terminology Criteria for Adverse Events (CTCAE) are frequently used to assess acute toxicity. Late toxicities can be assessed using the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) criteria and the Subjective Objective Management Analytic (SOMA) scale (Cox et al. 1995; Pavi et al. 1995; Denis et al. 2003).

3. Subjective Evaluation: Patient-Reported Quality of Life

Some of the instruments used to assess quality of life (QOL) in patients with head and neck cancer, including swallowing dysfunctions, include: the University of Washington Quality of Life tool (UWQOL) (Hassan and Weymuller 1993); the M.D. Anderson Dysphagia Symptom Inventory (MADSI-HN) (Rosenthal et al. 2007); the EORTC-QLQ H&N (Bjordal et al. 1995); the Performance Status Scale for Head and Neck Cancer patients (PSS-H&N) (List et al. 1996); the Radiation Therapy Instrument Head and Neck (QOL-RTI/H&N) (Trotti et al. 1998); the Functional Assessment of Cancer Therapy-H&N (FACT-H&N) (Long et al. 1996); and the Head and Neck Radiotherapy Questionnaire (HNRQ) (Browman et al. 1993). While these instruments all measure some aspects of head and neck cancer-related QOL, it is not clear which one best applies to the assessment of swallowing dysfunctions in patients with head and neck cancer and to various treatment modalities.

5.2.1.1 Baseline Swallowing Function in Patients with Head and Neck Cancer

Pauloski et al. (2000) compared 352 patients with head and neck cancer with 104 controls. Pretreatment, 59 % of patients complained of dysphagia. On VFG study, the majority of these patients had functional study suggesting inconsistency in perception of swallowing and actual swallowing ability. However, compared to controls, patients

had significantly longer oral and pharyngeal transit time, greater oropharyngeal residue, and lower swallowing efficiency. Swallow function worsened with increased tumor stage and in patients with oral and pharyngeal lesions compared to those with laryngeal lesions. It is not clear if the swallowing decrement was the result of tumor infiltration of muscles and nerves or of pain and ulceration. An algorithm suggested for the evaluation and treatment of swallowing dysfunction is shown in Fig. 5.

5.2.2 Larynx

Subjective: if laryngeal cancer is present prior to treatment, it is difficult to distinguish changes due to treatment. Perhaps hoarseness and pain, which is occasional becomes intermittent and persists. Likewise, difficulty in breathing can be assessed as minimal to labored strider. Various endpoints have been suggested to assess and grade radiation effects on the larynx (Table 1a, b).

6 Radiation Tolerance

6.1 Pharynx

6.1.1 Dose Time Fractionation

Rubin et al. (1991) suggested a 5 and 50 % risk of pharynx and larynx edema at 5 years with doses of 45 and 80 Gy, respectively. Moreover, it was felt that irradiation of less than 50 % of the larynx would not have changed these estimates (Figs. 6, 7, and 8).

6.1.2 Organ at Risk and the Dose-Volume-Effect Relationship

Laryngopharyngeal disorders resulting in late dysphagia and aspiration are not regimen-specific and are the result of edema and fibrosis (Pauloski et al. 1994). To correlate the relationship of radiation dose-volume-effect, it is critical to know the relative importance of the organs involved in swallowing physiology. Pauloski et al. (2006) used VFG to evaluate the "organ at risk" in 170 patients. Laryngeal elevation, tongue-base retraction, and the cricopharyngeal opening consistently predicted patients' ability to swallow different food consistencies. Eisbruch et al. (2004) reviewed the literature and identified the structures that, if damaged, could potentially cause abnormal swallowing physiology. From their study of 26 patients assessed with VFG, direct endoscopy, and CT scan, they identified pharyngeal constrictors (PC) and glottic and supraglottic larynx (GSL) as dysphagia- and/or aspiration-related structures (DARS). In a prospective study, Feng et al. (2007) established the dose-volume-effect relationship for DARS and the esophagus in 36 patients with stage 3/4 head and neck cancers treated with chemoradiation. For intensity modulated radiation

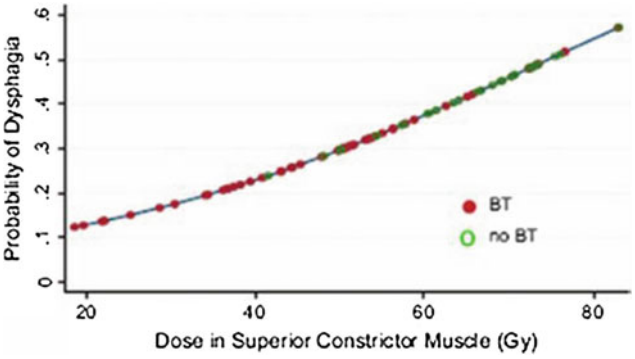

Fig. 6 Dose-effect relationship for the probability of having dysphagia (Performance Status Scale for normalcy of diet) and dose (Gy) to the superior constrictor muscle. BT, brachytherapy). (Reprinted from Teguh et al. (2008), with permission)

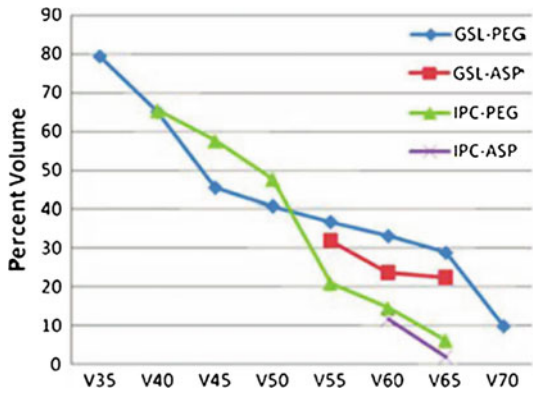

Fig. 7 Threshold dose-volume histogram for PEG tube dependence and aspiration (ASP). GSL, larynx; IPC, inferior pharyngeal constrictor; Vx: volume receiving x dose. (reprinted from Caudell et al. (2010), with permission)

therapy (IMRT) dose optimization, planning treatment volume (PTV) was excluded from the target organ (swallowing structures, major salivary glands, and oral cavity). However, the entire organ was used to establish the dose-volume-effect relationship. A strong correlation was observed between the mean dose to DARS and dysphagia endpoints Aspiration was observed when the PC mean dose exceeded 60 Gy and the dose-volume threshold was V40 = 90 %, V50 = 80 %, V60 = 70 %, and V65 > 50 %. For aspiration to occur, the GSL dose–volume threshold was V50 > 50 % (>50 % of volume receiving 50 Gy). For stricture, a mean dose of ≥66 Gy and a dose-volume threshold of V50 = 85 %, V60 = 70 %, and V65 = 60 % for PC was observed. For stricture formation to occur, no relationship between mean dose to the GSL and esophagus was observed. The mean dose to the PC and esophagus was correlated with liquid swallowing, while only the mean dose to PC was correlated with solid

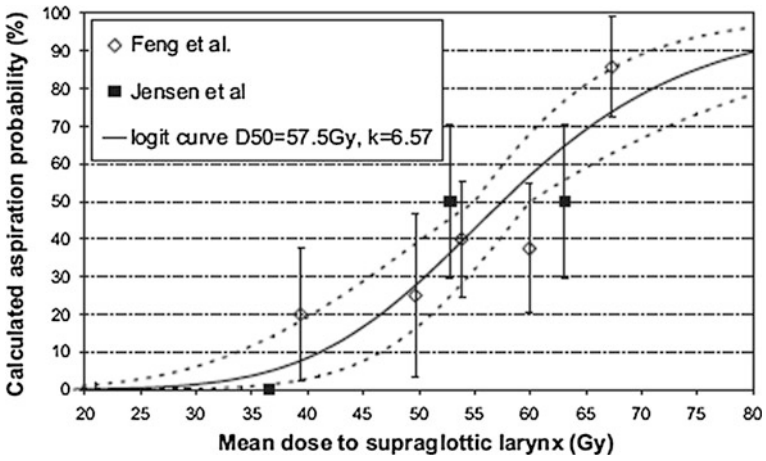

Fig. 8 Dose-effect relationship for dysphagia according to data from Fent et al. (14) and Jensen et al. (16) *Solid line* fit to combined data; dotted line fit to 68 % confidence area for normal tissue complication probability-logit curve (with permission from Rancati et al. 2010)

swallowing on patient-reported and observer-rated swallowing scores (Table 2; Figs. 6, 7, and 8).

In a retrospective study of 25 patients managed with radiation alone, Jensen et al. (2007) studied the dose-volume-effect relationship using FEES and the QOL questionnaires EORTC C30 and H&N 35. In this study, radiation dose to base of tongue and PC did not correlate with swallowing endpoints. However, doses <60 Gy to the supraglottic area, larynx, and upper esophageal sphincter resulted in a low risk of aspiration (Table 2).

Dornfeld et al. (2007) reported on 27 patients with head and neck cancer who were treated with IMRT radiation + chemotherapy and free of disease for at least 1 year following treatment. Swallowing difficulties and the type of diet tolerated (Diet Score) decreased progressively with radiation doses >50 Gy to the aryepiglottic folds, false vocal cords, and lateral pharyngeal walls near the false cord.

Levendag et al. (2007) reported on 81 patients with oropharyngeal carcinoma treated with 3-dimensional CRT or IMRT with or without brachytherapy ± chemotherapy. A significant correlation was observed between the mean dose to the superior and middle pharyngeal constrictor muscles and patient complaints of severe dysphagia. A median dose of 50 Gy predicted a 20 % probability of dysphagia. This probability increased significantly beyond a mean dose of 55 Gy, with an increase of 19 % associated with each additional 10 Gy to superior and middle constrictors.

Doornaert et al. (2007) using RTOG and EORTC-QOL questionnaires in 81 patients with head and neck cancer, correlated the mean dose to the pharyngeal wall structures (PWS), including mucosa and pharyngeal constrictor muscles and swallowing outcome. They reported a steep dose-effect relationship beyond 45 Gy to PWS and concluded that a mean dose of 45 Gy is the optimal threshold dose for predicting swallowing difficulties.

Coglar et al. (2007) in a study of 96 patients with head and neck cancer treated using IMRT ± chemotherapy, observed no aspiration when the mean radiation dose to the larynx and inferior pharyngeal constrictor was ≤48 and ≤54 Gy, respectively. A dose-volume-effect was observed. At V50 = 21 % for the larynx and V50 = 51 % for the inferior constrictor, no aspiration or stricture were observed. No stricture was observed if the mean dose to the inferior constrictors was kept below 54 Gy. The mean dose to the larynx did not correlate with stricture formation.

O'Meara et al. (2007) retrospectively reviewed the data of head and neck cancer patients treated with 2-dimensional radiation + concurrent chemotherapy. They observed an association between the median dose to the inferior hypopharynx (pharyngoesophageal inlet) and severe late toxicity (grade ≥ 3 pharyngolaryngeal dysfunction). The incidence was 46 %. The median dose to the inferior hypopharynx was 58 Gy among patients with severe late dysphagia, compared to 50 Gy in patients without severe dysphagia.

There is a paucity of dose/volume data about hypopharyngeal/upper esophageal stricture in head and neck cancer patients treated with radiation + chemotherapy. Laurell et al. (2003) compared radiation dose-volume data in 22 patients with proximal esophageal stricture versus 22 reference patients with no stricture following radiation. They recommend a mean dose of <65 Gy to the first 2 cm of proximal esophagus and a mean dose of <60 Gy to the first 5 cm of proximal esophagus as a tolerance dose below which the incidence of esophageal stricture is low. However, further studies are needed to establish the dose modifying effect of chemotherapy given concurrently with radiation. Three reported dose response relationships for pharyngeal dysfunction (e.g. dysphagia or aspiration) based on doses to the constrictor muscles, larynx, and supraglottic larynx are provided in Figs. 6, 7 and 8.

Table 2 Organs at risk and dose/volume relationship above which swallowing dysfunctions increases significantly (Adopted from Rancati et al. 2010, Quantec review)

Author & Number of patients	Critical organs	Dose/volume data					End point	Evaluation method
		Mean dose (Gy)	Median dose (Gy)	V50 (%)	V60 (%)	V65 (%)		
Eisbruch/Feng 26pts 36pts IMRT RT + Chemo	Larynx PC	>60 >66		>50 80 85	70 70	>50 60	Aspiration Aspiration Stricture	VFG
Coglar 96 pts IMRT RT ± Chemo	Larynx IC	<48[a] <54		21 51			Aspiration and stricture	VFG
Doornaert 81 pts RT ± Chemo	Pharyngeal mucosa and constrictors	45					QOL	RTOG EORTC C-30 & H/N 35
O'Meara 148 pts 2DRT + Chemotherapy	Pharyngo-esophageal inlet		50				Grade 3 + Pharyngo-esophageal Dysfunction	RTOG late toxicity
Levendag 81 pts 3DCRT/ IMRT + Brachy ± Chemo	Superior and middle constrictors	55					Grade ≥ 3 EORTC PSS H&N MDADI	RTOG QOL QOL
Dornfeld 27 pts. IMRT Radiation ± Chemo	Aryepiglottic fold False cord Lateral pharyngeal Wall near false cord	>50					Diet score H & N QOL Weight loss PEG tube	QOL Clinical assessment
Jensen 25 pts. 3DCRT Radiation alone	Larynx Upper esophageal Sphincter	>60					Aspiration QOL	EORTC, QOL, FEES

PC pharyngeal constrictors, *IC* inferior constrictor
[a] No correlation with stricture formation

6.2 Larynx

6.2.1 Dose Time Fractionation

Rubin et al. (1991) suggested a 5 and 50 % risk of pharynx and larynx edema at 5 years with doses of 45 and 80 Gy, respectively. Moreover, it was felt that irradiation of less than 50 % of the larynx would not have changed these estimates (Table 3).

6.2.1.1 Normal Tissue Complication Probability Models

Burman et al. (1991) provided the first fit of laryngeal injury events to the Lyman model (Lyman 1985) with DVH reduced to the effective volume with the Kutcher-Burman method (Kutcher et al. 1991) (LKB). They considered cartilage necrosis with $n = 0.11$, $m = 0.075$, and TD50 = 80 Gy and laryngeal edema with $n = 0.08$, $m = 0.17$, and TD50 = 70 Gy (Table 3).

Recently, Rancati et al. (2007) fitted two Normal Tissue Complication Probability (NTCP) models to the same study population analyzed by Sanguineti et al. (2007). They consider G2–G3 edema within 15 months from radiotherapy as an endpoint: 38/66 patients were available for this purpose and 21/38 experienced G2–G3 edema. Two NTCP models were fitted using a maximum likelihood analysis: (a) LKB model and (b) the Logit model (Mohan et al. 1992) with DVH reduced to the equivalent uniform dose (Deasy et al. 2002; Niemierko 1999) (EUD) (LOGEUD).

A significant volume effect was found for edema, consistently with a prevalent parallel architecture of the larynx for this endpoint. Both NTCP models fit well the clinical

Table 3 Larynx edema: estimated parameter values for various NTCP models with their 1D-68 % confidence intervals (from Rancati et al. 2010)

LKB model	TD50	m	n
Burman et al. (1991)	70 Gy	0.17	0.08
Rancati et al. (2007)	46.3 Gy	0.16	0.45
1D-68 % CI	1.8 Gy	0.05	0.28
LOGEUD model	*D50*	*k*	*n*
Rancati (2007)	46.0 Gy	9.95	0.47
1D-68 %CI	1.85 Gy	3.46	0.3

data: with LOGEUD, the relationship between EUD and NTCP can be described with $n = 0.47 \pm 0.3$, TD50 = 46.0 ± 1.85 Gy, and a steepness parameter $k = 9.95 \pm 3.46$ Gy. Best fit parameters for LKB are $n = 0.45 \pm 0.28$, $m = 0.16 \pm 0.05$, and TD50 = 46.3 ± 1.8 Gy (Table 3). Based on these findings, the authors suggest an EUD <30–35 Gy in order to drastically reduce the risk of G2–G3 edema.

6.2.2 Dose-Volume-Effect Relationship

6.2.2.1 Laryngeal Edema

More recently, RTOG protocols 0025 and 0022 on IMRT for Head and Neck Small Cell Cancer recommended a mean laryngeal dose less than 45 Gy and less than 2/3 of the glottic larynx to receive 50 Gy, respectively, though no references or specific endpoints were provided for these estimates (Table 4).

In a rigorous analysis, Sanguineti et al. (2007) showed a significant relationship between mean larynx dose or laryngeal V50 Gy and rates of grade ≥2 laryngeal edema. They analysed 66 patients with biopsy-proven squamous cell carcinoma of the head and neck region. Radiotherapy fractionation schedules included standard fractionation at 2 Gy/fraction to a total dose ranging from 60 to 70 Gy or altered fractionation, in the forms of hyperfractionation and/or accelerated fractionation. 12/66 patients received chemotherapy.

The larynx was contoured from the tip of the epiglottis superiorly to the bottom of the cricoid inferiorly; the external cartilage framework was excluded from the laryngeal volume.

All dosimetric variables, but V20 Gy, were predictors of laryngeal edema in univariate analysis. In addition, both neck stage at radiation treatment and the diameter of the largest node correlated with endpoint. At multivariate analysis, mean laryngeal dose/V50 Gy and neck stage at RT were the only independent predictors of laryngeal edema. Because mean laryngeal dose and V50 Gy are highly correlated, they are basically interchangeable. Moreover, V50 Gy may be preferable over mean dose because it provides a more specific statement of dose-volume relationship that can be directly translated into a precise IMRT optimization point. In their conclusions, the author suggest that in order to minimize the risk of edema, V50 Gy and mean laryngeal dose should be kept as low as possible, ideally ≤27 % and ≤43.5 Gy (20 % actuarial incidence at 1 year), respectively.

6.2.2.2 Vocal Dysfunction

A number of studies have shown a good voice outcome as measured by the VHI following radiation for T1 laryngeal cancer (van Gogh et al. 2006; Cohen et al. 2006; Loughran et al. 2005).

These patients typically receive 60–66 Gy of radiotherapy without chemotherapy and without significant voice decrement.

In the locally advanced setting, there is far less information on voice quality following treatment.

Dornfeld et al. (2007) analyzed 27 patients with locally advanced head and neck cancer receiving IMRT (22/27 patients received concurrent chemotherapy) (Table 4). This is the first work directly addressing to the correlation between vocal function and dose to selected anatomical structures. They looked at point doses to various structures in the head and neck (including base of tongue, lateral pharyngeal walls, and laryngeal structures) and tested their correlation with voice-related quality of life of the HNCI. They found a strong correlation between speech and doses delivered to the ary-epiglottic folds, pre-epiglottic space, false vocal cords, and lateral pharyngeal walls at the level of the false vocal cords. In particular, they noticed a steep drop off in function after 66 Gy to these structures. Their study was limited by not having full 3-D dose metrics, so that endpoints such as mean dose and V50 Gy could not be assessed.

There are other studies coping with vocal dysfunction, but they do not explicitly include dose-volume measurements/consideration.

As part of a Phase II clinical trial, Fung et al. (2005) conducted a prospective study of speech, in order to determine if larynx preservation is associated with improved voice compared with results in patients with persistent or recurrent disease who require salvage laryngectomy 56 patients were alive and free of disease at the time of survey (37 patients with larynx preserved and 19 with laryngectomy), with a minimum follow-up of 8 months. Voice quality was evaluated using VR-QOL. Mean VR-QOL scores in the study patients are lower compared with normal population data, but higher for organ preservation patients compared with patients who underwent salvage laryngectomy. Longer follow-up time was found to be a significant predictor of better voice function: improved function with time may be explained by the

Table 4 Larynx toxicity: summary of dose-volume relationship and of suggested constraints

Author (Ref) Number of patients	Critical organs	Dose/volume data	Endpoint
Dornfeld (Laver et al. 1981) 27 pts (22/27 pts CT + RT)	Aryepiglottic folds pre-epiglottic space false vocal cords lateral pharyngeal walls	Point dose <68 Gy	Vocal function (HNCI)
Sanguineti (Hirano 1981) 66 pts (12/66 pts CT + RT)	Larynx	V50 Gy <27 % mean dose <43.5 Gy	Laryngeal edema (fiberoptic examination)
Rancati Maciejewski et al. (1983) 38 pts	Larynx	EUD <30–35 Gy ($n = 0.45$)	Laryngeal edema (fiberoptic examination)

ability of patients to alter their voice producing strategies with time and practice. Nonetheless, longer follow-up of larynx preservation patients is needed to properly evaluate late toxicity and organ function because fibrosis after aggressive radiation regimes increases over time.

Fung et al. (2001) (retrospective cohort study) evaluated subjective and objective parameters of vocal function in non-laryngeal patients (17 patients) compared with a control group of patients irradiated for early glottic tumors (13 patients). All subjects received external beam RT. For non-laryngeal patients, a three-field isocentric technique was used. The primary site and entire head and neck lymphatic distribution were included in the treatment volume (i.e., "wide-field" RT). Total dose to isocenter ranged from 60 to 74 Gy (2 Gy/fraction) and the mean dose to the larynx was 50 Gy. For patients irradiated for early glottic tumors, small portals (6 cm long × 5 cm wide) covering only the primary lesion were used together with lateral parallel opposed pairs or an anterior wedge pair technique. Patients were treated to an isocentric dose of 61 Gy in 25 fractions over 5 weeks. Vocal Function was evaluated through videostroboscopy, aerodynamic measurements, acoustic analyses, and VHI. Videostroboscopy demonstrated increased supraglottic activity in the non-laryngeal group (20 % in this group compared with 0 % in the laryngeal group). Microanalytical acoustic parameters were worse for 75 % of the acoustic measures of vowel production in the non-laryngeal group. Macroanalytical acoustic analyses revealed no difference in fundamental frequency, but numerically smaller phonational frequency range in the non-laryngeal group. All aerodynamic measures were decreased in the non-laryngeal group. Qualitative vocal handicap was worse across all domains in the non-laryngeal group. The inference of this study is that wide-field head and neck RT adversely affects voice, even in the absence of laryngeal pathology. The conclusions which the authors draw are reasonable: dose to the larynx is not the unique predictor for voice changes. Dose to the pharynx and the oral cavity with its effects on reduction in saliva and pharyngeal lubrication as well as soft tissue and structural changes within the surrounding musculature play an important role on voice function.

Meleca et al. (2003) reported on retrospective functional evaluation of 14 patients treated with chemoradiation for stages III and IV squamous cell carcinoma of the larynx. Function evaluation was carried out through videostroboscopy, voice perception analysis, aerodynamic testing, and VHI. Results demonstrated that, on average, these patients exhibited impaired functional voice and speech abilities after treatment. Numerous anatomical, biomechanical, acoustic, speech aerodynamic, and perceptual abnormalities were registered. Despite these objective findings, the patients judged themselves to suffer only mildly with respect to overall quality of life.

7 Chemotherapy Tolerance

7.1 Chemoradiation-Induced Swallowing Dysfunctions

Over the past two decades, the intensity of treatment using chemotherapy and radiation has increased, resulting in better tumor control and organ preservation. However, acute and late toxicities have also increased (Henk 1997; Adelstein et al. 1997). Forastiere et al. (2003) reported RTOG 91-11 data, where 1 year post-treatment only 9 % of patients treated with radiation alone needed liquid or soft food, compared to 23 % of patients in the chemoradiation group.

In two separate studies, Lazarus et al. (1996, 2000) reported that the swallowing mechanics in head and neck cancer patients treated with concomitant chemoradiation protocols and compared the results with age-matched controls. A large percentage of patients exhibited abnormal swallow mechanics similar to those seen in patients treated with radiation alone; also seen were reduced tongue-base movement toward the posterior pharyngeal wall, reduced tongue strength, reduced laryngeal elevation, lower OPSE, an increased number of swallows needed to clear the bolus, and a high incidence (89 %) of aspiration of liquids.

Neuman et al. (2002) compared the effects of treatment using high-dose intra-arterial cisplatinum with radiation

versus intravenous chemotherapy and radiation. A large percentage of patients exhibited abnormal swallow measures that were similar in both groups, except that the intra-arterial group exhibited less aspiration with 1–3 ml of liquids.

Eisburch et al. (2002), Kotz et al. (1999), Mittal et al. (2001), Nguyen et al. (2006) have also reported a high incidence of oropharyngeal dysfunctions following concomitant chemoradiation. Most of these patients exhibited some degree of aspiration, base of the tongue weakness, pharyngeal residue, reduced laryngohyoid movement, decreased epiglottic inversion, swallow reflex delay, and velopharyngeal incompetence. Upper esophageal stricture was also observed in several patients.

Disorders resulting from radiation and chemotherapy can affect both oral and pharyngeal phases of swallowing. Swallowing biomechanics are altered as a result of reduced lingual manipulation and propulsion of bolus, reduced tongue strength, delayed triggering of the pharyngeal motor response, impaired tongue-base motion, pharyngeal contraction, laryngohyoid motion, laryngeal vestibule closure, and cricopharyngeal opening (Lazarus et al. 2007).

Over time (3–12 months), these disorders may reduce in severity, (Rademaker et al. 2003) although this is not always the case. A substantial number of patients experience deterioration of swallowing function over time as a result of vascular damage and fibrosis (Lazarus 1993; Law 1981; Smith et al. 2000; Watkin et al. 2001). This discrepancy highlights the importance of objective evaluation of swallow physiology before and at several points following treatment. Additional research is needed on the measurement and treatment of swallowing disorders after various chemoradiation protocols (Logemann 2005). The confounding effects of tumor site and stage, pre-existing dysphagia, dental status, smoking history, and other comorbidities also need to be studied.

Dysphagia resulting from radiation and chemotherapy could also be a result of stricture formation in the hypopharyngeal or upper esophageal area. There is evidence to support the increased incidence and severity of stricture formation following treatment with radiation plus chemotherapy compared to radiation alone. Laurell et al. (2003) reported a 3.4 % incidence of stricture formation in head and neck cancer patients treated with radiation alone compared to an incidence of 21 % observed by Lee et al. (2006) in a group of patients treated with radiation plus chemotherapy. This study reported a higher incidence of stricture formation in patients receiving hyperfractionation, in patients with hypopharyngeal primary tumors, and in women.

Chemotherapy in pharyngeal and laryngeal cancers is always used as an adjunct to radiation with the goal being preservation of the ability to swallow (pharynx) and speech (larynx). Meta-analysis of 63 randomized trials including approximately 10,000 patients has shown only an absolute improvement of 4 % mainly with concurrent chemoradiation which doubled the improvement to 8 %. Of all the pharyngeal cancers, nasopharynx cancers are particularly responsive to Cisplatinum and SFU infusion improving survival from 50 to 80 %. The randomized and landmark VA stud of laryngeal preservation with chemoradiation proved comparable to surgical laryngectomy and radiation. Reasons for dysphagia in head and neck cancer patients are complex; some are host patient related and others can be treatment related.

Combined chemoradiation was used in many of the studies in Table 2.

8 Special Topics

8.1 Xerostomia

Xerostomia, as result of either radiation and/or chemotherapy impacts on the ability to swallow or speak. This topic is also addressed in "Radiation-Induced Ototoxicity".

8.1.1 Pathophysiology of the Radiation Effect

The high prevalence of xerostomia following treatment of head and neck cancer is related to the extreme radiosensitivity of the salivary glands. One week after the start of irradiation, after $\approx$10 Gy (out of 60–70 Gy typically delivered over the course of radiotherapy) has been delivered, the salivary output declines by 60–90 %, with some late recovery if the radiation dose is moderate (Mossman 1983; Ship et al. 1997; Shannon et al. 1978).

The mechanism of acute salivary damage is not well understood. The parenchymal tissue of the salivary glands has a low mitotic activity. Reproductive death due to DNA damage is therefore unlikely during and shortly after radiation. Acute inflammatory infiltrates parallel degenerative changes in parenchymal cells 24 h after a single radiation dose, more in serous than in mucous cells (Kashima et al. 1965). Following a high radiation dose, the degenerative changes progress over time and the glands atrophy and become fibrotic. Stephens et al. (1986) observed in primates' glands an increase in the intensity of the degenerative changes with dose and time, especially in the serous acinar cells. They described two types of damage: apoptosis at low doses and necrosis at high doses (Stephens et al. 1986; Savage et al. 1985). The higher sensitivity of the serous acinar cells causes an initial reduction in the watery content of saliva relative to its mucins, other proteins, and mineral content. As a result, an initial rise in the concentration of these contents occurs. The initial reduction of the watery content causes the sticky saliva reported by patients soon after radiation starts. Over time, the mucinous salivary contents diminish, and the sticky saliva disappears.

Based on studies in rats, Nagler (2003) hypothesizes that the radiation damage is due to autocatalytic oxidation induced by oxidation–reduction active metals, such as iron and copper, contained in secretory granules (Nagler 2003), while apoptotic mechanisms did not seem to be important (Paardekooper et al. 1998 Jun). This proposed mechanism prompted trials of salivary stimulation during radiotherapy (RT) in order to gain long-term benefit (see below). Konings et al. (2005) have argued that both the apoptotic and granule leakage theories do not explain the lack of cell loss during the first days after radiation started, while salivary production is dramatically diminished. Their review of the experimental literature showed that water secretion is selectively hampered due to plasma membrane damage which disturbs muscarinic receptor-stimulated water secretion (Burlage et al. 2001; Coppes et al. 2002). These authors suggested that this acute effect may be ameliorated by prophylactic treatment with specific receptor agonists (Konings et al. 2005).

8.1.2 Dose-Response Relationships

Comparisons of the sensitivity to radiation of the parotid versus the submandibular glands, using scintigraphy or selective gland saliva measurements, have demonstrated conflicting results. Some studies showed a higher sensitivity of the parotid glands, as would be expected from their higher content of serous cells (Liem 1996; Murdoch Kinch et al. 2008). However, studies in rats found no difference, (Burlage et al. 2001; Valdez et al. 1992) or even higher sensitivity of the submandibular glands (Coppes et al. 2002). It should be noted that all the studies which compared directly parotid and submandibular glands radiation sensitivity in humans showed higher sensitivity of the parotid glands [detailed in Murdoch Kinch et al. (2008)]. The differences between the findings in humans and in laboratory animals highlight the limits of our ability to extrapolate experimental findings in this field to the clinic.

Studies of dose-volume-response relationships in the major salivary glands have primarily focused on the parotid glands because they typically lie outside or at the periphery of the targets in head and neck cancer. In contrast, the submandibular glands often lie within nodal targets (submandibular lymph nodes, or nodal level IB), or, if they lie outside the targets, they are immediately anterior to upper neck jugular nodes (level II) which are almost always included in the targets. Recent advances in RT treatment planning include the ability to construct dose-volume histograms (DVHs), facilitating an accurate assessment of the dose distributions in the glands. Several recent studies have been published assessing dose-response relationships based on DVHs (Eisbruch et al. 1999, 2001; Roesink et al. 2001; Schilstra and Meertens 2001; Chao et al. 2001; Maes et al. 2002). The common finding in all these studies is the correlation of the post-RT gland function with the mean gland dose. This is expected in an organ with a "parallel" organization of its functional subunits (Withers et al. 1988). The studies differ in the methods of salivary collection: selective parotid flows (Eisbruch et al. 1999; Roesink et al. 2001; Schilstra and Meertens 2001) or whole mouth saliva, (Chao et al. 2001) and in the RT technique: standard 3-field RT (Roesink et al. 2001; Schilstra and Meertens 2001) or various methods of intensity modulated radiotherapy (IMRT) (Eisbruch et al. 1999; Chao et al. 2001; Maes et al. 2002) causing different spatial dose distributions within the glands. This topic is addressed in more detail in "Radiation-Induced Ototoxicity".

8.2 Pediatrics

Inadvertent radiation exposure of the laryngeal cartilage especially thyroid cartilage, which encompasses the larynx, is similar to growing bone and is radiosensitive. Thus, the glottis development is arrested.

8.3 Surgery and Radiation-Induced Swallowing Dysfunctions

Surgery-related swallowing disorders usually occur during the first few months following surgery. Abnormal swallowing biomechanics depend on the site of surgery, the extent of resection, and the type of reconstruction (Logemann 1998; Logemann and Bytell 1979; McConnel et al. 1998).

Pauloski et al. (1998, 1994) studied the effect of postoperative RT in a surgical resection-matched patient population. Patients receiving postoperative radiation had increased oral transit time, greater pharyngeal residue, lower OPSE, and shorter duration of cricopharyngeal opening. Patients without postoperative radiation demonstrated improvement in swallowing efficiency up to 12 months postsurgery, while patients with adjuvant radiation did not show any improvement in swallowing function.

9 Prevention and Management

9.1 Prevention

9.1.1 Radiation Modulation

Using current technologies, it is possible to reduce the radiation doses and the volume of critical structures involved in swallowing without compromising the target. Eisbruch et al. (2004) identified the larynx and PC as playing an important role. By decreasing radiation to these

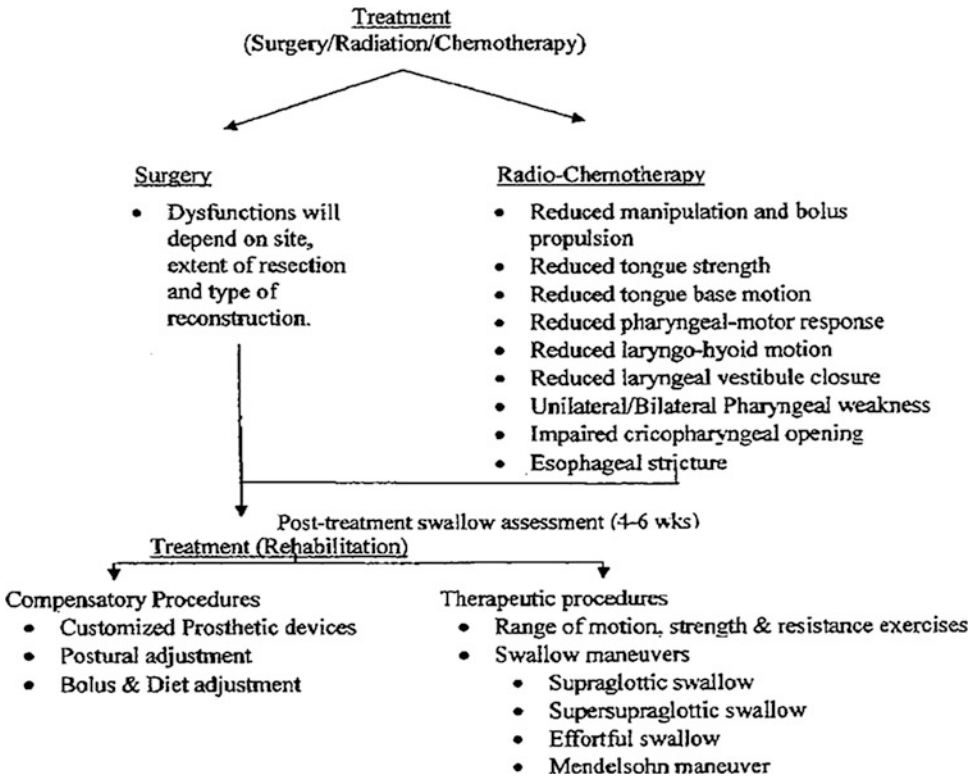

Fig. 9 Algorithm for evaluation and treatment of swallowing dysfunctions in patients with head and neck cancers

structures using IMRT, they were able to reduce the incidence of aspiration and swallowing disorders (Feng et al. 2007). Similarly, Mittal et al. (2001) were able to decrease swallowing disorders with the use of static multisegmental IMRT. The incidence of early and late feeding tube placement was also decreased with IMRT (Koneru et al. 2007). However, Milano et al. (2003) and Garden et al. (2003) observed no difference in swallowing disorders with the use of IMRT. Garden (2003) and Chao et al. (2004) also observed no difference in the need for a feeding tube when IMRT was used.

IMRT is time-consuming and organs at risk need to be defined to prevent excessive doses to the larynx and postcricoid esophagus, which can be spared using conventional radiation techniques with a small midline shield (Amdur et al. 2004). The use of this technique is also supported by the dosimetry study of Fua et al. (2007) They were able to decrease the pharyngoesophageal axis (PEA) mean dose from 55.2 to 27.2 Gy using junctional IMRT (J-IMRT) with a midline shield as opposed to whole-field IMRT (WF-IMRT). The incidence of dysphagia and the duration of a feeding tube requirement were significantly less when the J-IMRT technique was used. However, the PEA can be classified as a dose-avoidance structure during WF-IMRT in order to decrease the radiation dose to the PEA. Further studies are needed to identify the dose-volume relationship to the critical organs and neuromuscular systems involved in swallowing.

9.2 Management

9.2.1 Oral Feeding Versus Feeding Tube

More than 70 % of patients treated with intensive concurrent chemoradiation for head and neck cancer required a feeding tube by the end of treatment (Lee et al. 2006; Ang et al. 2005; Kies et al. 1998). One year following treatment, at least 20 % of patients still required a feeding tube to supplement their oral intake (Dornfeld et al. 2007; Ang et al. 2005; Kies et al. 1998). The use of a prophylactic feeding tube is controversial (Al-Othman et al. 2003). Rosenthal et al. (2006) support the use of oral feeding to the maximally tolerated food viscosity as long as possible even if the patient already has a feeding tube. Gillespie et al. (2004) reported a worse swallowing outcome in patients who had not had oral intake for more than 2 weeks. Patients should continue oral intake to reduce the risk of long-term tube dependency and dysphagia (Murphy et al. 2006). Rosenthal et al. (2006) and Mekhail et al. (2001) suggest that a nasogastric (NG) feeding tube decreases the need for esophageal dilatation versus a percutaneous endoscopic gastrostomy (PEG) tube. They hypothesized that the NG tube serves as a stent to prevent stricture formation. However, when using the NG tube, it is necessary to take care to avoid trauma to the PEA. We also support continual oral feeding so long as it does not compromise the patient's nutritional status and increase the risk of aspiration. An

algorithm for the assessment of patients' post-treatment is provided in Fig. 9.

9.2.2 Cytoprotectors

Amifostine (WR 2721) is the most commonly used cytoprotector for reducing the incidence of xerostomia and mucositis (Brizel et al. 2000; Büntzel et al. 2002; Sasse et al. 2000). However, there is no data to support its role in decreasing late swallowing disorders. Further studies are needed.

9.2.3 Oropharyngeal Exercises

Oropharyngeal exercises are designed to improve swallowing biomechanics by increasing the excursion of swallowing organs and strengthening the musculature involved in deglutition. Range of motion exercises are available for the oral tongue, base of tongue, and the hyoid-laryngeal complex (Logemann 1998, 2007; Veis et al. 2000). Isometric resistance exercises are used to strengthen the tongue, jaw, larynx, and lips (Robin et al. 1992). Some exercises can facilitate opening of the upper esophageal sphincter (Shaker et al. 1997).

10 Future Research (Reference: Quantec S69 section B9)

Late dysphagia is often a consequential effect of acute mucositis. Careful assessment and reporting of the severity of acute mucositis might shed light on the likelihood of late dysphagia and its predictors, and whether successful reduction in acute dysphagia would lead to improvements in late swallowing abnormalities.

10.1 Validation of Assessors of Dysphagia

The most commonly used observer-rated dysphagia grading tool is the CTCAE dysphagia item, which has not been validated formally. Similarly, multiple patient-reported QOL instruments have been used, as detailed in the present report, and few have formally been validated regarding their dysphagia components.

The issue of what are the most important anatomic structures and substructures whose damage is the likely cause of dysphagia is the subject of current research by many investigators.

An important aspect of this research is the effects of the tumor on pretherapy swallowing and on the functional results after therapy. To capture these effects, prospective studies that have included pretherapy evaluations are essential.

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Thyroid

Michael T. Milano and Louis S. Constine

Contents

Abstract

- The thyroid gland consists of follicles, lined with a single layer of epithelial cells that actively transport iodine into the follicle as well as generate and secrete thyroid hormones, T3 and T4.
- Initial radiation injury is to the endothelium of small vessels, and with additional radiation exposure, the follicular epithelial cells degenerate as a result of further damage to the vasculature.
- The follicular epithelial cells synthesize and release triiodothyronine (T3) and thyroxine (T4).
- Late radiation injury to the thyroid can result in hypothyroidism, hyperthyroidism, benign nodularity, and/or malignancy; Hypothyroidism is the most common late reaction after therapeutic radiation exposure of the thyroid gland.
- Most studies show the incidence of hypothyroidism progressively rising in the first 3–5 years after radiation, with most patients manifesting clinical signs or symptoms 2–4 years after radiotherapy.
- Neck dissection, increased radiation dose to the thyroid, and greater volume of thyroid radiation exposure are well-accepted risk factors for hypothyroidism.
- Radiation-induced hyperthyroidism is a well-documented complication, albeit much less common than hypothyroidism.
- Thyroiditis is a non-specific condition referring to inflammation of they thyroid gland; thyroiditis can result in hyperthyroidism and/or hypothyroidism.
- Radiation has also been reported to result in benign adenoma formation as well as thyroid cancer.
- The risk of thyroid cancer is increased by 10–50-fold after therapeutic radiation exposure to the thyroid, and persists many decades after radiation.
- Younger patients appear to be at a greater risk of thyroid cancer after thyroid irradiation.
- The risk of cancer induction may increase with dose to the thyroid, but then decrease after 20–30 Gy; this is a

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different dose–response relationship compared with most other secondary malignancies.
- Patients receiving radiation dose to their neck should undergo routine physical examination of the neck as well as regular thyroid function tests. The role of surveillance imaging is unclear.

Abbreviations

CCSS	Childhood cancer survivor study
PTU	Propylthiouracil
RiSK	Registry for the evaluation of side effects after radiotherapy in childhood and adolescence
SEER	Surveillance epidemiology end results
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone

1 Introduction

The thyroid gland may be intentionally or incidentally exposed to therapeutic radiation dose in the treatment of many malignancies. The thyroid gland is exposed to therapeutic doses of radiation with prophylactic or therapeutic treatment of the cervical lymphatics in the treatment of Hodgkin's disease and non-Hodgkin's lymphoma, head and neck cancer, and cervical esophageal cancer. The cervical lymphatics are generally treated to doses of 20–40 Gy for Hodgkin's disease and non-Hodgkin's lymphoma as compared to 45 to >70 Gy for head and neck cancers. Thyroid gland exposure also results from supraclavicular irradiation, craniospinal irradiation (generally 18–36 Gy) or total body irradiation (generally 6–12 Gy). Scattered radiation from radiotherapy to the brain, head and neck, breast and thorax may lead to low-dose exposure to the thyroid. For example, the dose to the thyroid from cranial radiation is on the order of 1–2 % of the prescribed radiation dose Constine et al. (1993). Historically, the treatment of benign conditions, such as tinea capitis, acne, thymic enlargement, and tonsillitis resulted in thyroid gland exposure. There is also an increased risk of thyroid abnormalities and thyroid cancer after radiation disasters. This chapter will focus on late thyroid abnormalities in patients treated with therapeutic external beam radiation.

The late effects of radiation exposure to the thyroid gland include hyperthyroidism, hypothyroidism, thyroiditis, benign nodule formation, and malignancy Rubin et al. (1968) Hancock et al. (1995); Jereczek-Fossa et al. (2004). The effects on the thyroid gland resulting from radiation to the hypothalamic-pituitary axis are discussed in "Endocrine complications of cancer therapy chapter". Certainly both central and primary hypothyroidism can result from radiation exposure to the hypothalamic-pituitary axis and neck, which often occurs with the treatment of nasopharyngeal and nasal sinus malignancies (Bhandare et al. 2007; Daniell 2002) and brain tumors (i.e., cranial-spinal irradiation).

Table 1 Global/focal thyroid changes after radiation

	Focal	Global
Subclinical	Histopathologic thyroid gland changes (not routinely assessed)	Changes in thyroid hormone levels (TSH and/or T4)
Clinical	1. Generally no clinically overt thyroid changes 2. Thyroid nodularity 3. Goiter	1. Clinical symptoms of hypothyroidism (see text) 2. Clinical symptoms of hyperthyroidism (see text)

There are abundant studies, both in humans and animals, investigating the late effects of radiation on the thyroid gland. Many of these studies are reviewed here. Despite the large number of studies, it is difficult to quantify the overall incidence, types and severity of late radiation-induced thyroid disorders, in part due to many confounding variables such as the age at the time of exposure, radiation dose and dose fractionation, radiation technique (i.e., external beam, radioactive iodine, brachytherapy), volume of exposure, and the use of other treatment modalities such as surgery and/or chemotherapy. Jereczek-Fossa et al. (2004) additionally, there are no consensus definitions of what constitutes a thyroid disorder and how to quantify the extent of dysfunction. The clinical syndromes associated with radiation injury to the thyroid are outlined in Table 1.

As early as the 1920s, Groover and colleagues reported that radiation therapy for hyperthyroidism resulted in hypothyroidism after doses 1500–2000 R (on the order of 15–20 Gy), with the incidence of severe hypothyroidism being 1.3 % of 305 patients (Groover et al. 1929). Some early animal studies had suggested that relatively high doses of radiation did not alter the microscopic appearance of the thyroid in the days and months following radiation, Bower and Clark 1923; Eckert et al. 1937; Warren 1943) but did result in a deficiency of physiologic compensatory hypertrophy when a portion of the thyroid has been resected (Eckert et al. 1937). Prior to 1960, hypothyroidism secondary to high doses from radioactive I131 therapy was well characterized, but hypothyroidism from external beam radiation was thought to be uncommon (Felix et al. 1961; Markson and Flatman 1965). In the 1960s, case studies reported that normal thyroid radiation exposure during therapeutic radiation resulted in clinical hypothyroidism months to years after radiation Felix et al. 1961; Markson and Flatman 1965. In a Swedish study of 41 patients treated with radiation for laryngeal and hypopharyngeal cancer, experimentally

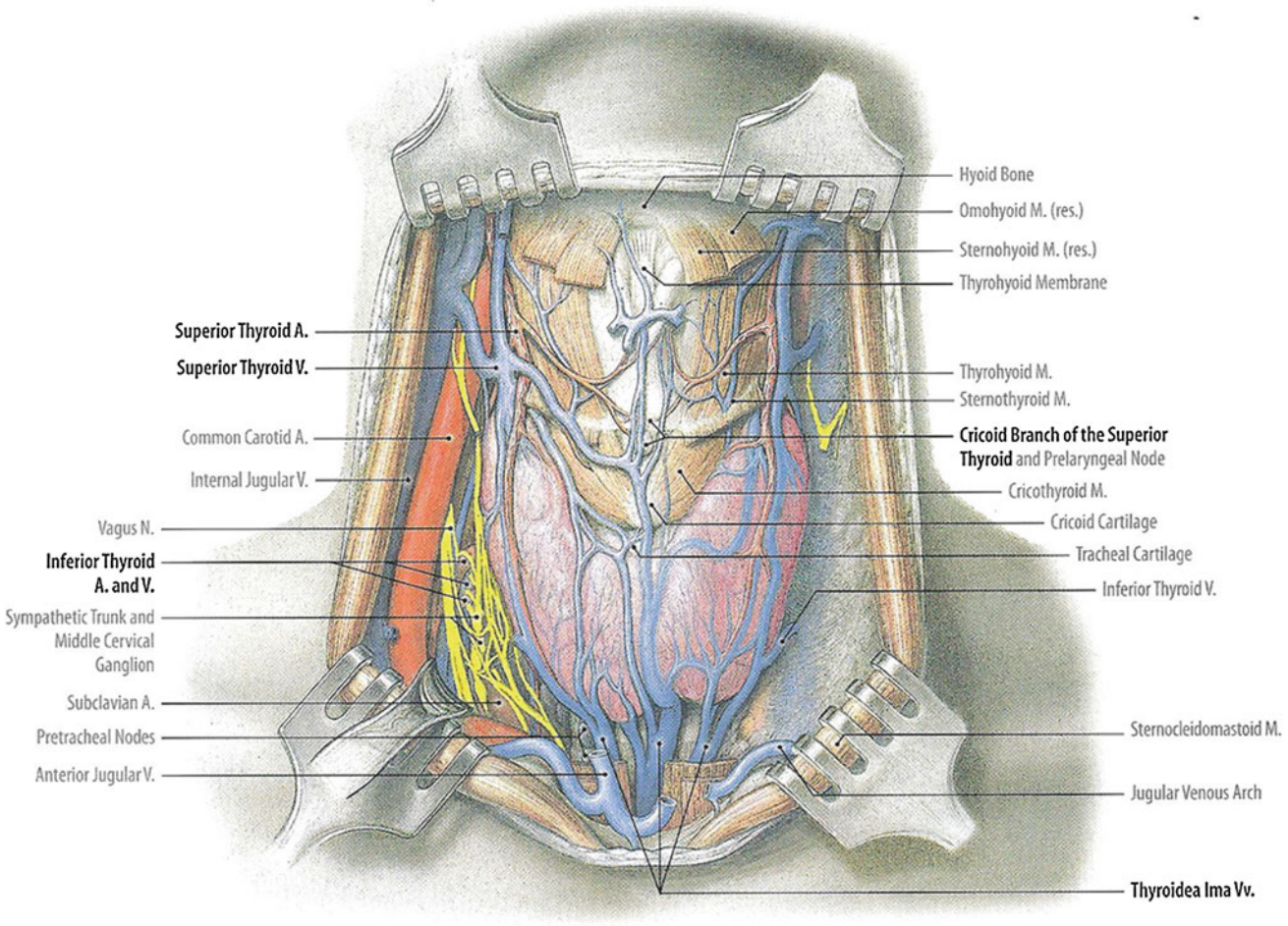

Fig. 1 Gross anatomy of the neck showing the thyroid gland in relation to nerves, vasculature, and muscles (with permission from Tillman 2007)

measured thyroid iodine uptake was diminished as compared to controls; 4 patients had clinical hypothyroidism, 1 of whom had severe hypothyroidism (Einhorn and Wilkholm 1967). In the 1970s, data began to emerge that thyroid malignancies were a late complication after low-dose radiation, particularly in those irradiated as infants and children (Beahrs 1976; Becker et al. 1975; Favus et al. 1056). In a study of over 1,000 patients treated with radiation to the head and neck, 17 % developed nodular disease and 11 % had nonpalpable lesions detected by nuclear imaging; one-third of those patients undergoing surgery for nodular disease had malignancy (Favus et al. 1056).

2 Anatomy and Histology

The thyroid gland is a bilobed, butterfly shaped endocrine gland, with right and left lobes connected by a narrow isthmus (Fig. 1). In some people, there may be a vestigial pyramidal lobe, which is a remnant of the lower end of the thyroglossal duct. The gland is surrounded by a fibrous capsule which attaches to the pre-tracheal fascia. It is situated in the low anterior neck, partially encircling the larynx and trachea anteriorly, extending superiorly from the thyroid cartilage and inferiorly to the tracheal rings (Hancock et al. 1995).

The thyroid gland consists of follicles, lined with a single layer of epithelial cells that actively transport iodine into the follicle as well as generate and secrete thyroid hormones, T3 and T4 (Fig. 2a, b). The follicles are filled with colloid, rich with the high molecular weight protein thyroglobulin necessary for thyroid hormone synthesis as well as the hormonally inactive monoido- and diiodo-tyrosines (Hancock et al. 1995).

3 Biology, Physiology, and Pathophysiology

3.1 Physiology and Biology

The follicular epithelial cells synthesize and release triiodothyronine (T3) and thyroxine (T4). Once released into the blood, the active thyroid hormones are bound to and

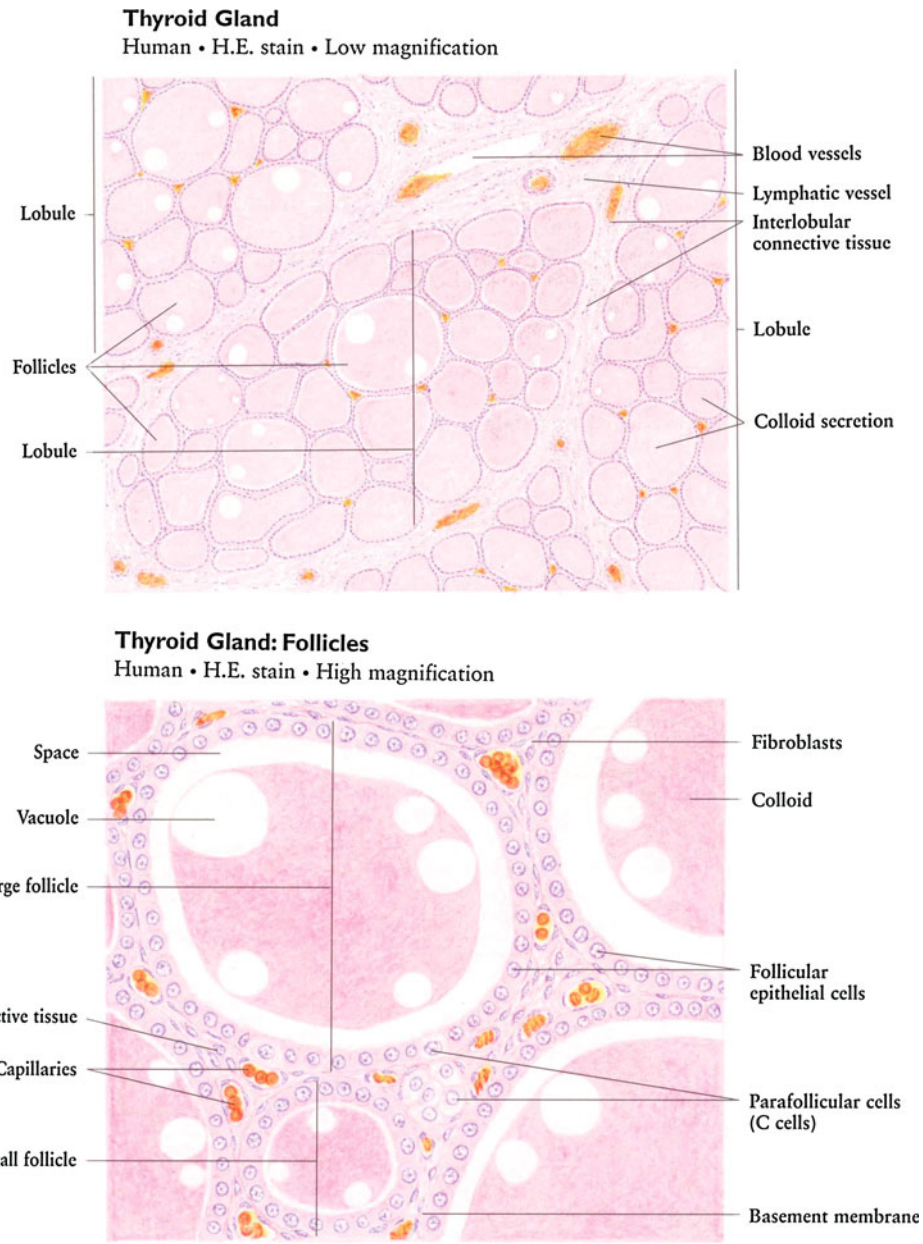

Fig. 2 Histologic appearance of the thyroid gland at low **a** and high **b** magnification. At high magnification, the follicular epithelial cells and parafollicular cells are readily apparent (with permission from Zhang 1999)

transported via thyroxine-binding globulin, transthyretin, and albumin, with only a small fraction remaining freely unbound (the unbound fraction is hormonally active). T4 is converted to T3 by peripheral organs; T3 is about ten times more active than T4.

The production of T3 and T4 is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary gland. TSH production is suppressed by high T4 levels and stimulated when T4 is low. TSH production is modulated by thyrotropin-releasing hormone (TRH), produced by the hypothalamus.

Parafollicular "C-cells," are sporadically situated between follicles; C-cells secrete calcitonin in response to hypocalcemia, opposing the effects of parathyroid hormone. There does not appear to be any clinically significant consequences from calcitonin deficiency or excess.

3.2 Pathophysiology/Mechanism of Radiation-Induced Injury

Generally, radiation changes in the thyroid result from damage to small vessels (remote branches off the superior and inferior thyroid arteries) and surrounding capsule, and presumably less so from direct damage to the follicular epithelial cells due to their slow turnover (Hancock et al. 1995; Jereczek-Fossa et al. 2004). Rubin and Cassarett postulated that the initial injury was to the endothelium of

small vessels, and with additional radiation exposure, the follicular epithelial cells degenerate as a result of further damage to the vasculature (Rubin et al. 1968). Late changes are primarily attributable to vascular damage, while acute and subacute changes may be more affected by repairable damage to the epithelioid cells (Jereczek-Fossa et al. 2004). Acute radiation changes to the thyroid include diminished follicle size with low cuboidal epithelium lining residual follicles, and with higher doses, including therapeutic I131 exposure, follicular necrosis, vasculitis, thrombosis, and hemorrhage followed by vascular sclerosis and lymphocytic infiltration (Hancock et al. 1995). Chronic changes after relatively low-dose exposure include focal and irregular follicular hyperplasia, hyalinization, fibrosis beneath the vascular endothelium, lymphoytic infiltration, thyroiditis, cellular and nuclear atypia, infarction and necrosis (Hancock et al. 1995; Carr and LiVolsi 1989).

In a study of late effects on the thyroid gland in 26 rhesus monkeys undergoing total body irradiation (thus undergoing thyroid as well as hypothalamic-pituitary radiation exposure), increased radiation dose was associated with diminished thyroid gland weight. (Bakker et al. 1999) Half of the thyroid gland specimens (and 6 of 7 in the higher dose group) were noted to have small follicles; one had macrofollicular goiter and papillary hyperplasia. There are scant histopathologic data from humans. In 4 patients from the University of Pennsylvania, undergoing thyroid surgery for palpable nodularity 8–20 years after cervical irradiation, discrete hypercellular adenomatous nodules and hyperplastic nodules (akin to multinodular goiter) were seen in all cases (Carr and LiVolsi 1989). Mild to severe cellular and nuclear atypia was also seen, in the absence of mitoses (Carr and LiVolsi 1989). Thyroid carcinoma can also result from low-dose exposure, though much less commonly. The clinical manifestation of radiation changes includes hypothyroidism, hyperthyroidism, thyroiditis, adenoma formation, and malignancy.

3.3 Cellular Dynamics and Radiation Response

The extent to which there is thyroid organ recovery and/or regeneration is not well documented in the literature. Likewise, the kinetics of the pathophysiologic changes resulting in late thyroid toxicity are not well understood. The latency period between radiation exposure and the clinical manifestation of late thyroid toxicity varies widely. Radiation-induced occult hypothyroidism progresses to clinical hypothyroidism in about a quarter of patients, (Constine et al. 1984) suggesting progression and/or evolution of radiation-induced damage (Hancock et al. 1995). However, rarely hormone levels spontaneously normalize, suggesting a mechanism for repair in some patients (Hancock et al. 1995; Constine et al. 1984). Late transient "silent" thyrotoxicosis has also been observed, albeit uncommonly. This is generally followed by overt hypothyroidism, suggesting that the recovery from thyrotoxicosis leaves a hypo-functioning gland.

4 Clinical Syndromes

To date, there are no compelling data to suggest that susceptibility to radiation-induced thyroid abnormalities has a component of genetic predisposition. The focal and global effects of radiation on the thyroid are briefly summarized in Table 1.

4.1 Hypothyroidism

Hypothyroidism may manifest with classic symptoms, including weight gain, cold intolerance, dry skin, brittle hair, constipation, menstrual irregularities, muscle cramping, and slower mentation; classic signs include periorbital and peripheral edema, hypotension, bradycardia, pericardial effusions, pleural effusions, and prolonged relaxation of deep tendon reflexes. Hypothyroidism is a common condition of the elderly, and thus the contribution of radiation in the development of hypothyroidism in elderly patients may not be readily determined. Hypothyroidism may be occult, detected only by low thyroxine levels and/or elevated TSH (Boomsma et al. 2011). This is often referred to as subclinical or covert hyothyroidism, as opposed to clinical or overt hypothyroidism, in which the hypothyroidism is associated with clinical symptomatology. Compensated hypothyroidism occurs when the pituitary gland releases high levels of TSH, and thus overworks the thyroid gland to maintain adequate levels of circulating thyroid hormones. With uncompensated hypothyroidism, T4 remains low despite elevated TSH. Radiation-induced occult hypothyroidism is likely to progress to clinical hyothyroidism, (Hancock et al. 1995) though TSH levels can spontaneously normalize over long time intervals (Hancock et al. 1995; Constine et al. 1984).

The reported incidence of hypothyroidism after thyroid radiation ranges from >15–50 % (Boomsma et al. 2011). Most studies show the incidence of hypothyroidism progressively rising in the first 3–5 years after radiation, with most patients manifesting clinical signs or symptoms 2–4 years after radiotherapy (Bhandare et al. 2007; Tell et al. 2004; Kim et al. 1980). Some studies demonstrate additional cases of hypothyroidism beyond 5 years, (Garcia-Serra et al. 2005; Mercado et al. 2001; Vrabec and Heffron 1981; Tamura et al. 1981; Hancock et al. 1991) and

others show minimal to no appreciable additional risk beyond 5 years (Bhandare et al. 2007; Tell et al. 2004; Kumpulainen et al. 2000).

In a recent study from the University of Florida, in which 312 patients with nasopharynx, nasal cavity, and nasal sinus cancers, the thyroid dose associated with primary hypothyroidism ranged from 36.5 to 65.6 Gy (median 45 Gy); increased radiation dose was significantly correlated with a greater risk of primary hypothyroidism (Bhandare et al. 2007). The median clinical latency was 3.1 years; latency was independent of dose. Ten-year rates of clinical and occult hypothyroidism were 33 and 29 % (of those without clinical hypothyroidism) respectively. These values are similar to those reported by other groups with a large patient population and long follow-up for both head and neck cancer (Tell et al. 2004; Vrabec and Heffron 1981; Kumpulainen et al. 2000) and Hodgkin's disease (Tamura et al. 1981; Hancock et al. 1991). In an earlier study from the University of Florida, 50 Gy delivered as elective nodal treatment in patients with oropharyngeal cancer resulted in hypothyroidism in 30–50 % of patients at 5 years (Norris et al. 2006). In a Swedish study in 391 patients with head and neck cancer, the 10-year rate of 'overt' hypothyroidism (elevated TSH and decreased T4, or requirement of thyroid replacement) was 27 % with a latency of 0.3–8.1 years (median 1.8) (Tell et al. 2004). In a study from Cleveland Clinic, the 8-year actuarial incidence of hypothyroidism was reported to be 67 %, higher than that reported in other series (Mercado et al. 2001). In the Childhood Cancer Survivor Study (CCSS) cooperative group trial, in which 1791 patients with childhood Hodgkin's disease were studied, hypothyroidism developed 0–27 years (mean 7 years) after diagnosis (Sklar et al. 2000). Significantly increased risk was associated with doses $\geq$ 45 Gy versus 35–45 Gy vs. <35 Gy versus no radiation.

4.2 Hyperthyroidism

Hyperthyroidism can manifest with classic symptoms including palpitations, heat intolerance, anxiety, fatigue and insomnia, diarrhea, menstrual irregularities, weight loss, weakness. Clinical signs include goiter, tachycardia, tremor, warm moist skin, thinner skin, fine hair and alopecia, infiltrative ophthalmopathy. Grave's disease is a autoimmune form of hyperthyroidism resulting from the production of antibodies which bind to and chronically stimulate the receptor for thyroid-stimulating hormone (which are expressed in on the follicular cells of the thyroid gland) causing increased production of the T3 and T4 hormones.

Radiation-induced hyperthyroidism is a well-documented complication, albeit much less common than hypothyroidism. In Stanford's series of 1,787 patients treated with radiation for Hodgkin's disease, hyperthyroidism was observed in 30 patients (1.7 %) 3 weeks to 18 years (mean 5.3 years) posttreatment (Hancock et al. 1991). Ten of these 30 patients were previously diagnosed and treated for hypothyroidism. An additional 4 patients developed infiltrative ophthalmopathy consistent with Grave's disease, despite being clinically hypothyroid ($n = 3$) and euthyroid ($n = 1$). In a Hungarian study, 2 of 151 patients (1.3 %) treated with radiation for Hodgkin's disease developed hyperthyroidism, (Illes et al. 2003) and in a French study of 478 patients treated with total body irradiation, one patient developed hyperthyroidism (Thomas et al. 2001). In the CCSS cooperative group trial, including 1,791 patients with childhood Hodgkin's disease, hyperthyroidism developed in 82 patients (4.5 %) 0–22 years (mean 8 years) after diagnosis (Sklar et al. 2000). Significantly increased risk was associated with doses $\geq$ 35 Gy.

4.3 Thyroiditis

Thyroiditis is a non-specific condition referring to inflammation of the thyroid gland; thyroiditis can result in hyperthyroidism and/or hypothyroidism. Hashimoto's thyroiditis is an auto-immune related condition, generally resulting in hypothyroidism. Thyroiditis is an uncommon complication from therapeutic external beam radiation as opposed to the relatively high incidence of thyroiditis resulting from radioactive iodine therapy.

In Stanford's series of 1,787 patients, 4 patients developed Hashimoto's thyroiditis and 6 patients developed transient 'silent' thyrotoxicosis 10–24 months (except 1 patient at 15 years) after radiation; 'silent' thyroiditis was described as elevated thyroid hormone levels, low TSH, and low radio-iodine uptake (Hancock et al. 1991). In addition to Stanford's series, there have been a few case reports of 'silent' thyrotoxicosis several months to years after radiation, generally transient in nature, and usually followed by overt clinical hypothyroidism (Blitzer et al. 1985; Fachnie and Rao 1980; Petersen et al. 1989). In a French study of 478 patients treated with total body irradiation, 6 patients developed thyroiditis, though the clinical presentation and method of diagnosis are not described (Thomas et al. 2001). In one case report, 'silent' thyroiditis was noted 2 weeks after radiation (Bryer-Ash et al. 2001).

In the above-mentioned Hungarian study of 151 patients treated with radiation for Hodgkin's disease, 28 patients were found to have serum anti-thyroglobulin antibodies; 38 patients (mostly those undergoing neck radiation) developed subclinical ($n = 26$) and clinical ($n = 12$) hypothyroidism (Illes et al. 2003). Of those with detectable serum anti-thyroglobulin antibodies, 53.6 % had thyroid dysfunction versus 20.3 %, mostly occult hypothyroidism, in those

without detectable serum anti-thyroglobulin antibodies. Hypothyroidism was significantly more common in patients undergoing neck radiation (>30 %) versus those receiving chemotherapy alone (5 % among 40 patients); the risk of thyroiditis was roughly twofold higher in patients treated with radiation (26 vs. 13 %), although this difference was not significant. The authors postulate that hypothyroidism may in part result from thyroiditis, which in turn might be result of changes in immune reactivity in patients with Hodgkin's disease (Illes et al. 2003).

4.4 Nodules: Benign and Malignant

Radiation has also been reported to result in benign adenoma formation as well as thyroid cancer. Generally, radiation-induced thyroid malignancies are localized to the thyroid, and readily curable (Schneider et al. 1986). Historically, low-dose radiation (as low as 0.1 Gy) for benign disease (such as tinea capitis, thymic enlargement, lymphoid hyperplasia, lice, acne) has been a well-established risk factor for thyroid nodules and malignancy, with increasing dose (Favus et al. 1056; Adams et al. 2010; Ron et al. 1995) and decreasing age at exposure increasing the risk (Ron et al. 1995). In the 1970–1980s, case-reports were published suggesting that the higher therapeutic radiation doses used to treat malignancy could also induce thyroid nodules and thyroid cancer (McDougall et al. 1980). The vast majority of radiation-induced solid tumors occur within the radiation field (Bhatia et al. 2003; Garwicz et al. 2000).

In MD Anderson's series of 145 child and adult patients treated with radiation for Hodgkin's disease, 7 patients developed palpable thyroid tumors, of which 2 were malignant (Liao et al. 2001). In Roswell Park's series of 126 adult patients treated for Hodgkin's disease and non-Hodgkin's lymphoma, 12 patients (11 of whom were women) developed thyroid nodules 1–6 years after treatment, 5 of whom did not undergo prior neck radiation (Tamura et al. 1981). No patient underwent thyroidectomy and 2 underwent biopsy, which revealed adenoma in one patient and thyroiditis in another.

In Stanford's series of 1,787 child and adult patients, palpable thyroid nodules were appreciated in 44 patients (2.5 %) from 1.5 to 25 years after radiation (Hancock et al. 1991). Eighteen patients had clinically benign disease, including nodules that concentrate radioiodine ($n = 12$), cysts ($n = 4$, based on ultrasound and aspiration), and multinodular goiter ($n = 2$). Twenty-six had pathologically benign disease (which was clinically worrisome for malignancy given the lowered radioiodine uptake), including adenoma ($n = 10$), adenomatous nodule ($n = 6$), and multinodular goiter ($n = 4$). Six patients had thyroid cancer 9–19 years after radiation therapy, with a relative risk of 15.6 ($p < 0.00001$) and absolute risk of 33.9 per 100,000 person years. All patients with cancer remained without evidence of disease recurrence at last follow-up.

In the CCSS cooperative group trial, including 1,791 patients with childhood Hodgkin's disease, thyroid nodules developed in 146 patients (8.2 %) 0–22 years (mean 14 years) after diagnosis, with a relative risk of 27 (Sklar et al. 2000). Significantly increased risk was associated with doses $\geq$ 25 Gy. Eleven of the 146 patients had thyroid cancer in addition to 9 patient with thyroid cancer not associated with thyroid nodularity.

In a multi-institutional retrospective study of 930 childhood Hodgkin's disease survivors, 1.5 % developed thyroid cancer, at 8.5–23 (median 14.4) years after Hodgkin's disease diagnosis, with $\sim$4 times as many females developing thyroid cancer as compared to males (Constine et al. 2008).

5 Radiation Tolerance and Radiation-Induced Injury Risk Factors

5.1 Hypothyroidism

The risk of radiation-induced hypothyroidism is dependent on many factors, including the method of detection (i.e., clinical symptoms versus biochemical hypothyroidism), patient related factors, cancer related factors, treatment related factors, and adequacy and length of follow-up; as a result, the reported risk of hypothyroidism varies widely (Jereczek-Fossa et al. 2004). For example, in one study from the Joint Center of Radiation Therapy, the calculated actuarial incidence of hypothyroidism at 1 year was 27 %, but when the calculation included only patients with $\geq$5 months follow-up, the 1-year incidence was 49 %, which highlights the importance of adequate follow-up when reporting late toxicity (Colevas et al. 2001).

Factors that have been reported to increase the risk of radiation-induced hypothyroidism include older age, (Colevas et al. 2001; Tell et al. 1997) younger age, (Hancock et al. 1991; Sklar et al. 2000; Glatstein et al. 1971) female gender, (Tell et al. 2004; Alterio et al. 2007; Vrabec and Heffron 1981; Hancock et al. 1991; Wu et al. 2010; Posner et al. 1984) caucasian race, (Mercado et al. 2001; Metzger et al. 2006a) smaller thyroid volume, (Alterio et al. 2007; Diaz et al. 2010) baseline TSH, (Tell et al. 2004) concurrent or adjuvant chemotherapy, (Hancock et al. 1991; Posner et al. 1984) (with one study suggesting chemotherapy lowers the risk of hypothyroidism (Tamura et al. 1981)), resection/hemithyroidectomy, (Tell et al. 2004; Garcia-Serra et al. 2005; Turner et al. 1995; Vrabec and Heffron 1981; Liening et al. 1990; Kumpulainen et al. 2000; Tell et al. 1997; Posner et al. 1984; Leon et al. 2002; Ozawa et al. 2007; Smolarz et al. 2000; Shafer et al. 1975) and

Table 2 Radiation dose to the thyroid gland and the risk of hypothyroidism

Institution	Patient population	#	Risk of hypothyroidism
Stanford U (Constine et al. 1984)	Children with Hodgkin's lymphoma	119	Thyroid disorders (mostly hypothyroidism): 78 % for >26 Gy vs. 17 % for ≤26 Gy
Stanford U (Hancock et al. 1991)	Adults and children with Hodgkin's lymphoma	1,787	Clinical hypothyroidism: 20 % for ≥30 Gy vs. 5 % for 7.5–30 Gy at 20 years, $p = 0.001$
			Subclinical or clinical hypothyroidism: 44 % for ≥30 Gy vs. 27 % for 7.5–30 Gy at 20 years, $p = 0.008$
Childhood cancer Survivor study (Sklar et al. 2000)	Children with Hodgkin's disease	1,791	Patient reports "underactive thyroid" 50 % for ≥45 Gy vs. 30 % for 35–45 Gy vs. ~20 % for <35 Gy at 15 years
Joint center for Radiation therapy (Kaplan et al. 1983)	Childhood cancer	95	Elevated TSH: 68 % for ≥30 Gy vs. 15 % for <30 Gy p = 0.007
RiSK Study(Bolling et al. 2010)	Childhood cancer	404	Elevated TSH, versus prophylactic cranial RT 15–25 Gy to thyroid gland, RR 3.1 ($p = 0.002$)>25 Gy to thyroid gland, RR 3.8 ($p = 0.009$)Cranio-spinal radiation, RR 5.7 ($p < 0.001$)
U. Florida (Bhandare et al. 2007)	Adults with head and neck cancer	197	Clinical hypothyroidism: 39 % for ≥45 Gy vs. 21 % for <45 Gy at 10 years, $p = 0.04$
Federico II U. (Cella et al. 2011)	Teenagers and adults with Hodgkin's lymphoma	53	Subclinical or clinical hypothyroidism: 11.5 % for thyroid V30 ≤ 62.5 % 70.8 % for thyroid V30 > 62.5 %, $p < 0.0001$
Vanderbilt U. (Diaz et al. 2010)	adults with head and neck cancer	63	Not significant: area under the DVH curve, V10, V20, V30, V40, V50, V60, V70, or median, minimum, or maximum thyroid dose
U. Milan (Alterio et al. 2007)	adults with head and neck cancer	57	V10, V30, V50 not significant for clinical or subclinical hypothyroidism

comorbid diabetes (Bhandare et al. 2007). Radiation dose is also significant in several studies, as summarized in Table 2 (Bhandare et al. 2007; Constine et al. 1984; Hancock et al. 1991; Sklar et al. 2000; Glatstein et al. 1971; Weissler and Berry 1991; Kaplan et al. 1983; Kuten et al. 1996). A cohort of childhood Hodgkin lymphoma survivors treated between 1970 and 1986 were evaluated for thyroid disease by use of a self-report questionnaire in the CCSS. Among 1,791 survivors, 34 % reported that they had been diagnosed with at least one thyroid abnormality. For hypothyroidism, there was a clear dose response, with a 20-year risk of 20 % for those who received <35 Gy, 30 % for those who received 35–44.9 Gy, and 50 % for those who received >45 Gy to the thyroid gland. The relative risk for hypothyroidism was 17.1. Elapsed time since diagnosis was a risk factor, where the risk increased in the first 3–5 years after diagnosis (Sklar et al. 2000). The cumulative incidence of hypothyroidism among survivors 15 years following leukemia diagnosis has also been evaluated in the CCSS and was 1.6 %. In multivariate analysis, survivors who received ≥ 20 Gy cranial radiotherapy plus any spinal radiotherapy had the highest risk of subsequent hypothyroidism (hazard ratio 8.3) compared with those treated with chemotherapy alone. In radiation dosimetry analysis, pituitary doses ≥20 Gy combined with thyroid doses ≥10 Gy were associated with hypothyroidism (Chow et al. 2009). Figure 3 shows the dose dependence of hypothyroidism risk from one study of survivors of childhood cancer. In the German "Registry for the Evaluation of Side Effects After Radiotherapy in Childhood and Adolescence" (RiSK) study of 404 patients (with various diagnoses), higher doses to the thyroid were associated with increased risks of TSH elevation (Bolling et al. 2010).

Some studies suggest that age, (Bhandare et al. 2007; Constine et al. 1984; Mercado et al. 2001; Tamura et al. 1981; Illes et al. 2003; Kumpulainen et al. 2000; Tami et al. 1992; Kaplan et al. 1983; Smith et al. 1981; Boomsma et al. 2012) gender, (Bhandare et al. 2007; Constine et al. 1984; Colevas et al. 2001; Mercado et al. 2001; Tamura et al. 1981; Liening et al. 1990; Tell et al. 1997; Glatstein et al. 1971; Diaz et al. 2010; Tami et al. 1992; Weissler and Berry 1991; Kaplan et al. 1983; Smith et al. 1981; Bethge et al. 2000) race, (Bhandare et al. 2007; Garcia-Serra et al. 2005) prior neck dissection, (Smith et al. 1981; Garcia-Serra et al. 2005; Colevas et al. 2001; Norris et al. 2006; Sinard et al. 2000; Weissler and Berry 1991; Boomsma et al. 2012) concurrent or adjuvant chemotherapy administration, (Bhandare et al. 2007; Constine et al. 1984; Mercado et al. 2001; Sklar et al. 2000; Illes et al. 2003; Norris et al. 2006; Tell et al. 1997; Sinard et al. 2000; Weissler and Berry 1991; Kaplan et al. 1983; Smith et al. 1981; Bethge et al. 2000; Nelson et al. 1978) comorbid chronic illness (including diabetes) (Kumpulainen et al. 2000; Boomsma et al. 2012) are not significant for the development of radiation-induced hypothyroidism. The radiation dose to the neck was also not a significant risk factor in several studies in patients with head and neck cancer, (Colevas et al. 2001; Mercado et al. 2001; Kumpulainen et al. 2000; Tell et al.

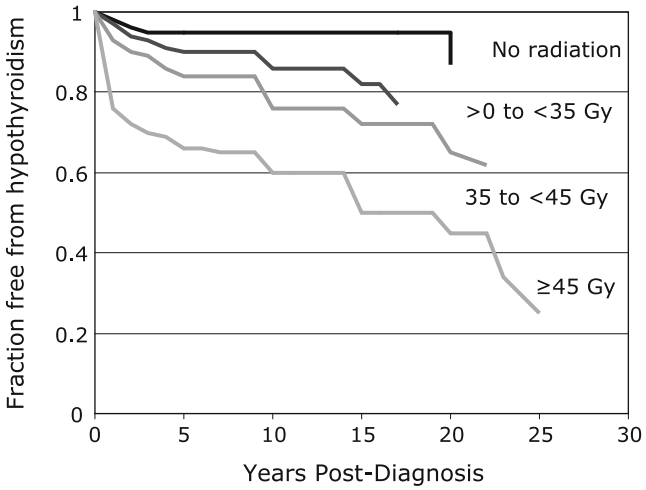

Fig. 3 Dose dependence of hypothyroidism risk from a study of 1,791 survivors of childhood cancer. Data and figure was derived from reference (Sklar et al. 2000), in which actuarial rates of hypothyroidism were calculated among 377 patients who received no radiotherapy, and 1,210 patients for whom sufficient data were available to estimate the dose of radiation to the thyroid gland (median 35 Gy and range 0.004–55 Gy)

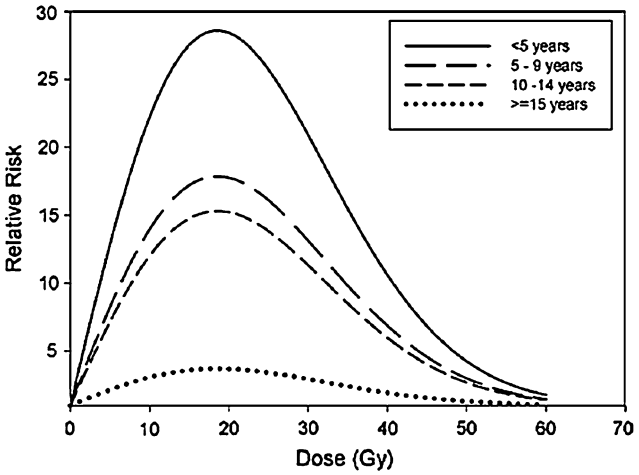

Fig. 4 Data-based model of risk of thyroid cancer as a function of dose and age at diagnosis, copied from a CCSS cohort study (reference Bhatti et al. 2010 with permission)

1997; Posner et al. 1984) though this may in part be reflective of a more uniform dose distribution in these studies and/or doses exceeding 45 Gy in most patients treated for head and neck cancer. For example, in one study, the risk of hypothyroidism after a dose of >65 Gy was not greater than the risk after doses of 45–65 Gy (Posner et al. 1984).

Conflicting data with respect to which variables are significant for developing hypothyroidism is likely a reflection of differences in patient populations, treated diseases, and cancer treatment strategies, as well as differences in length of follow-up, definition of hypothyroidism and follow-up strategy with respect to detecting hypothyroidism. Furthermore, most of the studies which have investigated post-treatment hypothyroidism are single institution retrospective analyses, often with small numbers of patients, and are therefore limited in their ability to ascribe significance or lack of significance to prognostic variables.

5.2 Hyperthyroidism and Thyroiditis

Because hyperthyroidism and thyroiditis are much less common late effects after radiation than hypothyroidism, the risk factors associated with these complications are not well documented. In a Hungarian study, women treated with radiation for Hodgkin's disease were 4 times more likely to have serum anti-thyroglobulin antibodies (Illes et al. 2003). In Stanford's series of 1,787 patients treated with radiation for Hodgkin's disease, of which 30 developed hyperthyroidism, age, gender, radiation dose, and chemotherapy exposure were not significant on univariate analysis (Hancock et al. 1991). In an earlier study from Roswell Park, the authors found that the addition of chemotherapy to radiation significantly reduced the risk of thyroid auto-antibodies (17 vs. 48 %, $p < 0.01$), with the risk with chemotherapy similar to the baseline prevalence of that seen in the general population (Tamura et al. 1981). In the CCSS cooperative group trial, including 1,791 patients with childhood Hodgkin's disease, radiation dose was significant for increased risk of hyperthyroidism.

5.3 Nodules: Benign and Malignant

Roughly one-tenth to one-third of thyroid nodules developing in adult patients who received radiation as children can prove to be malignant years to decades after radiation (Sklar et al. 2000; Kaplan et al. 1983; Acharya et al. 2003; Metzger et al. 2006b). This translates into a >10–50-fold increased risk of thyroid cancer (Sklar et al. 2000; Bhatia et al. 2003; Tucker et al. 1991; Sankila et al. 1996; Wolden et al. 1998; Taylor et al. 2009). Though the risk of cancer induction appears to increase with dose, (Tucker et al. 1991; Svahn-Tapper et al. 2006; Ronckers et al. 2006; Sigurdson et al. 2005) incremental dose exposure beyond 20–30 Gy apparently reduces the risk of cancer induction, perhaps as a result of a cell-killing effect (Svahn-Tapper et al. 2006; Ronckers et al. 2006). Figure 4 shows the dose dependence of thyroid cancer risk from a CCSS cohort study. The risk of thyroid cancer induction appears to persist beyond 40 years post-radiation treatment (Metayer et al. 2000). A younger age of therapeutic radiation exposure is also associated with a greater risk of cancer induction (see Fig. 4) (Bhatia et al.

Table 3 The common terminology criteria for adverse events (version 3)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma

2003; Metayer et al. 2000; Neglia et al. 2001; Sigurdson et al. 2005; Bhatti et al. 2010). One study suggests that the relative risk increases with earlier age of treatment, but that the absolute risk is relatively constant across pediatric age groups, and perhaps younger children, who tend to receive lower radiation doses, are more susceptible to lower radiation doses (Tucker et al. 1991).

A Surveillance Epidemiology End Results (SEER) database study has suggested that irradiation for breast cancer does not increase the risk of thyroid cancer (Huang et al. 2001). Although specific information on the radiation ports used were not available, presumably women with node positive disease received supraclavicular fossa radiation, though likely not resulting in significant dose to the thyroid.

In one Italian study of children receiving total body irradiation with >10 years follow-up, the regimen using larger fraction size (9.9 Gy in 3.3 Gy daily fractions versus 12 Gy in 2 Gy twice daily fractions) was associated with a significantly greater risk of nodule formation (80 vs. 2.7 %, $p = 0.002$) (Faraci et al. 2005). In that study, 60 % of patients developed nodules, of which one-quarter proved to be malignant.

In a series of 87 patients treated with radiation to the neck for childhood cancer at the Joint Center for Radiation Therapy, 32 developed palpable thyroid abnormalities including nodules ($n = 25$), diffuse enlargement ($n = 7$) (Kaplan et al. 1983). The risk of palpable abnormalities was independent of radiation dose, and more commonly seen in patients with longer follow-up, who were more likely to have received orthovoltage radiation. Ten of the 32 patients underwent resection; 8 had multiple hyperplastic follicular adenomas, and 3 developed papillary thyroid cancer, one of which also was found to have an atypical malignant schwannoma.

5.4 Grading/Prognosis

The Common Terminology Criteria for Adverse Events (version 3) grading of thyroid toxicity is shown in Table 3 (Trotti et al. 2003). Grade 5 (death) is not shown in the Table. Grade ≥ 3 thyroid toxicity is quite unusual. Generally, patients with grade 2 toxicity are easily managed medically, and do not suffer from a poor prognosis as a result.

5.5 Dose-Volume Effects

There is scant data on quantitative dose-volume parameters that might help predict the risk of hypothyroidism (Boomsma et al. 2011; Boomsma et al. 2012; Yoden et al. 2004; Bakhshandeh et al. 2012). Several studies demonstrate a significantly greater risk of hypothyroidism with bilateral versus unilateral neck radiation (Bhandare et al. 2007; Tell et al. 2004; Tell et al. 1997; Glatstein et al. 1971). In a Finnish study of patients treated for head and neck cancer, hypothyroidism occurred in 9 % of patients treated with fields <7 cm in length (equating to ~30–35 % of the thyroid gland being in the field) as compared 36 % of patients treated with fields >7 cm (Kumpulainen et al. 2000). A SEER database study has suggested that in elderly breast cancer patients, irradiation of the supraclavicular fossa (assumed to have been delivered in women with ≥ 4 lymph nodes involved) does not increase the risk of hypothyroidism (Smith et al. 2008). In a French study of 153 patients treated with total body irradiation for childhood acute lymphoblastic leukemia, the single dose regimens (median 10 Gy) resulted in a significantly greater risk of hypothyroidism versus the fractionated regimens (median 1 Gy × 6), with a relative risk of 5.9 ($p < 0.001$) (Berger et al. 2005). In an Italian study of 53 Hodgkin's lymphoma patients undergoing chemotherapy and involved radiation therapy (30–36 Gy) showed thyroid dose-volume parameters predicted risk of hypothyroidism, with the thyroid volume receiving >30 Gy (V30) being most predictive ($p < 0.0001$) (Cella et al. 2011). In two studies, dose-volume metrics of the thyroid gland (i.e., V10–V70) were not associated with hypothyroidism, perhaps partially attributable to the relatively uniform dose delivery among their patient (Alterio et al. 2007; Diaz et al. 2010). In a recent, prospective study of 105 head and neck patients from the Netherlands, treated with radiation, a normal tissue complication probability (NTCP) model analysis demonstrated that a higher mean thyroid gland dose and smaller thyroid gland volume were most predictive of radiation-induced hypothyroidism (Boomsma et al. 2012). Another NTCP model study from Iran, of 65 head and neck cancer patients, also showed mean thyroid gland dose as most predictive of late hypothyroidism, with a dose resulting in 50 % probability of hypothyroidism of 44 Gy (Bakhshandeh et al. 2012).

6 Special Topics

6.1 Radioiodine I^{131}

The use of radioiodine I^{131} is designed in Thyroid cancer to obliterate residual thyroid gland. This total loss of follicular thyroid structure is evident in Fig. 5a, b based on animal model. Clinically, I^{131} has been utilized in thyrotoxicosis and in thyroid cancer, specifically given post surgery (total thyroidectomy).

- Thyrotoxicosis: the oral administration of I^{131} is designed to result in the thyroid ablation of 6 miCi ($\sim$80–90 miCi/gm) delivering approximately 60–70 Gy to the gland, resulting in resolution of hyperthyroidism in 80 % of patients in 6 months. The incidence of hypothyroidism is 10 % the first year and increasing at an average rate of 5 % per year over the next 2 decades.
- Thyroid ablation in thyroid cancer patients occurs with I^{131} doses of 100 + 5 mli resulting in severe necrosis of follicles, acute vasculitis, thrombosis, hemorrhage, edema beginning after 2 weeks, gradual replacement by fibrosis after 6–8 weeks, lymphocytic infiltrates begin in 10–12 weeks.

The process continues over 1–3 years when only a dense scar remains, remarkably without damage to parathyroid gland (Fig. 5c).

Large atypical cells can appear several years later but never become neoplastic. Their resemblance to hurtle cells and lymphocytic infiltrates suggests Hashimoto's thyroiditis. In fact, anti-thyroid antibodies have been well documented suggesting an autoimmune basis for radiation ablation of the thyroid (Fig. 5d).

Thyroid nodularity and neoplasia induced by therapeutic irradiation of thymus gland in infants is well documented. Modest dose irradiation in children and adolescents for acne is well known after doses up to 18 Gy to head, neck, and thorax. Fajardo cautions over interpretation of irradiated glands because the presence of large bizarre cells and invagination of intranuclear cytoplasms similar to papillary carcinomas, particularly in needle biopsies.

7 Prevention and Management

Efforts to minimize radiation dose exposure to the thyroid may prevent post-radiation thyroid sequelae. After radiation exposure to the neck, routine examination of the neck should be performed to assess for nodularity and/or growth. Free T4 and TSH should be used to monitor thyroid function after therapeutic radiation exposure to the neck. The NCI recommends annual laboratory assessment up to 10 years post-radiation, although the risk for first demonstrating abnormality may extend beyond this timepoint (Common Late Effects of Childhood Cancer by Body System 2008). Fine needle aspiration of newly diagnosed thyroid nodules, particularly those that do not demonstrate I125 uptake is suggested. Interpretation of the fine needle aspiration may be confounded by radiation-induced atypia. In patients with prior radiation exposure, suspicious nodules should be aspirated even if small (<1.0 cm) as opposed to patients with no prior radiation exposure, where the threshold for aspiration is generally >1.5 cm (American Association of Clinical Endocrinologists and Associazione 2006). Researchers from University of Illinois and Michael Reese Hospitals in Chicago have investigated thyroid abnormalities in a cohort of 4,296 patients irradiated between 1939 and 1962 for benign conditions, of whom 1,059 developed thyroid nodules and were evaluable for study (Mihailescu and Schneider 2008). Their study demonstrated a slight decrease of cancer risk with increased nodular size, though not enough of a risk reduction to effect management. In fact, if only one or two of the largest nodules were aspirated, 42 and 17 % of cases would have been misdiagnosed respectively. Suspicious nodules or biopsy proven thyroid cancer should be resected. In the study from Chicago, more than half of patients with thyroid cancer had multiple cancer nodules, and more than half of these patients had cancer involving both lobes. Thus, total thyroidectomy is suggested by these authors as well as the American Thyroid Association (Cooper et al. 2006; Mihailescu and Schneider 2008).

Hypothyroidism can be managed with thyroxine replacement therapy. Levothyroxine is a synthetic form of thyroxine (thyroid hormone), used for hormone replacement for patients with radiation-induced hypothyroidism. Controversy persists as to the indications for thyroid function testing and thyroxine replacement therapy (Karmisholt et al. 2008; Karmisholt et al. 2011). Rationale for replacement therapy includes restoration of clinical well-being for patients with symptoms, prevention of potential symptomatology but also diminishing the risks for cardiovascular sequelae, and carcinogenesis from persistently elevated TSH. Hyperthyroidism can be managed with propylthiouracil (PTU), I131, or thyroidectomy. PTU inhibits the enzyme thyroperoxidase, which is involved in thyroxine synthesis, and enzyme 5'-deiodinase which converts T4 to the active form T3. There is a potential to reduce late thyroid toxicity simply by minimizing exposure of the gland to radiation (as described in Sect. 5.1).

8 Future Directions

Future studies should examine the dose-volume effects on the thyroid in a rigorous manner. While the size of the thyroid gland is small, novel treatment approaches such as IMRT and

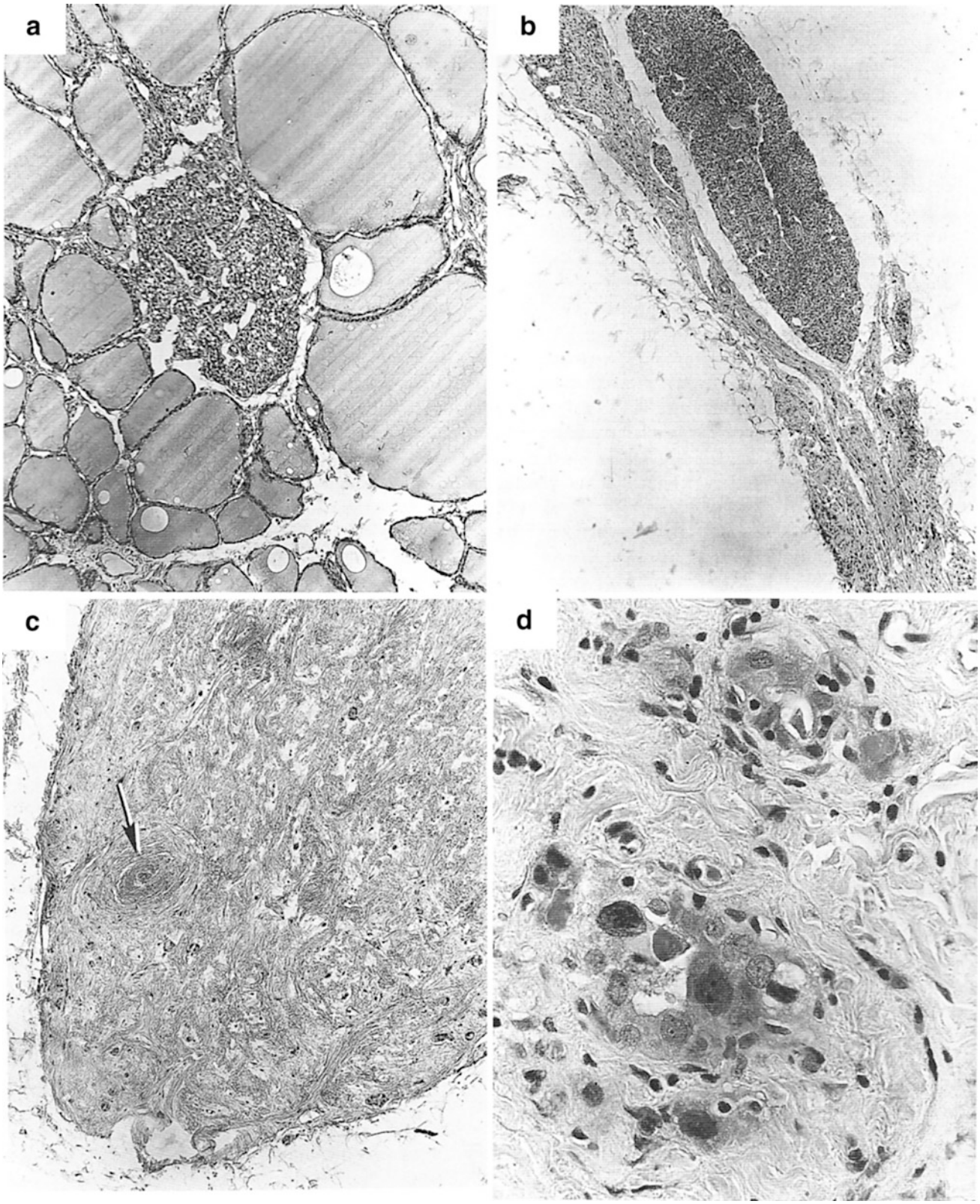

Fig. 5 Histopathologic changes in the thyroid gland. As opposed to the normal thyroid tissue (**a**), the subacute (<1 year) changes following radioiodine I131 (2 mCi) in a rabbit model include near total loss of follicles, replaced with a fibrous tissue gland (**b**). Notably, the parathyroid gland (*center of slides*) appears intact. After 1–3 years, only a dense scar remains (**c**) as shown in this slide from a treated patient. In another patient, large atypical cells are seen several years later (**d**). Their resemblance to Hurtle cells and lymphocytic infiltrates suggests thyroiditis. (Fajardo et al. 2001 with permission)

SBRT may result in a gradient of dose across the thyroid gland. Accurate Investigation into possible serum markers that could potentially predict thyroid toxicity after radiation would also be of interest. Putative serum markers that may prove predictive for late thyroid toxicity could be assayed before radiation, indicative of host susceptibility factors and after radiation, indicative of host-response factors.

9 Review of Literature and Landmarks

- Eckert et al. (1937). Found that radiation is tolerated in moderate radium doses in the normal thyroid gland but suppresses compensatory hypertrophy.
- Warren (1943) Published a review article on the pathologic changes following irradiation of the thyroid.
- Freedberg et al. (1952) Published an excellent article relating the clinical results with the pathologic changes in normal thyroid glands after I131 therapy.
- Einhorn et al. (1965); Eckert et al. (1937) Demonstrated that, although a transient antibody reaction occurred immediately after I131 therapy, there was no evidence of a progressive autoimmune reaction process to account for late hypothyroidism.
- Rogoway et al. (1966). Noted fivecases of myxedema developing after lymphangiography and 4000 R to the neck.
- Rubin et al. (1968) Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.
- Constine et al. (1984) This is a retrospective study of 119 children demonstrated a dose–response relationship between radiation dose and risk of hypothyroidism.
- Hancock et al. (1991) This is comprehensive retrospective study of thyroid disease among 1,789 patients treated for Hodgkin's lymphoma at Stanford University from 1961 to 1989. The development of hypothyroidism, hyperthyroidism, thyroiditis, and thyroid nodules is investigated. He authors demonstrate high risks of thyroid disease persist more than 25 years after patients have received radiation therapy for Hodgkin's disease.
- Sklar et al. (2000) This is comprehensive CCSS of thyroid disease among 1,791 patients treated for Hodgkin's lymphoma. The development of hypothyroidism, hyperthyroidism, and thyroid nodules is investigated. The authors demonstrate appreciable risks of thyroid disease, associated with higher radiation doses delivered to the thyroid.
- Bolling et al. (2010). This is comprehensive German "Registry for the Evaluation of Side Effects After Radiotherapy in Childhood and Adolescence" (RiSK) study of 1,086 patients who received radiation the thyroid or hyphysis. Greater relative risks of hypothyroidism were correlated with cranio-spinal radiation, and higher doses to the thyroid gland.
- Bhandare et al. (2007) In this study, 312 patients treated with radiation for head and neck cancers were investigated. Significantly greater risks of hypothyroidism were associated with thyroid doses in excess of 45 Gy.
- Ronckers et al. (2006) and (Bhatti et al. 2010) These studies examined risks of thyroid cancer induction after treatment for childhood cancer. The first was a case–control study of 69 thyroid cancer cases and 265 controls from a cohort of 14,054 childhood cancer survivors; the second analyzed 12,547 5-year survivors of a childhood cancer. Both studies revealed that the risk of cancer induction increases with dose to the thyroid, but then decreases beyond 20–30 Gy; representing a different dose–response relationship compared with most other secondary malignancies.

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Skin Surface, Dermis, and Wound Healing

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Abstract

- More commonly, the skin is exposed to therapeutic radiation incidentally, during treatment of relatively superficial but noncutaneous malignancies such as breast cancer, or head and neck cancer.
- The skin is a multifunctional organ composed of three layers: the epidermis, dermis, and underlying hypodermis.
- There are five cell layers in the epidermis: from deep to superficial these are the strata basale, spinosum, granulosum, lucidum, and corneum.
- The microvasculature in the dermal layer regulates body temperature by dilation and constriction.
- Acute radiation dermatitis progresses through stages of severity based on accumulation of radiation-induced changes to dermal vascular and appendageal structures, epidermal stem cells, and activation of inflammatory pathways.
- TGF-β is expressed in irradiated tissue within hours of exposure (Rodemann and Bamberg 1995; Rubin et al. 1992; Rodemann et al. 1991), and has been correlated with late fibrotic changes in several tissue types (Anscher et al. 1998; Anscher et al. 2003), including skin (Kumar et al. 2008).
- The clinical hallmarks of late radiation dermatitis are fibrosis, atrophy, and telangiectasia.
- The risk of late necrosis correlated with increasing field size and appeared to be increased when the dose was delivered to greater depth.
- Retrospective review of concurrent chemoradiotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) compared to breast radiotherapy alone, the addition of concurrent therapy doubled the incidence of grade 2 or greater dermatitis.
- Radiation Recall: Radiation recall is a phenomenon first described several decades ago (D'Angio et al. 1959), describing a cutaneous reaction in the area of previous radiation exposure, in response to specific systemic agents.

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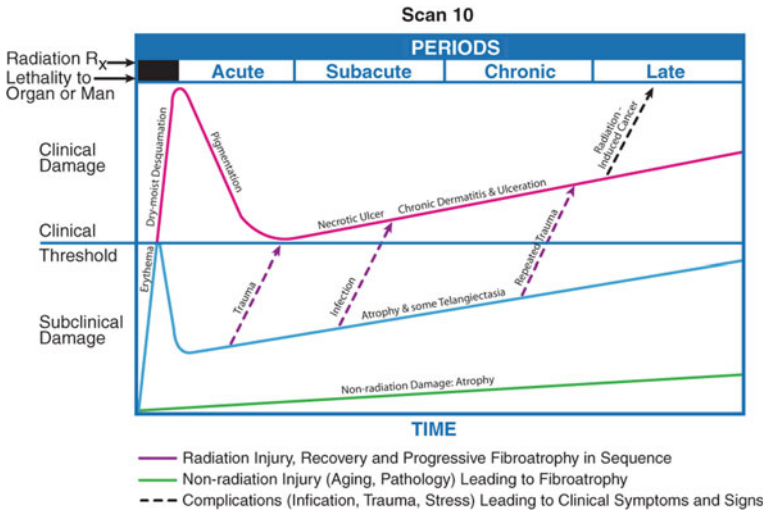

Fig. 1 Biocontinuum of adverse and late effects of the skin surface (with permission from Rubin and Casarett 1968)

- SMT: The role of therapeutic radiation in the induction of nonmelanoma skin cancer has been established in several large retrospective studies.
- Genetic Syndromes: Patients with AT are prone to severe cutaneous side effects.
- Comorbid Condition: The presence of active collagen vascular disease (CVD) is often cited as a relative contraindication to radiation treatment, due to concern for severe late fibrosis.
- Wound Healing and Grafts: Grafts are more prone to breakdown, and tissue flaps more likely to fail, especially when the site of origin also lies within the radiation field.
- Pharmaceutical treatment of fibrosis has been successful with pentoxifylline and vitamin E.

1 Introduction

Change in the appearance, texture, or protective capabilities of the skin due to radiation exposure are a commonly noted side effect both during and following therapeutic radiation treatment (Fig. 1). Exposure can occur either by design, for targets at or near the skin surface, or incidentally due to entrance or exit dose for targets deep to the skin surface. Superficial malignancies, typical primary skin cancer, have been long treated with radiation therapy either definitely or as adjuvant therapy. While radiation is reserved for advanced or high-risk lesions, the high absolute incidence of skin cancer makes this a reasonably common indication for treatment. In such cases, radiation treatment plans are specifically designed to deliver full dose to the skin, and treatment is therefore associated with robust acute and late skin changes.

More commonly, the skin is exposed to therapeutic radiation incidentally, during treatment of relatively superficial but noncutaneous malignancies such as breast cancer, or head and neck cancer. One of the most significant advances in radiation therapy technology over the past several decades is the advent of high-energy treatment units (megavoltage linear accelerators), which provide treatment that is more skin sparing than their predecessor, lower-energy, treatment machines. Depending on the specific energy used and the depth from the skin of the target lesion, the radiation dose at the skin surface might range from 5 (e.g., for a prostate treatment) to 90 % or more (e.g., for a breast or head and neck treatment).

The side effects of therapeutic radiation treatment are typically divided into acute and late effects. Acute effects are those that occur during fractionated treatment, or within a relatively arbitrary number of days of cessation of treatment (i.e., within 90 days). These symptoms are mainly the result of permeability changes in the tissue stroma (i.e., inflammation) and depletion of rapidly dividing tissue stem cells. These occur, progress, and regress in a relatively well-described series of events. Both the timing and severity are related to the volume of skin exposed, the radiation dose, and the fractionation schedule. The severity may be modified by treatment technique (e.g., the use of bolus materials), patient factors, and concomitant radiosensitizers.

Late effects are usually defined, solely for the purpose of evaluating treatment toxicity, as those which occur more than 90 days after radiation treatment. In truth there are signs and symptoms which may develop months to years later. These are often related to long-term loss of stromal microvasculature, and fibrotic replacement of normal tissue architecture. They are more loosely correlated to the dose and volume of radiation, but are more likely to be affected by clinicopathologic factors that affect local circulation and inflammatory response, as well as by genetic predisposition.

Treatment for acute radiation toxicity is generally supportive, addressing the symptoms and attempting to ameliorate the loss of normal skin barrier function. Late

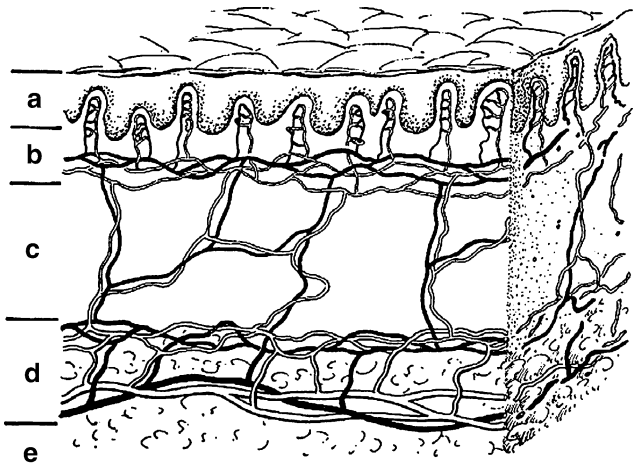

Fig. 2 Schematic drawing of skin showing the epidermal, dermal, and subcutaneous shells while emphasizing the critical microvascular components. The part labeled **a** is the epidermis (epidermal shell). **b** is the papillary dermis containing microvessel tufts arising from the papillary plexus. **c** is the rete dermis with arcuate vessels connecting the subdermal with papillary plexus. **d** is the dermal subcutaneous junction with the dermal plexus. **e** is the subcutaneous layer (From Archambeau et al. 1995, IJROBP LENT SOMA)

radiation toxicity is more effectively prevented than treated, although there is now accumulating evidence that late radiation changes can be ameliorated with appropriate medical and management. The Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The skin can be divided into its surface sectors and the lymph node region that drains a sector (Figs. 2, 3a, b).

- The head and neck includes the face and scalp. The vast majority of cancers arise on the skin of the face. Therefore, it is the face and scalp that demand careful attention clinically because of the complex functions, cosmesis, and special senses. All need to be preserved when resecting the cancer. The lymph node drainage of the integumentary surface differs from the upper aerorespiratory and digestive passages.
- Anterior chest wall from the clavicles to the navel in males tends to be hirsute. Lesions on the skin of the anterior thoracic wall drain to the anterior axillary nodes.
- Posterior chest wall to the same level tends to be less hirsute, is exposed more often to the sun, and subject to forming cancers. The regional nodes are along the posterior wall of the axilla although all axillary nodes are at risk.
- Upper extremity is an infrequent sector involved with skin cancer, but can be a site for burn and chronic inflammation. It is notorious for radiation-induced cancer in dentists who finger-held dental films during their practice. Endless resections occur with loss of fingers, then the hand, then the forearm. Involvement of epitrochlear node, then axillary nodes invariably leads to demise from pulmonary metastases.
- Anterior abdominal wall drains into the femoral and inguinal nodes but this sector of skin is rarely involved with skin cancers.
- Posterior abdominal wall or skin of the lower back is an infrequent site of malignancy and also drains to femoral and inguinal nodes anteriorly.
- Lower extremity is not a common site for skin cancers. Burns or chronic inflammation may cause lesions to evolve from hyperplasia to dysplasia and on to neoplasia. Popliteal nodes drain the foot and leg and ultimately drain into superficial femoral lymph nodes, which also drain the thigh.

Skin cancers are predominantly located on and in the face. To fully appreciate the anatomy, it is important to be aware of the surrounding structures and especially underlying muscle and nerves. As the cancer advances and invades, the reconstruction is more than cosmesis. A particularly troublesome area is over the parotid gland because perineural invasion of the widely branching facial nerve is a major concern.

N-oncoanatomy of the skin surfaces emphasizes the anterior location for most if not all lymph node stations.

The skin lymphatics of the face are different from head and neck cancers, since the drain to a ring of nodes that hang like a necklace from the occiput to below the ear, the parotid and anteriorly to the submaxillary and submandibular region. Once the cancer invades and advances involving deeper underlying structures then the deeper cervical nodes can become at risk for involvement.

There is a rich network of venous channels beneath all skin surfaces that allows for venous hematogenous spread once the dermal and hypodermal layers are penetrated by invading cancers (Fig. 2). These venous collateral channels and plexus are rich and appear once obstruction occurs. Metastatic spread via superficial and deep jugular vein is to lung predominantly. With extensive recurrent and destructive basal cancers which seldom metastasize early, aspiration into lung has been postulated but is an unlikely mechanism. Squamous cell cancers as they invade lymph nodes disseminate via focal veins. Merkel cell cancers are more virulent and are more prone to become metastatic (Rubin and Hansen 2008).

2.1.1 Skin Functional Unit

The smallest unit of skin that retains all the characteristics of skin (a unit of skin structure) consists of a microvessel

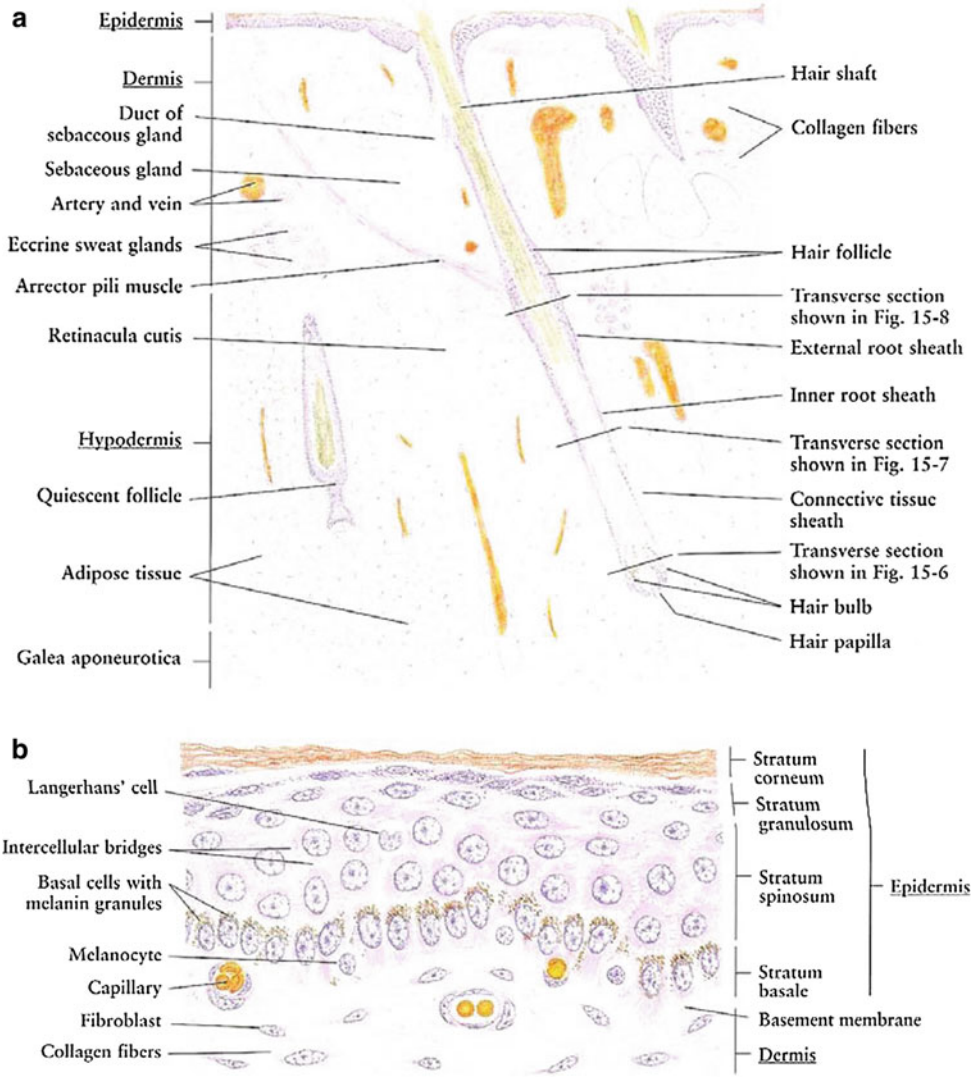

Fig. 3 **a** Scalp low magnification longitudinal section. **b** Thin skin: abdomen. High magnification (with permission from Zhang 1999)

with associated epidermis and dermis. This element of skin is referred to as a "skin functional unit" (FU_s). The FU_s is a core about 30 μm in diameter and 350 μm in length. There are an estimated 30,000 FU_ss per cm^2 in swine, with an associated 135 basal cells overlying a microvessel tuft 80–150 μm long. The skin configuration model emphasizes that the dose response of the FUs defines the dose response of the skin.

2.2 Histology

The skin is a multifunctional organ composed of three layers: the epidermis, dermis, and underlying hypodermis (Fig. 3a). The skin provides protective barrier function, and serves as an important role in hydration, temperature balance, and immunity (Fig. 3a).

The epidermis is the outer layer of the skin, composed of stratified squamous epithelium (Fig. 3b). It varies in thickness from 0.05 (on the eyelids) to 1.5 mm (on the soles of the feet). There are five cell layers in the epidermis: from deep to superficial these are the strata basale, spinosum, granulosum, lucidum, and corneum. The stratum basale, or basal layers, contain mitotically active basal cells, which migrate superficially to replace the nondividing outer layers. As the cells migrate away from the vascular supply in the dermis, they lose their cytoplasm, change shape and composition, and begin to accumulate keratin. The outer stratum corneum is composed of layers of flattened dead skin cells that continuously shed. This keratinized layer of the skin is responsible for barrier function, retaining water and shedding chemical irritants and pathogens. In addition to keratinocytes, the epidermis contains specialized elements such as melanocytes, Langerhans cells, and Merkel cells.

The dermis is composed of connective tissue and is connected to the epidermis by a basement membrane. The dermal layer contains blood and lymphatic vessels, sensory receptors, and skin adnexa (hair follicles, sweat and

sebaceous glands, and apocrine glands) (Fig. 3a). The microvasculature in the dermal layer regulates body temperature by dilation and constriction. The papillary region of the dermis is more superficial, and is composed of looser connective tissue arranged in projections or papillae. The underlying reticular dermis is thicker and composed of denser connective tissue. The reticular dermis contains the largest concentrations of extracellular matrix proteins, as well as the adnexal structures.

2.2.1 Hair

- Each hair arises in a tubular invagination of the epidermis into the dermis. The epithelium of the hair is arranged in three concentric layers: the medulla, the cortex, and cuticle. The hair follicle is tubular sheath composed of an inner epithelial sheath continuous with the epidermis and an outer connective tissue sheath. At the lower end, the root and follicle form a hair bulb connected to a papilloma consisting of fibroblasts, collagen, and rich in capillaries. Normal hair is divided into three parts: the infundibulum, the isthmus, and the inferior segment described above.
- Hair growth is cyclical and is divided into three separate and distinct phases: anagen, telogen, and catagen.
  - Anagen Phase is mitotically active and there is rapid growth i.e., scalp hair.
  - Telogen Phase is a dormant and mitosis is arrested i.e., eyebrows, pubic hair, and axillary hair. This phase lasts for months to years.
  - Catagen Phase occurs when the root is separated from the hair bulb, pigment is terminated and the hair root is separated from the bulb.
- Radiation in modest does to scalp (10–20 Gy) can initiate hair loss within 2–4 weeks and if the total dose is less than TD50; hair will regenerate. It is important to note that telogen hairs in eyebrows are often spared when scalp hair is shed.

2.2.2 Sebaceous Glands

Sebaceous glands are lined by actively proliferating stratified epithelium continuous with the germinal layer of skin. Mitoses are frequent in cells close to walls of excretory duct; newly produced cells move into secretory regions. Modest low doses of radiation have utilized to treat skin acne on face and chest when sebaceous gland activity is stimulated in adolescents.

2.2.3 Sweat Glands

Sweat Glands are simple coiled tubular glands deep in the dermis with its secretory merocrine myoepithelial cells which are specialized post mitotic cells. Sweat glands are more radioresistant and require large doses comparable to producing acute moist dermatitis to ablate. This can occur when the axilla is in the field when irradiating breast cancers.

The hypodermis or subcutis connects the dermal layer to the underlying muscle, bone, and fascia and is, by volume, composed primarily of fat. This layer serves as one of the major sites of fat storage by the body, and also contains macrophages, fibroblasts, and larger caliber blood vessels. The subcutaneous layer normally provides a loose layer of connective tissue to allow for cushioning and articulation during body movement. It is the primary site of fibrotic replacement following high-dose radiation.

3 Physiology and Biology

Skin has been utilized for numerous radiobiologic studies to characterize its radioresponsiveness (Table 1). Pig skin was initially favored because of its histologic characteristics being similar to humans however, more recently mouse leg has been adopted more widely. Radiation reactions have reproducible grading scales and dose time fractionation has been well studied. The clinical course of radiation skin murine reactions is similar to humans and useful for studying the genetic and molecular basis for radiosensitive versus radioresistant strains (Hall and Okunieff).

The pathophysiologic mechanism of late changes, particularly fibrosis, in response to radiation is incompletely understood. Transforming Growth Factor Beta (TGF-β) is a secreted protein that serves a regulatory role in normal tissue inflammation and remodeling by controlling proliferation, differentiation, and secretory functions. TGF-β is expressed in irradiated tissue within hours of exposure (Rodemann and Bamberg 1995; Rubin et al. 1992; Rodemann et al. 1991), and has been correlated with late fibrotic changes in several tissue types (Anscher et al. 1998, 2003), including skin (Kumar et al. 2008). Abrogation of downstream mediator Smad3, a pro-inflammatory signaling molecule induced in response to TGF-β, appears to protect tissue from late fibrotic changes after radiation exposure (Arany et al. 2007; Flanders et al. 2008, 2002; Martin et al. 2000).

TGF-β serves a complex regulatory role in wound healing and tissue remodeling. It is synthesized and secreted by several cell types including tissue macrophages, epithelial and endothelial cells, and fibroblasts. The most prominent isoform (TGF-β1) is synthesized and secreted in an inactive form, and activated by various proteases in the extracellular matrix. It then binds to serine/threonine kinase receptors on the cell surface of mature and immature fibroblasts, endothelial cells, and hematopoietic cells, among others (Rodemann and Blaese 2007).

TGF-β regulates extracellular matrix remodeling by increasing fibroblast proliferation, differentiation, and activation (Rodemann et al. 1991, 1996; Lara et al. 1996; Burger

Table 1 Cytokines and growth factors implicated as mediators for the development of late radiation effects on skin

Cytokines, growth factors, and other proteins	Potential mechanisms of actions
IL-1 beta	Stimulates proliferation of keratinocytes and fibroblasts (Shenkier and Gelmon 1994; Yeo et al. 1997) Stimulates metallomatrix proteases (Shenkier and Gelmon 1994; Yeo et al. 1997) Increases dermal angiogenesis (Schwartz et al. 2003) Inflammatory mediator (Vujaskovic et al. 2002; Camidge and Price 2001; Cassady et al. 1975)
IL-6	Inflammatory mediator (Vujaskovic et al. 2002; Camidge and Price 2001; Cassady et al. 1975)
IL-8	Chemokine (Saif et al. 2008)
Eotaxin	Chemokine (Saif et al. 2008)
TGF-B1	Enhances collagen production in response to radiation (Denham and Hauer-Jensen 2002; Cassady et al. 1975; Khanfir and Anchisi 2008) Accelerates the terminal differentiation of progenitor fibroblast to postmitotic functional fibrocytes Stimulates the synthesis of extracellular matrix proteins and MMPs (Bostrom et al. 1999)
PDGF	Induces fibroblast differentiation (Hird et al. 2008)
CCN2	Involved with TGF-B1 in stimulating fibrosis (Hird et al. 2008)
TNF-α	Inflammatory mediators (Vujaskovic et al. 2002; Camidge and Price 2001; Cassady et al. 1975)
CTGF	Promotes fibrosis and secreted by fibroblasts and endothelial cells (Greco et al. 1976)
Smad3	Transduces signaling effects through TGF-B1 (increases chemoattraction and elaboration of extracellular matrix by fibroblasts, inhibitory effects of keratinocyte proliferation, and migration) (Cassady et al. 1975)

Human radiation injury (Table 44.2, p.501). CTGF, connective tissue factor; IL, interleukin; MMPs, matrix metalloproteinases; PDGF, platelets derived growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor

et al. 1998; Herskind et al. 1998; Hakenjos et al. 2000), and thereby increasing secretion of extracellular matrix component proteins (Canney and Dean 1990; Vozenin-Brotons et al. 1999; Schultze-Mosgau et al. 2002). TGF-β promotes its own secretion by fibroblasts in a self-amplifying cascade (Burger et al. 1998). In response, the secretion of most matrix proteins, including collagen, is increased, and matrix proteinases are decreased (Mayer 1990; Hageman et al. 2005; Zhao et al. 2001). Epithelial cell proliferation is diminished, and there is chemotaxis of mast cells and macrophages. The result is increasing production, processing, and deposition of collagen (fibrosis), and loss of epithelial reconstitution of normal tissue structure.

The initiating event in TGF-β activation in response to radiation is poorly understood. Latent TGF-β in the extracellular matrix may be activated by exposure to ionizing radiation (Rodemann and Blaese 2007; Barcellos-Hoff et al. 1994; Barcellos-Hoff 1998). This may involve proteolytic enzymes which act in the presence of radiation-induced reactive oxygen species. This is supported by experimental evidence that free radical scavengers may prevent TGF-β increases as well as fibrosis in irradiated lung (Vujaskovic et al. 2002; Epperly et al. 1999). Other potential sources of TGF-β include endothelial cells, which may release TGF-β in direct response to radiation, or from normal dermal components such as fibroblasts, epithelial cells, macrophages, or endothelial cells as a response to tissue damage. The latter may be the predominant mechanism of consequential late fibrosis following severe acute skin injury, as the severe acute epidermal and dermal tissue injury activates a generalized fibrotic response.

Endothelial cell damage may be a direct result of radiation exposure (endothelial apoptosis or necrosis) or indirectly thorough loss of epithelial barrier function or adjacent tissue necrosis. Damaged endothelial cells secrete TGF-β, which then promotes fibrotic replacement of the damaged dermis. It also increases endothelial permeability, which results in inflammation, and activates the coagulation cascade (Denham and Hauer-Jensen 2002). The inflammatory response includes the chemotaxis and proliferation of macrophages and mast cells which is then direct neovascularization. The histologic result is hypovascular, fibrotic dermis, with a network of tortuous vessels, and telangiectasia. Cytokines that have been implicated in late skin effects from RT are summarized in Table 1.

4 Pathophysiology

Following a large single or fractionated dose there is a linear loss of basal cells, reaching a nadir at ~21 days, followed by exponential reepithelialization to control levels and above by 28–32 days (Fig. 4). The mitotic index and labeling index are increased during this period of

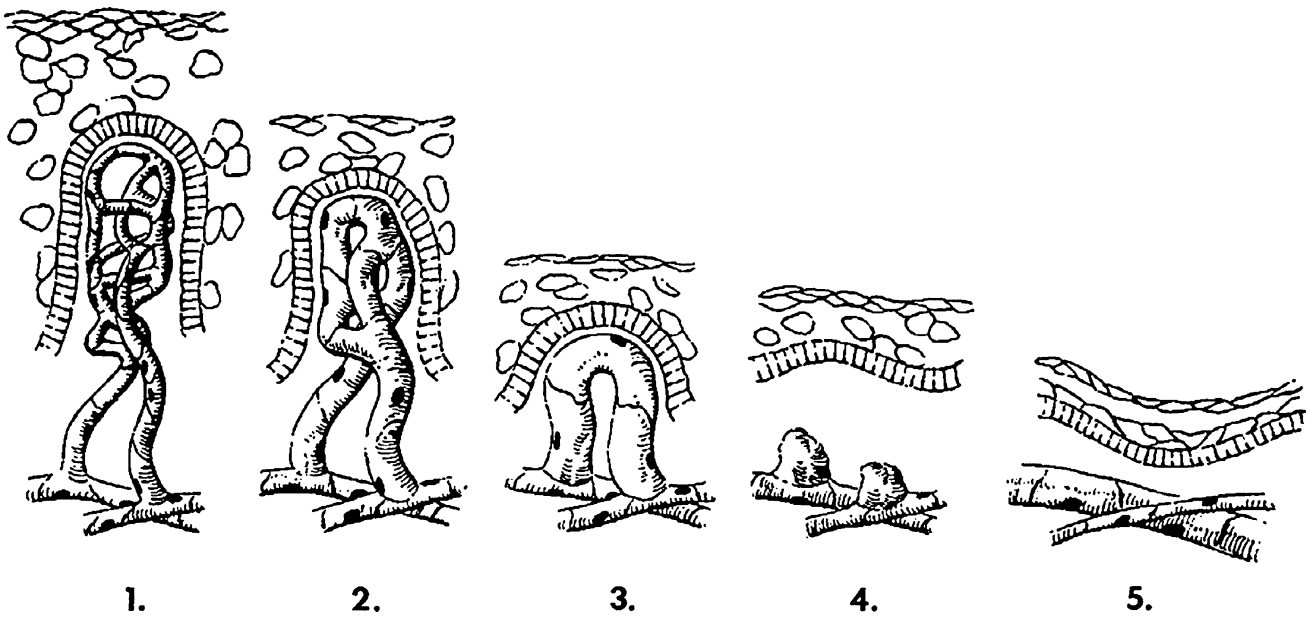

Fig. 4 A diagram of the sequence of microvessel changes in the skin functional unit in time following irradiation. The microvessel tuft is shown as a folded manifold. This model incorporates the loss of cells with vessel shortening and the loss of cells with loss of the short branch of the manifold. A time scale is ignored but must be represented by months and years with the development of telangiectasia. The telangiectasia produced is represented as formed in the vessels of the rete plexus that supplied the tuft. (From Archambeau et al. 1995, IJROBP LENT SOMA)

regeneration. The generation time for this period is estimated to be 15 h. Complete regeneration of the epidermis is produced at all dose fractions up to 45 Gy. Reepithelialization at 32–36 days can then be followed by a second ulceration and necrosis. During the period of basal cell degeneration and regeneration the endothelial population parameters do not change.

Change produced by irradiation in the microvessel endothelium, which exits as a line of 10–20 single cells without supporting adventitia, is not well documented. Endothelial proliferation has not been observed; therefore, the principle change is one of cell loss without replacement. The changes documented histologically are cell loss, a decreased in the number of vessel lumens seen on microscopic section (representing vessel shortening), decrease in tuft density and dilatation. The turnover time or replacement time of endothelial cells is not known, but is estimated to take months of years as evidenced by the time required for late effects to be produced.

A diagram of the sequence of microvessel changes in the skin functional unit in time following irradiation. The microvessel tuft is shown as a folded manifold. This model incorporates the loss of cells with vessel shortening and the loss of cells with loss of the short branch of the manifold (Fig. 3b). A time scale is ignored but must be represented by months and years with the development of the telangiectasia. The telangiectasia produced is represented as formed in the vessels of the rete plexus that supplied the tuft.

5 Clinical Syndromes

5.1 Acute Erythema Phase

Hyper-acute reactions (within hours of RT): Skin changes after radiation exposure follow a predictable course dictated by radiation dose, timing, and the biology of the human inflammatory reaction (Tables 2, 3). The earliest clinically evident reaction is erythema that may occur and resolve within hours, and is normally only evident after relatively high-dose exposure. The threshold dose is 2 Gy or greater, and this effect is noted in therapeutic courses aimed at cutaneous targets, lower energy treatment courses (kilovoltage), or hypofractionated treatment regimens. Histologically, there is a vasodilation and a transient permeability increase in capillaries that results in mild erythema and edema at 2–24 h following exposure (Hall and Giaccia 2005).

Prior to adoption of the Roentgen (R), and later the Gray (Gy), as a measure of radiation dose, skin erythema dose (SED) was used as a crude clinical measure of patient radiation exposure (Khan 2003). For lower energy radiation, this was a reasonable measure of the total dose deposited because the maximum dose was deposited at the skin surface. This transient acute reaction is no longer commonly noted due to the increased use of multiple or rotational fields and megavoltage therapy, high-energy, relatively skin sparing, radiation treatment beams, and the use of fraction size of $\leq$ 2 Gy per day. Acute, transient skin erythema is still commonly

Table 2 LENT SOMA Skin/Subcutaneous tissue

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Scaling/roughness sensation	Present/ asymptomatic Hypersensitivity, pruritus	Symptomatic Intermittent pain	Require constant attention Persistent pain	Debilitating dysfunction
Objective				
Edema Alopecia(scalp) Pigmentation change Ulcer/Necrosis Telangiectasia Fibrosis/Scar Atrophy/Contraction (depression)	Present/ asymptomatic Thinning Transitory, slight Epidermal only Minor Present/ asymptomatic Present/ asymptomatic	Symptomatic Patchy, permanent Permanent, marked Dermal Moderate < 50 % Symptomatic Symptomatic/ $< 10\%$	Secondary dysfunction complete, permanent Subcutaneous Gross ≥ 50 % Secondary dysfunction Secondary dysfunction/ 10–30 %	Total dysfunction Bone exposed Total dysfunction Total dysfunction/ > 30 %
Management				
Dryness Sensation Ulcer Edema Fibrosis/Scar		Intermittent medical intervention	Medical intervention Continuous medical intervention Medical intervention Medical intervention Medical intervention	Surgical intervention/ amputaion Surgical intervention/ amputaion Surgical intervention/ amputaion
Analytic				
Color photographs	Assessment of changes in appearance			

Table 3 Late skin changes may be broadly, and somewhat arbitrarily, segregated into categories and associated examples as shown

	Focal	Global
Subclinical	1. Latent reduced capacity to tolerate future insults (e.g., difficulty with wound healing) 2. Imaging abnormalities	1. Reduced tolerance to alterations in temperature
Clinical	1. Ulceration 2. Fibrosis/retraction 3. Hair loss 4. Atrophy and skin thinning	1. Cosmetic changes and secondary challenges with socialization 2. Reduced mobility of joints underlying fibrotic areas of skin 3. Abnormalities in thermoregulation

Table 4 Gross skin changes produced by irradiation

Acute changes	Late changes
Erythema	Atrophy
Pigmentation	Scaling
Dry desquamation	Pigmentation
Moist reaction	Atrophy
That heals	Fibrosis
Heals partially	Telangiectasia
Does not heal	Necrosis

reported following interventional diagnostic and therapeutic procedures with prolonged fluoroscopy screening times, due to less penetrating kilo-voltage beams. The SOMA LENT system provides a systematic manner to assess, categorize and grade acute reactions to the skin (Table 2), and to specific organs where the skin reaction is a prominent component (e.g., the Breast, see "Breast Cancer"). Skin changes may also be broadly, and somewhat arbitrarily, segregated into focal versus global, and clinical versus subclinical (Table 3).

5.2 Detection and Diagnosis

Since the integument is readily visible on physical examination, the gross skin changes produced by irradiation are summarized in Table 4.

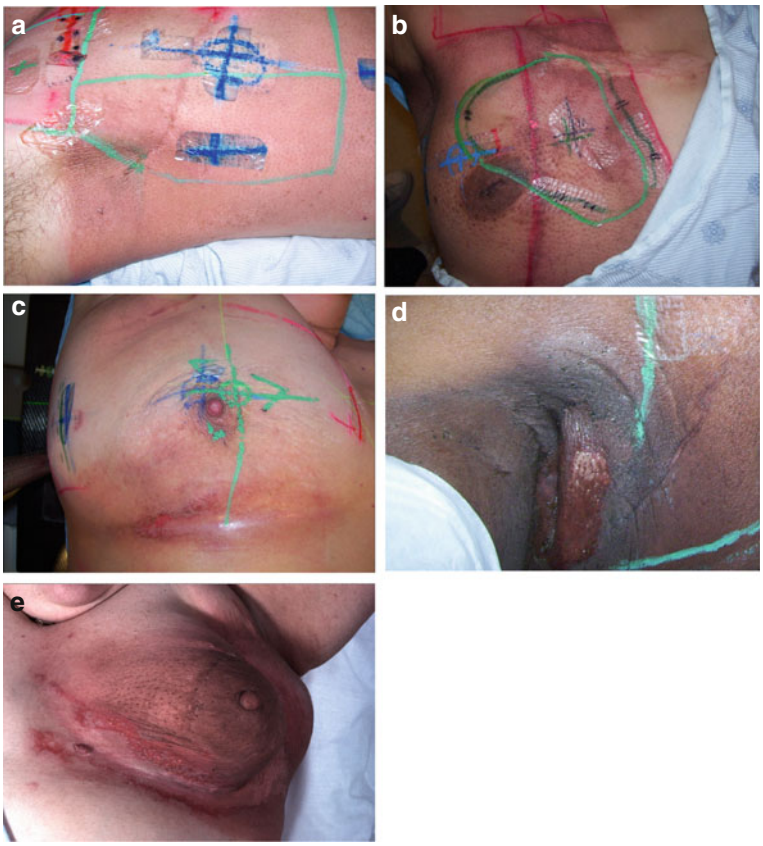

Fig. 5 Acute Dermatitis. **a** Early erythema during radiation therapy for breast cancer. **b** Hyperpigmentation as an early manifestation of radiation dermatitis. Note that the scar tissue in the upper inner quadrant is spared. **c** Dry desquamation of the inframammary fold. **d** Patchy moist desquamation in an axillary skin fold. **e** Confluent moist desquamation

5.2.1 Acute Moist Dermatitis

The more sustained, common, and relevant reactions take place over a matter of weeks following initial exposure (Fig. 5a, b, c, d, e). Acute radiation dermatitis progresses through stages of severity based on the accumulation of radiation-induced changes to dermal vascular and appendageal structures, epidermal stem cells, and activation of inflammatory pathways. The severity of dermatitis is a function of accumulated damage and therefore related to radiation dose. Dermatitis may be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). This scale is symptom-based, and does not inherently distinguish between acute and late reactions based on the timing of the symptom in relation to radiation exposure. Common acute and late dermatologic symptoms not included as radiation dermatitis by the CTCAE.

Grade 1 dermatitis manifests as faint skin erythema within the treatment area, or dry desquamation. Erythema is seen in two contexts: first, as discussed above, there may be a transient vasodilation in the hours after a single fraction skin exposure of 2 Gy or higher. More commonly, erythema develops over the first two to three weeks of fractionated radiation with accumulated exposure (Fig. 5a). In some patients, this manifests as hyperpigmentation (Fig. 5b). With continuing or higher dose radiation exposure, damage to the basal cells in the epidermis may progress until this stem cell population is lost in localized areas, resulting in dry desquamation (Fig. 5c).

Further and more widespread damage to the basal layer leads to further desquamation, and the production of a fibrinous exudate due to increased arteriole permeability and edema in the underlying dermis. This is moist desquamation. The CTC differentiates moist desquamation based on whether it is patchy and localized to skin folds (grade 2, Fig. 5d), or confluent affecting a more widespread area (grade 3, Fig. 4e). Skin folds and creases are particularly susceptible to such reactions since the local dose may be increased due to a "local loss of skin sparing". Additionally, these areas may be subject to additional trauma associated with friction between the two "opposing sides" of the skin fold during normal movement, and/or overlying clothing (e.g., waist-bands of pants or a women's brassiere). More widespread moist desquamation in areas less prone to mechanical trauma is indicative of additional accumulated damage.

The outer strata of the epidermis are composed of fully differentiated and nondividing epithelial cells, which are continuously renewed from proliferating cells in the basal layer of the epidermis. Newly formed daughter cells in the basal layer migrate outward as they differentiate, over approximately 14 days, to reconstitute the outer strata. The turnover time is a function of the local thickness of the

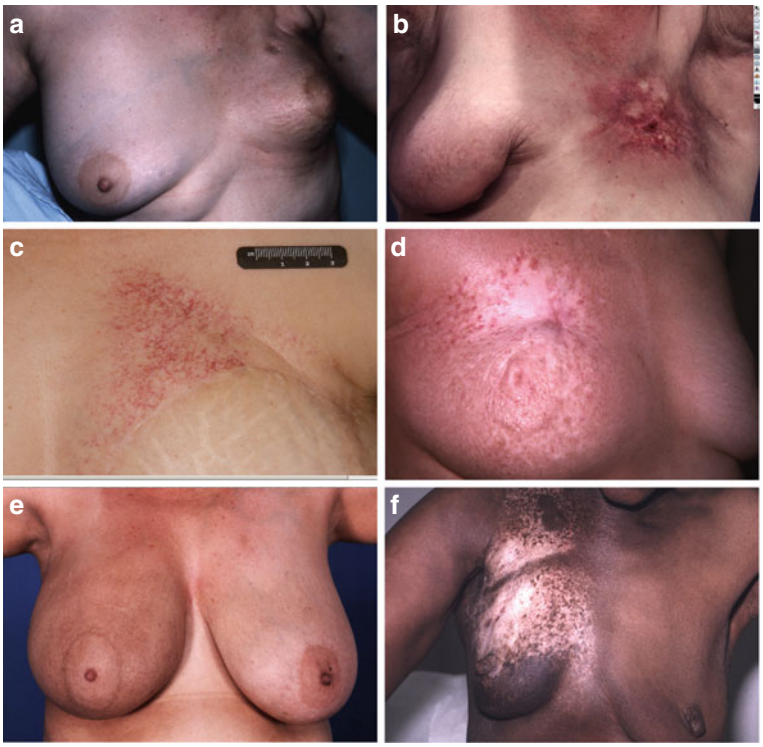

Fig. 6 Chronic Fibrosis. In panel **a**, there is retraction of the treated left breast, with mild to moderate overlying fibrosis. **b** More significant and localized fibrosis with loss of normal skin markings, pigmentation changes, skin retraction, and early ulcerative changes. **c** Telangiectasia which have developed years after radiation. **d** Pigmentation changes -mixed hypo- and hyperpigmented areas. **e** Hyperpigmentation one year after completion of radiation. **f** Hypopigmentation

epidermis, and can vary from 10 to 40 days. Desquamation occurs due to radiation-induced loss of this basal layer, and manifests in the second or third week of fractionated radiation, as the loss of basal stem cells becomes clinically evident. Moist desquamation is an indication of more complete loss of the basal layer; the fibrinous exudate is a result of increased permeability in the dermal vasculature, along with loss of normal epidermal basement membrane integrity.

5.2.2 Dermis

The underlying dermis is composed of connective tissue and houses the vascular and lymphatic network, as well skin adnexa including hair follicles, sweat and sebaceous glands, and sensineural structures. Acutely, most clinically evident changes in the dermis occur due to vascular changes. Vasodilation and increasing vascular permeability occur early (Fajardo and Berthrong 1988), and the resulting perivascular inflammation results in clinically characteristic erythema and edema. Skin adnexal cells are relatively radiosensitive as well, and may not regenerate following exposure. The process of epilation begins within days of radiation exposure (Sieber et al. 1993). Sebaceous glands have similar sensitivity, and eccrine sweat glands become dysfunctional shortly afterwards in a fractionated radiation treatment course. Histologically, these glandular structures demonstrate apoptosis, necrosis, and loss of normal mitotic activity (Malkinson and Keane 1981). Clinically, this leads to either acute and chronic hypohydrosis or anhidrosis.

5.2.3 Regeneration

Regeneration of areas of moist desquamation occurs primarily through replacement of epidermal basal cells either from islands of intact cells within the epidermis or by the migration of such cells from adjacent, uninvolved areas. Normal healing of the radiation wound becomes clinically evident approximately 2 weeks after exposure, consistent with the basal cell turnover time. Widespread confluent mucositis (CTCAE grade 3), or more severe toxicity such as necrosis of the epidermis or underlying dermis, may not undergo complete regeneration of the structural and adnexal elements. Instead, there is prolonged inflammation and progression to early fibrosis. Histologically, the normal epidermis is replaced by fibroblasts and a collagen scar. This is in contrast to the more common late fibrosis, which arises following the regeneration of relatively normal-appearing skin. "Consequential late effects" (Dorr and Hendry 2001) are those directly related to the severity and extent of acute events, and result from the failure of normal healing of the radiation wound, rather than the more commonly noted chronic toxicity, the severity of which is not always predicted by the extent and severity of acute events.

5.2.4 Late Changes of Atrophy and Fibrosis

Late radiation toxicity occurs months to years following exposure, following a period during which the skin may not exhibit significant abnormalities (Figs. 6a, b, c, d, e, f, and 7a, b, c, d, e). Unlike consequential late effects, the risk and severity of true late skin changes are not thought to be

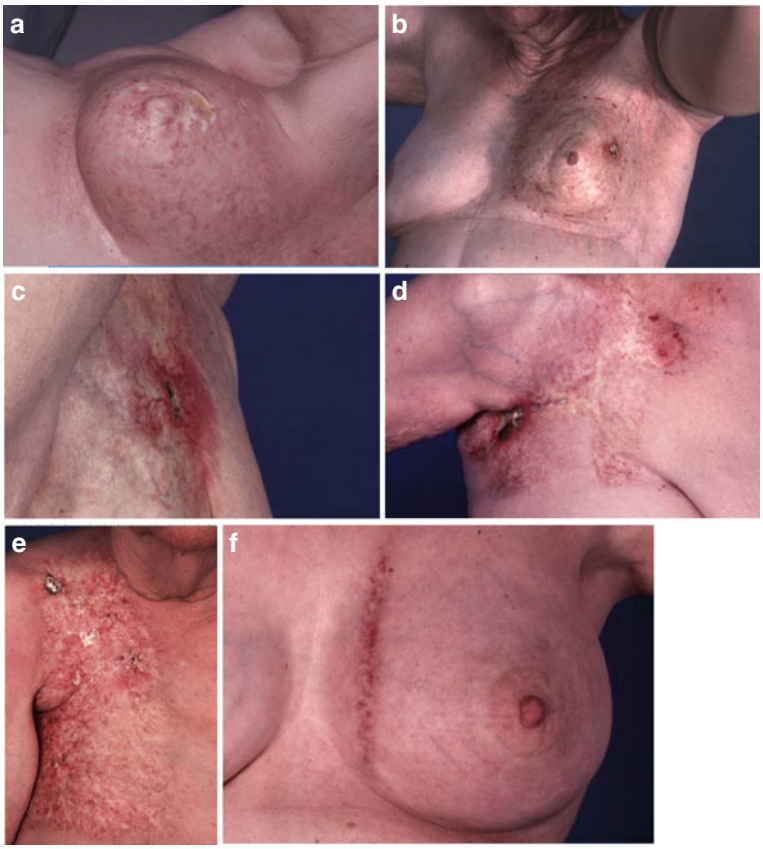

Fig. 7 Late radiation necrosis. **a** A superficial area of necrosis. **b** A necrotic ulceration in the background of marked fibrosis. **c** Necrosis with superficial erosion into the subcutaneous layer. **d** Advanced necrosis. **e** A large area of severe fibrosis. **f** Match line fibrosis at the junction of a breast tangent field with an internal mammary field. The most significant skin changes are limited to the area of overlap, which received radiation from both fields

associated with the risk and severity of acute dermatitis, except that both occur as a function of radiation dose. The clinical hallmarks of late radiation dermatitis are fibrosis, atrophy, and telangiectasia.

The late skin toxicity with the most functional consequence is subcutaneous fibrosis. Activation of growth factors induces replacement of the subcutaneous adipose tissue with fibrous tissue, leading to limitations in range of motion, contraction, pain, and poor cosmesis (Fig. 6a, b). Fibrosis of hair follicles may lead to permanent alopecia. Even in cases where dermal and subcutaneous fibrosis is not clinically evident, there may be atrophy of the skin adnexa. Hair follicles, sebaceous, and sweat glands may be absent in previously irradiation skin because these are not regenerated during normal radiation wound repair.

Loss of glandular elements leads to anhidrosis when extensive skin areas are irradiated, such as in total skin electron therapy. The microvasculature of the dermis and subcutis may develop excess myointimal proliferation, leading to a functional hypovascularity. Tortuosity within small vessels, and microthrombi, results in visible telangiectasia (Fig. 6c). Irregular regeneration of the basal layer of the epidermis may be evident as dyspigmentation (Fig. 6d, e, f).

Paradoxically, there may be a decrease in the population of resident skin fibroblasts in atrophic skin, with loss of the normal collagen structure leading to increased skin fragility and poor wound healing. Necrosis can occur in response to minor trauma or spontaneously, as a consequence of poor tissue perfusion, because of impaired normal tissue repair (Fig. 7a, b, c, d). Care should therefore be taken when considering a biopsy or other procedure involving irradiated skin.

The pathologic severity of late fibrosis is dependent on the radiation dose and volume, and may be modified by underlying comorbid illness and the genetic background. The clinical severity may range from poor cosmesis to significant loss of function, and additionally depends on the anatomic restrictions to motion that result from the underlying fibrosis (Fig. 7e).

6 Radiation Tolerance

6.1 Dose Time Fractionation

One of the earliest reports to systematically document time dose fractionation, was by Strandquist (1944), who treated many skin cancer patients with superficial (100 kv) and orthovoltage (2–400 kv) radiation. The biologic effect in skin was suggested to be proportional to the total dose delivered, under specified conditions of fractionation of dose. The series of isoeffect lines were plotted based on the cure of the skin cancer versus the healing of the skin. This clinical study is the

first observation of a therapeutic ratio, mainly there is a fractionated radiation schedule that can heal the skin cancer as well as the skin. When the doses exceeded the level for ablating the skin cancer, the larger doses resulted in skin necrosis. This was the beginning of establishing favorable radiation therapeutic ratios, wherein cancers can be eradicated without producing severe late effects.

6.2 Radiation Dose and Volume Relationships

Acute and late cutaneous toxicity following radiation therapy is a function of both the inherent radiation sensitivity of the epidermal and dermal structures, as well as the radiation energy, fractionation, and field size. One of the earliest attempt to systematically and comprehensively examine the tolerance of cutaneous tissue to megavoltage-energy radiation was published by Emami et al. (1991). The authors examined retrospective data from patients and compiled estimates of radiation doses that would confer 5 and 50 % risk of late side effects at 5 years—the TD5/5 and TD50/5, respectively. For skin toxicity, they used telangiectasia and necrosis as endpoints, and estimated dose tolerances for treatment of 10, 30, and 100 cm^2. For the endpoint of necrosis and for a 100 cm* field, the estimated TD 3/5 was 5100 cGy, TD 5/5 5500 cGy, and TD 50/5 was 7000 cGy. For a 30 cm* field, the estimated TD 3/5 was 5700 cGy. For a 10 cm^2 field, the TD 3/5 was 6900 cGy. For the endpoint of telangiectasia with an area of approximately 100 cm*, the TD 10/5 was 5000 cGy, TD 30/5 was 5900 cGy, and the TD 50/5 was 6500 cGy (Table 5).

A subsequent review summarized the dose-dependent changes in gross appearance, function, and histology following radiation (Table 5; Archambeau et al. 1995). Larger and more modern series have corroborated these doses. In a series of 468 patients treated for primary skin cancer, in which the prescription dose was delivered to the skin surface, the risk of late skin necrosis was 5.8 % (Locke et al. 2001). The dose delivered was 40 to greater than 60 Gy in fraction sizes of 2–4 Gy per day, and patients were treated with kilovoltage photons and/or electrons with appropriate bolus material to bring the skin dose to 100 %. Notably, the risk of late necrosis correlated with increasing field size and appeared to be increased when the dose was delivered to greater depth.

Interpreting toxicity data from series of noncutaneous malignancy, in which the skin exposure is incidental, is more problematic because the skin dose is rarely measured or reported, and the relative skin dose is a function of radiation energy and technique. For example, a dosimetric study undertaken specifically to compare the skin dose with various radiation techniques in breast cancer patients found the measured skin dose to be 58–71 % of the prescription dose (Selvaraj et al. 2007). Most clinically apparent radiation fibrosis in breast cancer patients is noted in areas of radiation field junctions, where there was unintended overlap (Fig. 6f). Other late effects in breast cancer, such as telangiectasia, which can occur at lower doses, can be seen in the inframammary area or other regions of localized excess dose. A randomized trial in extremity soft tissue sarcoma was conducted specifically to evaluate late radiation morbidity, including subcutaneous fibrosis. Patients were randomized to 50 Gy preoperative radiation or 66 Gy posteroperative. Late grade 2 or greater fibrosis was significantly higher in the postoperative arm, likely due to both increased dose and the prior surgery (Davis et al. 2005). Taken together, the available evidence suggests that doses in excess of approximately 60 Gy increased the risk and severity of clinically significant fibrosis. Additionally, the latency the period between cessation of radiation and clinically apparent skin changes may be shorter in patients exposed to higher doses (Herrmann and Baumann 2006).

More complex methods of predicting normal tissue complications have evolved for many tissue types, particularly lung and liver, related to an effort to escalate radiation dose using more complex beam arrangements (Kong et al. 2007; Milano et al. 2007). These efforts acknowledge that the risk and severity of early and late side effects are a function of not only the maximum radiation dose but also the volume of normal tissue exposed to both high and intermediate doses. The metrics that have evolved range from the addition of low-dose or mean-dose thresholds to the calculation of normal tissue complication probability (NTCP) using mean equivalent dose. No such formalism is in widespread use for evaluating dose to the skin, and data to suggest parameters for similar relationships are lacking. Examination of a large series of skin cancers treated with primary radiotherapy does suggest that increasing tumor size (and by extension, increasing field size) does correlate with an increasing risk of poor cosmesis (Locke et al. 2001), independent of the prescription dose, and this supports a similar volume effect to that seen in other anatomic sites.

Normal tissue dose limits are determined by both the total dose and the fractionation schedule. Most of the clinical experience regarding normal tissue dose tolerance is based on daily treatment with fraction size in the range of 1.8–3 Gy. Equivalent dosing can be estimated for modest alterations in dose using well-accepted models; for more significant increases in daily dose these models may not provide accurate estimates. As stereotactic body radiotherapy, and other hypofractionated treatment regimens, are more commonly employed, normal tissue dose constraints for one to five high-dose fractions are becoming more important. In a recently published series from Memorial Sloan–Kettering Cancer Center, skin toxicity was examined in 50 patients treated in 3 or 4 fractions, from 44 to 60 Gy

for pulmonary tumors (Hoppe et al. 2008). Grade 2 or greater skin toxicity (by the NCI-CTC criteria) correlated with skin dose of greater than 50 % of prescription (i.e., 22–30 Gy). One patient had Grade 4 changes (necrosis) and the authors estimated a skin dose of close to 90 % of prescription (54 Gy) in 3 fractions.

7 Chemotherapy Tolerance

7.1 Systemic Radiosensitization

Concurrent chemoradiatiotherapy is often administered in an effort to exploit the synergistic interaction between radiation and specific radiosensitizing chemotherapy agents (Table 6). Most such agents are nonspecific radiosenstizers; that is, they both increase the effect of the radiation on the tumor target and exacerbate the acute radiation effects on normal tissue. This has been clinically demonstrated in randomized trials of chemoradiotherapy versus radiotherapy alone, in which a significant increase in acute radiation-related mucosal toxicity has been noted in the treatment of esophageal cancer (Cooper et al. 1999), and head and neck cancer (Adelstein et al. 2003). Common chemotherapy drugs identified as radiosensitizers are listed in Table 6.

Concurrent radiosensitizing chemotherapy is indicated for selected lung, gastrointestinal, and gynecologic malignancies (among others) in which the radiation planning is relatively skin-sparing, and therefore the severity of the dermal reaction is typically mild. Dermatitis is more common, and more severe, during chemoradiation for head and neck cancer where the superficial dose may be focally high. Randomized trials assessing the benefit of concurrent chemotherapy have not demonstrated an increase in clinically significant dermatitis, however (Adelstein et al. 2003). This may reflect the fact that the superficial dose varies significantly due to both patient factors as well as treatment technique. Breast cancer may be a superior model, since the skin dose is relatively consistent among patients. Randomized and nonrandomized studies have examined the role of concurrent, rather than sequential, chemoradiation for patients with high-risk breast cancer (Bellon et al. 2004; Livi et al. 2008; Isaac et al. 2002). In one large, retrospective review of concurrent chemoradiotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) compared to breast radiotherapy alone, the addition of concurrent therapy doubled the incidence of grade 2 or greater dermatitis (Livi et al. 2008), although not to clinically significant levels. The ARCOSEIN study is a large multicenter trial that enrolled 297 breast cancer patients and randomized the subjects to either concurrent or sequential chemotherapy. Toxicity assessment was blinded. There was no increase in acute radiation toxicity with concurrent therapy, but the risk of late subcutaneous fibrosis was significantly increased (Toledano et al. 2006).

Tamoxifen is a hormonal agent given during or shortly after radiation in many patients with receptor-positive breast cancer and ductal carcinoma in situ. Tamoxifen is not a classic radiosensitizer, and there is no evidence that tamoxifen given concurrently with breast radiation increases the risk of acute dermatitis (Ahn et al. 2005). Interestingly, tamoxifen may induce TGF-β, which is implicated in the development of radiation fibrosis. A retrospective analysis of 147 patients, 90 of whom had concurrent rather than sequential tamoxifen, has found that late radiation fibrosis is increased in patients who received the drug during their breast radiation (Azria et al. 2004). This has not been a consistent finding; an analysis of 458 patients undertaken to determine the patient and treatment factors impacting on long-term cosmesis failed to find any effect of tamoxifen (Taylor et al. 1995).

7.2 Alopecia

Alopecia is very traumatic because sudden loss of hair is a precursor to loss of self image and identity. Alopecia occurs with numerous cytotoxic agents, acting in anagen phase when hair is mitotically active. The hair becomes thin and brittle shedding resulting in baldness. Immediate anagen release, forcing hair into telogen, and leading to premature shedding occurs. The resulting telogen effluvium is dividing into subcategories:

- Acute with hair loss beginning in 2–3 weeks up to 2–3 months
- Chronic with hair shedding for $\geq$6 months.

Intravenous chemotherapy acts more rapidly versus oral intake. Once chemotherapy is completed, hair returns in 2–3 months. Numerous therapeutic interventions have been implemented with varying degrees of success.

8 Special Topics

8.1 Radiation Recall

Radiation recall is a phenomenon first described several decades ago (D'Angio et al. 1959), describing a cutaneous reaction in the area of previous radiation exposure, in response to specific systemic agents (Table 7). The most

Table 5 Changes produced by increasing total dose (adapted from Archambeau et al. 1995 with permissions)

Schedule dose range dose fraction single (cGy)	Multiple (200 cGy/ day)	Gross Change	Onset of change	Functional change	Histologic change
500–700	~2,000	Epilation	~18days	–	Empty follicle
1000–2000	2000–4000	Erythema	12–17 days	Hyperemia	None noted
2000–3000	–	–	2–6 days	–	–
1000–2000	~4500	Pigmentation		None	Increased melanin
1000–2000	~4500	Dry desquamation	30–70 days	–	Hyperplasia
2000–2400	4500–5000	Moist desquamation that heals	30–50 days	Serum leakage; healing regenerates functional barrier	Linear decrease in cell density exponential cell replacement
>2400	>5000 >6000	Moist Desquamation does not heal > 50 %	30–50 days	Loss of protective Barrier	Linear decrease in cell density
1700–2400	4500–5000	Telangiectasia	6 months–years	None	Cell and vessel Loss; lumen dilatation
>2700	> 6000	Necrosis nonhealing	Months, years	Loss of protective barrier	Necrosis

commonly cited chemotherapeutic agents are anthracyclines (Camidge and Price 2001; Cassady et al. 1975; Greco et al. 1976), taxanes (Shenkier and Gelmon 1994; Yeo et al. 1997), and gemcitabine (Schwartz et al. 2003). The relative incidence of a recall reaction, with regard to any specific system agent, is difficult to discern. There is likely a reporting bias reflecting the relative prevalence of administration of certain agents in patients who have received radiation treatment that includes the skin (i.e., the use of anthracyclines and taxanes in breast cancer patients). Additional systemic agents implicated in radiation recall reactions (listed in Table 7) include standard chemotherapeutic agents, newer targeted therapeutics (Saif et al. 2008; Khanfir and Anchisi 2008), hormonal therapy agents (Parry 1992; Bostrom et al. 1999), as well as non-oncologic medications (Hird et al. 2008).

The clinical manifestations of radiation recall occur with the inital administration of the systemic agent, within minutes to days with intravenous drug, or days to weeks with oral medication. The timing of presentation may be related to the drug dose (Cassady et al. 1975), and both the severity and timing of the reaction may be related to the prior radiation dose (Stelzer et al. 1993). The duration of the responses reported ranges from weeks to months. Interestingly, readministration of the same systemic agent does not consistently lead to recurrence of the phenomenon.

While a recall reaction can occur in any organ, skin is the most common site. It occurs in a well-demarcated area defined by the borders of the previous treatment field, and can occur despite the lack of any clinically significant skin reaction during the previous radiation treatment. The clinical signs and symptoms mimic acute radiation hypersensitivity dermatitis, and this can range from erythema and a maculopapular rash to desquamation and necrosis. The pathogenesis is not well understood. An early hypothesis was that tissue stem cells remained depleted long after radiation, making the tissue more sensitive to cytotoxics. This does not explain, however, radiation recall reactions elicited by noncytotoxics or the lack of a reaction to subsequent drug exposure in some cases. The clinicopathologic manifestations are best explained by a local, acquired drug hypersensitivity reaction. Prior radiation therapy may locally alter the normal dermal immunologic response by changing basal and stimulated cytokine production (Azria et al. 2005; Hallahan et al. 1989). This is consistent with histologic findings of acute inflammation (vasodilation, infiltration of inflammatory cell mediators) in affected tissue, as well as the response of recall dermatitis to treatment with corticosteroids.

8.2 Secondary Malignancy

Radiation exposure is an established cause of solid and non-solid tumors in animals and humans. Some of the earliest of evidence of this link was the observation of an increased risk of skin malignancies in radiation workers including uranium miners and radiologists (Hall and Giaccia 2005). Basal and squamous cell skin cancers were also noted to occur in excess in survivors of Hiroshima and Nagasaki, and their incidence significantly related to radiation exposure with an excess relative risk of 1.0 per sievert (Thompson et al. 1994).

Table 6 Non-specific radiosensitizers

Chemotherapy Agents
Bleomycin
Capecitabine, 5-Fluorouracil
Cisplatin, Carboplatin, Oxaliplatin
Dactinomycin, Doxorubicin
Docetaxel, Paclitaxel
Gemcitabine
Gemcitabine
Methotrexate

Chemotherapeutic agents which enhance acute radiation toxicity when given concurrently

The role of therapeutic radiation in the induction of nonmelanoma skin cancer has been established in several large retrospective studies. An analysis of 1805 patients enrolled on a skin cancer prevention trial found that prior radiation therapy predicted a significantly higher risk of basal cell tumors, with a relative risk of 2.3. The risk of squamous cell cancers was not elevated, although the overall incidence was lower than that of basal cell. The relative risk of developing a basal cell cancer was highest in those treated at a younger age, and increased with time since radiation exposure (greatest at 20 years (Karagas et al. 1996)). These cancers occurred within the radiation field, and the risk appeared to be highest for those who were treated to the face and neck, raising the possibility that sun exposure may increase the risk of radiation-induced skin cancer. A case–control study from the New Hampshire Skin Cancer Study Group included 592 cases of basal cell cancer and 289 cases of squamous cancer, with age- and gender-matched controls (Lichter et al. 2000). There was an increased risk of both basal and squamous cell cancer in patients who reported a history of radiotherapy (relative risk of 3.3, and 2.94, respectively).

8.3 Genetic Syndromes

Several genetic syndromes are associated with an increased risk of cutaneous toxicity following radiation exposure. Many of these involve impaired DNA damage repair pathways, and most patients are predisposed to excess normal tissue effects in all organs.

Ataxia telangiectasia (AT) is a rare autosomal-recessive disorder in which both copies of the ATM gene are mutated. This leads to a loss of recruitment of DNA damage repair proteins to double-strand breaks, and enhances cellular radiation sensitivity. Patients with AT are prone to severe cutaneous side effects. Patients who are heterozygotes for the mutant AT trait do not demonstrate any of the characteristic neurologic or cutaneous manifestations of the syndrome, but may be predisposed to excess radiation toxicity. A high rate of late skin complications has been observed in breast cancer patients with an ATM mutation (Iannuzzi et al. 2002). Since the prevalence of the heterozygous mutation may be as high as 1 % in the U.S. population, this has been posited to explain part of the observed heterogeneity in patient sensitivity to radiation. This observed increase in sensitivity has not been consistently demonstrated, however (Bremer et al. 2003).

Other syndromes associated with defects in DNA repair are less prevalent. These include Fanconi's anemia, Bloom and Gardner's syndrome, and Dysplastic Nevus Syndrome. Although an increase in radiation-mediated DNA damage has been demonstrated in some of these syndromes, there is no compelling evidence that this generally translates into a clinically significant risk of increased tissue effects.

Basal cell nevus syndrome (BCNS, Gorlin's syndrome) is a hereditary disorder associated with the abnormalities in the PTCH gene, a tumor suppressor in the Hedgehog signaling pathway (Bale 2002). The syndrome is characterized by skeletal abnormalities, an elevated risk of childhood medulloblastoma, and a predilection for developing multiple basal cell carcinomas of the skin beginning at an early age. In murine models of BCNS, animals have an increased risk of secondary malignancy following exposure to radiation therapy (Hahn et al. 1998). In human patients with BCNS who are treated with therapeutic radiation, there is a markedly increased risk of secondary malignancy. Published reports include secondary brain tumors and innumerable basal cell skin cancers arising within the radiation field of adults who were treated with radiation therapy for childhood medulloblastoma (O'Malley et al. 1997; Atahan et al. 1998).

8.4 Comorbid Medical Illness

The severity of late radiation dermatitis may be increased in the presence of any of several comorbid medical conditions. The clinical manifestations of radiation fibrosis are a function of the extent of the fibrotic response, and the ability of the impaired dermal microvasculature to perform normal cutaneous organ function. Conditions that impair the normal microvasculature are expected to exacerbate fibrotic replacement of the normal epidermis and dermis, and worsen the clinical symptoms of late radiation injury such as poor wound healing, contracture, loss of range of motion, atrophy, and dyspigmentation. Hypertension and diabetes are both associated with diminished dermal microvasculature, and are implicated in worsening late radiation injury (Baker and Krochak 1989). In particular, the combination of hypertension and diabetes is a predictor of more severe late radiation toxicity (Chon and Loeffler 2002). Other patient

Table 7 Agents reported to induce a radiation recall reaction

Cytotoxic chemotherapy	Targeted or hormonal agents	Non-oncologic systemic
Arsenic Trioxide	Bevacizumab	Gatifloxacin
Bleomycin	Pemetrexed	Isoniazid
Capecitabine	Tamoxifen	Levofloxacin
Cyclophosphamide		Simvastatin
Cytarabine		
Dacarbazine		
Dactinomycin		
Daunorubicin		
Docetaxel		
Doxorubicin		
Epirubicin		
Etoposide		
Fluorouracil		
Gemcitabine		
Hydroxyurea		
Idarubicin		
Lomustine		
Melphalan		
Methotrexate		
Paclitaxel		
Vinblastine		

factors, such as advanced age, tobacco use, and distal extremity location may similarly increase the risk.

The presence of active collagen vascular disease (CVD) is often cited as a relative contraindication to radiation treatment, due to concern for severe late fibrosis (Holscher et al. 2006). This loosely defined family of disorders, including systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis (RA), polymyositis or dermatomyositis, and mixed connective tissue disorders (MCTD) among others, share a propensity for an inappropriately active immune response. SLE and scleroderma in particular are often associated with cutaneous fibrotic manifestations. Several retrospective and case–control studies have examined the incidence of late cutaneous toxicity in these populations. Because of the relatively low prevalence of some disorders, the occasional uncertainty of diagnoses, and the range of clinical severity, a clear evaluation of the effect on radiation sensitivity is not always feasible. In a study in breast cancer patients, severe late fibrosis was found in irradiated patients with scleroderma, but not other CVDs (Chen et al. 2001). Similar finding were made regarding more generally defined late toxicity in patients who received radiation to other sites, that non-RA CVDs, most commonly SLE and scleroderma, predicted for worse late toxicity (Morris and Powell 1997; Phan et al. 2003). One case–control study found that all CVDs, including RA, predicted for an increased severity of late toxicity, but that the most severe effects were seen in patients with scleroderma and SLE (Lin et al. 2008). These authors also examined radiation responses in patients with systemic vasculitides (polymyalgia rheumatica, temporal arthritis, Wegener's granulomatosis) and found a similar increase in late toxicity. It is important to note that the diseases most strongly correlated to increasing late fibrosis are those that commonly manifest with skin abnormalities. There has been no clear correlation with an increase in acute effects in this population, and as there are no reports of fatal or life-threatening sequelae, this remains a relative, rather than an absolute, contraindication to radiation treatment.

8.5 Wound Healing

Ionizing radiation can impair all stages of wound healing, depending on the anatomic area of skin irradiated, total radiation dose delivered, and the timing of exposure with respect to wound formation. Potential targets of such effects include local inflammatory cells and fibroblasts.

Wound healing within previously irradiated skin is impaired to an extent dependent upon the previous radiation dose, as well as the interval since exposure (Gorodetsky et al. 1990). The effects are mediated predominantly through fibroblasts, which are decreased in number, have decreased proliferative capacity, and are functionally insufficient in skin which is atrophied and fibrotic due to radiation treatment (Tibbs 1997). There is an attenuation of the normal fibroblast response to growth factor-induced chemotaxis and activation. There is both a decrease in collagen gene expression and failure of complete extra-cellular maturation (Bernstein et al. 1993a). There is some evidence that the latter may be mediated through alterations in growth factor expression, especially TGF-β (Bernstein et al. 1993b). The clinical consequence of this is a significant decrease in wound bursting strength, and an increased risk of wound dehiscence. Studies of wound integrity in irradiated skin demonstrate the most significant compromise in the 3–4 weeks following injury. The clinical manifestations may represent merely a delay in normal tissue remodeling, especially in skin which retains much of its normal microstructure and function. At later time points the strength of such wounds can approach that of wounds in unirradiated tissue.

The vasculature is also permanently altered by prior radiation. Acutely there is an increase in vascular

permeability, but in the long term there is vascular stasis, occlusion, and edema of vessel walls. This results in poor vascular supply to the irradiated area, which can lead to late dermal fibrosis and resultant loss of elasticity. The loss of vascularity also predisposes to infection, and impairs the supply of monocytes and fibroblasts available for wound healing (Doyle et al. 1996). Wounds in previously irradiated tissue are slow to heal, prone to dehisce and more frequently require skin grafting. Grafts are more prone to breakdown, and tissue flaps more likely to fail, especially when the site of origin also lies within the radiation field.

Wounding followed by radiation. After wounding, there is an acute rapid response (over several days) of the normal tissues to initiate wound repair. The "foundation" of successful wound healing is the laying down of a collagen network within the wound that occurs during this time. However, it takes many weeks to months for that collagen network to mature/remodel into a strong healed scar. The period of the initial rapid laying down of the foundation is typically a few days, and irradiating the wound during that time will manifest as a slower/blunted wound healing in the following weeks/months. However, if the radiation is given after this rapid laying down of a foundation (but before the foundation matures to a strong wound), the maturation of the scar, and the ultimate strength of the scar, will be less effected. Thus, the effects of radiation treatment on existing wounds is primarily timing dependent. Early irradiation can impair the proliferation, migration, and activation of fibroblasts, resulting in decreased collagen formation and cross-linking. Observed complications include decreased wound strength and dehiscence (Drake and Oishi 1995; Springfield 1993). In contrast, if irradiation is delayed until three to four weeks after wound formation, there is a much lower likelihood of complication (Tibbs 1997). At least one study has demonstrated that delaying as little as five to eight days results in a reduction of complications to the expected normal level, implying that a critical threshold of collagen formation and cross-linking has been completed. Even with such a delay, however, impaired neo-vascularization may occur, leading to late effects including skin atrophy, scar contraction, and fibrosis. The probability of such effects seems to be dose dependent (Gorodetsky et al. 1990), and thus there is a high incidence of such late complications after high dose radiation, and a lower but significant risk following low doses such as those used in the treatment of benign proliferative processes.

8.6 Skin Grafts

One of the commonly stated concepts in radiation therapy is that grafted skin tolerates irradiation poorly. Since the need for reconstructive surgery is increasing with the advent of more radical surgical procedures for various carcinomas, consideration of postoperative irradiation in grafted sites is not unusual. Very definite differences occur in the reaction to radiation between normal and grafted skin sites (Rubin et al. 1960).

Grafts less than 3 months old demonstrate greater radiosensitivity than normal skin. In grafts of intermediate age, the response to and recovery from irradiation parallels that of normal skin. In grafts older than 1 year, no reaction to irradiation is generally elicited, but in one instance, graft necrosis ensued at the 16th week.

On the basis of an experimental program (Rubin et al. 1960) with Chester White and Yorkshire pigs subjected to full thickness and split thickness grafts, the following conclusions were drawn:

1. Fresh grafts tend to react to ionizing irradiation more vigorously and earlier than normal skin, and they recover more slowly.
2. Split thickness grafts tend to react less vigorously than full thickness grafts.
3. The intensity of the reaction is inversely proportional to the quality of the radiation.
4. Fractionation and protraction have less impact on response, but the value of fractionation is aiding full recovery and is clearly established.
5. Irradiation should not be begun immediately after grafting.

Careful clinical observations and experimentation have clearly shown that, in a wide variety of circumstances, alteration in capillary anatomy and physiology has a profound effect on irradiated tissue and tumors. Knowledge of the changing blood supply pattern of an autograft is essential. The stages in graft union to host tissues are four: the stage of plasmic circulation, the state of vascularization, the stage of organic union, and the stage of cicatrization.

It is logical to anticipate that the more vascularized a graft is, the more sensitive the graft will be to irradiation. The injection of small quantities of radioisotopes intradermally or subcutaneously and the observation of the rate of their disappearance from the local site constitute a recognized method of studying vascular integrity.

The half-time of disappearance can be used as an expression of the vascular function of the graft site injected.

Therefore, the differences in vascularization of grafted skin and normal skin form a reasonable basis to explain the differences in the radiation responses of these structures. The radioisotopes half-time of disappearance following subcutaneous injection is an index of vascularity or vascular function of a graft and serves as a parameter to predict its radioresponsiveness.

1. Irradiation during the stage of plasmic circulation, prior to union of the graft, produces necrosis suppression of the budding of new capillaries from the host vascular bed, a process which is essential to graft survival.

2. Irradiation during the stage of vascularization elicits a greater reaction in the graft by virtue of the excessive capillary sprouting and in growth of vessels.
3. Irradiation during the stage of organic union evokes a reaction in the graft approximate that in normal skin as the fibroblastic and collagen responses progress. Normally vascularity of the graft at this stage is decreased as compared with the previous stage, and in transition it approximates that of normal skin.
4. Irradiation during the stage of cicatrization usually evokes no response in the graft, since vascularization is less than that in normal skin, and scar tissue is relatively radioresistant. If a reaction is elicited, the decreased vascularity may sufficiently compromise recovery powers so that necrosis may ensue.

On the basis of the results, the recommendations are:

1. Limit the total dose to a graft as much as possible, consistent with good treatment.
2. Exclude as much of the graft as possible from the radiation port, consistent with good treatment.
3. Fractionate and protract the dose as much as is practical, since fuller recovery is thus insured.
4. Employ megavoltage irradiation, because its skin-sparying effect lessens the severity of graft reaction.
5. Allow time for a good "take" of the autograft rather than begin irradiation immediately. Usually this is within 3–4 weeks after grafting.

9 Prevention and Management

Acute cutaneous toxicities are managed with preventative and supportive care measures. Prior to treatment, patients should be instructed to avoid chemical irritants, sun exposure, the application of extremes of heat or cold, and to minimize mechanical trauma within the treatment field. The topical application of moisturizers is often recommended prophylactically, and used to treat the dryness associated with early desquamation. During grade 2 and 3 toxicity, normal epidermal barrier function is disrupted, which makes the skin more prone to infection, and less able to retain moisture. Moisture exuding dressings may be applied to prevent or slow progressive dermal damage. Close observation for superinfection, and symptomatic management of discomfort should be part of standard on-treatment care. None of these measures has been demonstrated to lessen the severity of dermatitis, but are rather intended to support prompt tissue re-epithelialization.

Late cutaneous changes may occur long after radiation treatment, and may continue to progress over months to years. Although atrophy, telangiectasia, and dyspigmentation may contribute to poor cosmetic outcomes, cutaneous and subcutaneous fibrosis are the most likely to cause significant limitations to function and quality of life. The best method of primary prevention is to use the appropriate radiation techniques to limit the area and dose of skin exposure. Consequential late effects may be limited by both avoidance and appropriate supportive care of severe acute side effects.

The treatment of fibrosis may begin either during the early symptomatic period or during the latent period between the resolution of acute side effects and before the development of late ones. Preventative measures such as active and passive range of motion exercises are used to prevent loss of range of motion due to neck fibrosis in patients treated for head and neck cancer, or of the limbs in patients treated to the extremities or joints. Fibrosis may be exacerbated by further tissue trauma, so surgical procedures should be avoided in radiated areas when possible.

Pharmaceutical treatment of fibrosis has been successful with pentoxifylline and vitamin E. Pentoxifylline is a xanthine derivative that is currently approved for the treatment of intermittent claudication due to peripheral vascular disease. It decreases platelet aggregation, and increases microvascular blood flow. Laboratory evidence also suggests that it may decrease proliferation of fibroblasts, and decrease deposition of extracellular matrix proteins (Delanian and Lefaix 2007). Vitamin E is a free radical scavenger, which may diminish the ongoing inflammatory response.

Pentoxifylline and vitamin E have been tested concurrently with radiation in a randomized trial in the prevention of lung fibrosis due to chest radiation (Ozturk et al. 2004). Forty patients with lung or breast cancer were enrolled and randomized to receive pentoxifylline or placebo concurrently with radiation. There was a significant improvement in diffusion capacity, a clinical measure of lung fibrosis, in the patients receiving drug. Two randomized trials have tested pentoxifylline given prophylactically after radiation, specifically examining whether it decreased the development of cutaneous fibrosis. In 83 breast cancer patients (Magnusson et al. 2009) and 78 head and neck cancer patients (Aygenc et al. 2004), administration of the drug following radiation decreased fibrosis and improved post-treatment range of motion.

The combination of pentoxifylline and vitamin E has been most thoroughly evaluated in the treatment of established fibrosis, both in skin and other organs. Several retrospective series examines the effect of the combination in patients with radiation-induced fibrosis. Delanian et al. reported on 43 patients treated with pentoxifylline (800 mg per day) and vitamin E (1000 U per day) for 6 months, and found decreased area of fibrosis, and improved symptoms (Delanian et al. 1999). A decrease in the area of fibrosis has been similarly reported in other small series (Haddad et al. 2005;

Futran et al. 1997). Randomized trial results are promising, but not definitive, however. Delanian et al. conducted a two-way randomized trial of pentoxifylline and vitamin E, each versus placebo, in 24 patients treated for 6 months (Delanian et al. 2003). The patients that received both drugs had significantly decreased fibrosis compared to those in the arm that received two placebos; there was no improvement in the patient who received either of the drugs alone. A trial in 68 breast cancer patients with fibrosis treated with the same drug dose and duration failed to show any difference, however, in either arm volume or improved fibrosis. The disparate findings may reflect differences in outcome measures, patient selection, or duration of follow-up. A systematic, retrospective, evaluation of 44 patients treated with pentoxifylline and vitamin E for 6–48 months found that the regression of fibrosis was best seen after longer treatment intervals. Patients had 2/3 of the maximum response at 24 months treatment duration. Those patients treated for shorter duration (3–6 months) were prone to significant rebound increase in fibrosis after drug combination was discontinued.

Pentoxifylline has also been administered as a single agent in attempt to treat existing radiation-induced fibrosis. One prospective trial of 1200 mg per day for 8 weeks reported a one-third improvement in range of motion, and decreased edema (Okunieff et al. 2004). A randomized trial of 12 patients, treated for 6 months, failed to demonstrate any benefit of single-agent therapy (Delanian et al. 2003). The same trial examined Vitamin E alone versus placebo, and again showed no benefit.

Other strategies have been used in an empiric attempt to ameliorate the symptoms of subcutaneous fibrosis. Corticosteroids, nonsteroidal anti-inflammatories, and other immunosuppressives have been used, based on their activity in slowing the progressive fibrosis of some connective tissue disorders. Antioxidants other than vitamin E, including superoxide dismutase, have been tested in the laboratory in mice, but there are to date no clinically available active agents (Delanian and Lefaix 2007). Curcumin is an antioxidant that has been tested in mice, and found to decrease the early cytokine response to radiation (Okunieff et al. 2006). Hyperbaric oxygen has been used in two prospective studies in women with lymphedema after breast radiation therapy. In both, there was an improvement in patient-reported symptoms. One study reported a decrease in indurations in 8 of 15 patients (Gothard et al. 2004), the other reported no improvement in fibrosis (Carl et al. 2001). Angiotensin converting enzyme inhibitors and ethanol have some efficacy in decreasing late effects in other tissue, but have not been tested in skin (Delanian and Lefaix 2007). Given the lack of a compelling benefit to any standard medical therapy for radiation-induced fibrosis, all of these approaches warrant further study.

10 Future Research

The importance of skin research response to radiation has been heightened by the atomic age we live in currently. The "Cutaneous Syndrome" (CS), in reference to non-therapeutic exposure includes: Japan's nuclear reactor explosions, Chernobyl nuclear accident, threat of nuclear bomb terrorists, and warfare. Radiation deaths in 50 % of survivors occurred in Cutaneous Syndrome due to eventual skin-related reactions i.e., severe erythema and persistent pain, hemorrhagic desquamation, necrosis, and complete oncolysis. Regeneration of skin by stem cell grafts may be a future approach.

11 Review of Historic Literature

1898 Gassmann: Described histologic changes in two chronic roentgen ulcers.

1909 Wolbach: In a thorough description of chronic radiodermatitis, introduced the concept that vascular changes are progressive.

1927 Quimby: Determined that skin erythema is affected by both the quality and quantity of radiation.

1937 MacComb and Quimby: Developed the concept of cumulative dose, i.e., that the injurious effects of radiation accumulate in fractionated dose schedules.

1944 Strandqvist: Introduced a concept central to modern radiotherapeutic techniques—an isoeffect plot in which a relationship is demonstrated between time and dose.

1955 Devik: Beautifully correlated the epithelial and vascular changes after local roentgen irradiation of the skin of mice and concluded that the main cause of the acute skin reaction is epithelial cellular injury and that the secondary cause is injury to the stromal capillaries.

1956 Paterson: constructed tables and graphs to guide radiotherapists utilizing orthovoltage irradiation on time-dose-area levels that produce moist desquamation.

1960 Rubin, Casarett and Grise: Noted the difference in response between normal and grafted skin to irradiation and explained this on a pathophysiologic basis.

1968 Rubin and Casarett: Introduced the "biocontinuum" of radiation injury from acute to subacute to chronic and late changes i.e. carcinogenesis.

1984–1991 Turrensen and Notter: In clinical studies investigated a variety of radiation dose/time/fractionation studies on acute/late skin responses.

1992 Rubin et al.: LENT-SOMA Toxicity scales introduced for grading radiation induced reactions in skin.

1995 Archambeau: Meticulous presentation of microvessel changes in papillary dermis induced by radiation over time.

2003 Trotti and Rubin: Developed the CTC V3 toxicity scales for skin to be applicable to multimodality treatment of skin during cancer treatment.

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Breast Cancer

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Abstract

- The breast and chest wall are common targets for post-lumpectomy and post-mastectomy radiation.
- The pectoralis major and minor muscles, serratus anterior, along with the small subclavius muscle that is inferior to the clavicle, comprise the anterior axioappendicular muscles that are important in shoulder and upper humerus movement.
- Radiation can cause objective and subjective shoulder dysfunction, with a higher incidence seen after larger doses per fraction (>3 Gy/fraction).
- The prevalence of chest wall/upper extremity morbidity is highly variable: impaired range of motion ranged from 2 to 51 % decrease muscle strength 17–33 % and pain 12–51 %.
- Pain tends to be reported by patients somewhat more frequently than restricted shoulder movement, and those having mastectomy tend to have a higher rate of reported complaints compared to those undergoing breast conservation.
- Radiation, particularly of the axilla, increases the likelihood of shoulder morbidity following breast cancer surgery.
- Breast cosmesis is usually acceptable after 45–50 Gy at 1.8–2.0 Gy/fraction, or after 40–42 Gy in 12–16 fractions.
- The addition of a boost to the tumor bed does negatively impact cosmetic outcomes but also improves tumor control rates.
- Breast RT usually prevents normal lactation during subsequent pregnancy.
- Randomized control trials have demonstrated improved shoulder symptoms after surgery with a rehabilitative service such as physical therapy or exercise. There are studies to support the use of pentoxifylline and vitamin E for the treatment of fibrosis of the breast and/or surrounding soft tissues.

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Abbreviations

ADL	Activities of daily living
AND	Axillary node dissection
BCT	Breast conserving surgery and radiotherapy
BMI	Body mass index
CDT	Complete decongestive therapy
DBCG	Danish Breast Cancer Cooperative Group
HC	Hydrocolloid
NCCTG	North Central Cancer Treatment Group
QOL	Quality of life
ROM	Range of motion
RA	Rheumatoid arthritis
SCD	Scleroderma
SPADI	Shoulder pain and disability index
S or DL	Systemic or discoid lupus
START	Standardization of breast radiotherapy
VAS	Visual analog scale

1 Introduction

Breast cancer is one of the most common cancers treated by radiation oncologists. Radiation is widely used as part of breast conserving therapy following lumpectomy, and also in some patients undergoing mastectomy. Therefore, understanding the potential toxicities in these patients is important. Other chapters in this book address potential risks to the lung and heart. This chapter focuses more on the breast itself, and associated surrounding soft-tissues (e.g. skin, and chest wall), as well as the adjacent tissues at risk when regional nodal irradiation is added (e.g. the shoulder, brachial plexus, and axillary lymphatics).

In general, radiation for breast cancer post-lumpectomy and post-mastectomy is well tolerated, and most patients do not have impairments affecting their daily activities. Acute side effects of treatment, such as skin reactions and fatigue, are generally common, self-limiting, and resolve within 4–6 weeks after radiation is completed. Late toxicity or permanent sequelae can be divided into two groups. First, many patients have an altered appearance of the breast (e.g. persistent breast edema, hyperpigmentation, and fibrosis), and these are typically not too troubling. Second, a few percent of patients experience significant health consequences due to permanent injuries (e.g. brachial plexopathy, radiation pneumonitis, cardiac morbidity, or secondary malignancy). *The Biocontinuum of adverse acute and late affects for breast is similar to skin* (Fig. 1).

2 Anatomy and Histology

2.1 Gross Anatomy

2.1.1 Breast

The mammary gland consists of 15 to 20 lobes of glandular tissue with varying amounts of fat, in a dense fibroareolar stroma, and is attached to the anterior chest wall by pectoral fascia. In cross-sections starting from the nipple, there are openings of the lactiferous ducts and their lactiferous sinuses, which are the conduits for the secretions of the hormonally stimulated breast glands. These ducts are distinct and individual for each lobule; they first run dorsally from the nipple and then spread radially into the glandular tissue (Fig. 2a).

2.1.2 Breast Relative to Surrounding Connective Tissue

The female breast extends in the superior-to-inferior direction from approximately the 2nd through 6th ribs. Posterior (or "deep") to the breast is the pectoral fascia overlying the pectoralis major muscle. The lateral aspect of the pectoralis major makes up most of the anterior wall of the axilla.

Deep to the pectoralis major muscle is the pectoralis minor muscle. The pectoralis minor is shaped like a triangle, is nearly completely covered by the pectoralis major (Fig. 2b). The borders of the pectoralis minor muscle are used to (somewhat arbitrarily) define the anatomic levels of the axilla (level I is lateral, level II is deep, and level III is medial, to the muscle, respectively).

The serratus anterior muscle is a broad sheet that overlies the lateral part of the chest wall and forms the medial wall of the axilla.

The Pectoralis major and minor muscles, serratus anterior, along with the small subclavius muscle that is inferior to the clavicle, comprise the anterior axioappendicular muscles that are important in shoulder and upper humerus movement. Table 1 summarizes each of these movements. The intercostal muscles span from rib to rib. The primary role for the intercostals muscles is in respiration to support or provide rigidity for the intercostals spaces, resisting negative and positive intrathoracic pressures. (The diaphragm is the primary muscle of respiration.)

2.2 Histology

2.2.1 Breast

These changes are well described by Zhang (1999) as follows: "The terminal portion of the tubuloalveolar glands

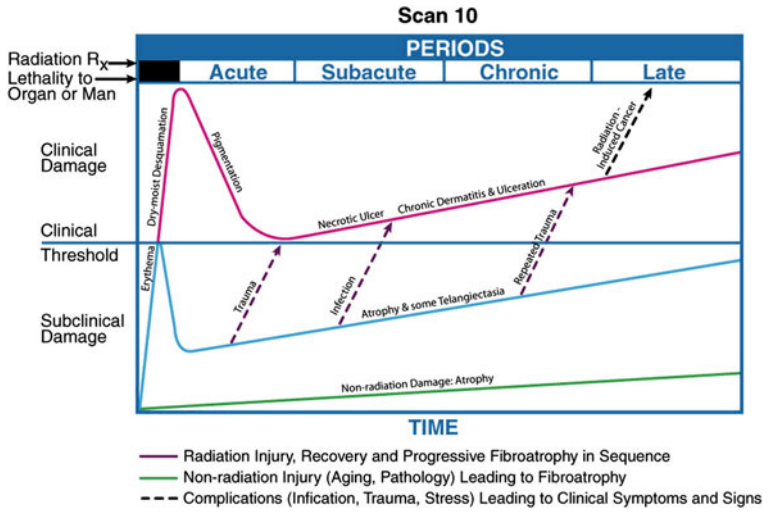

Fig. 1 Biocontinuum of adverse and late effects of the breast (with permissions from Rubin and Casarett 1968)

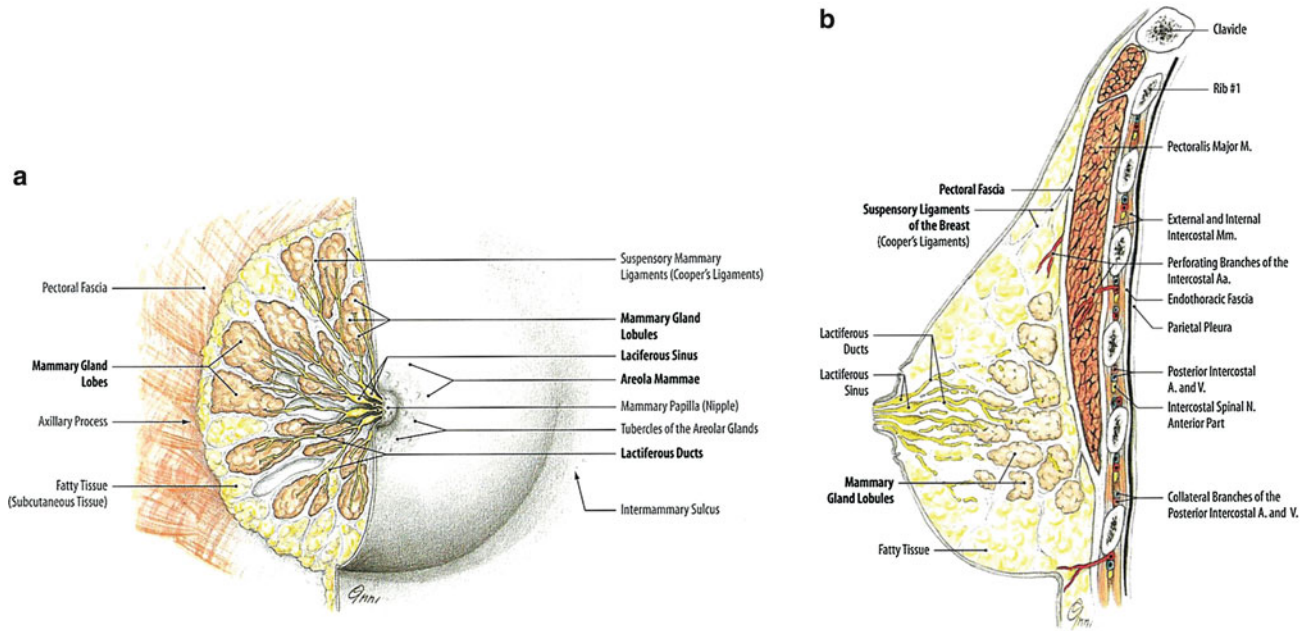

Fig. 2 **a** Right mammary gland of a woman before menopause. Glandular and fatty tissue and the efferent duct system have been dissented into the lateral half. **b** Sagittal section through the mammary gland and the anterior thoracic wall near a woman's nipple (reprinted with permission from Tillman 2007)

shows several lobules with numerous branching ducts lined by epithelial cells. The epithelial cells of the ducts appear to be more often transformed into cancer (i.e. ductal carcinoma) than are the corresponding cells of the lobules (i.e. lobular carcinoma). With pregnancy and lactation, there are marked hormone-mediated cellular changes. Declining ovarian function at menopause leads to cellular regression" (Fig. 3a, b).

2.2.2 Chest Wall Muscle

The skeletal muscles of the chest wall connect to the humerus, scapula, clavicle, and ribs via tendons, and contract and relax to coordinate shoulder movement. Muscles are composed of bundles of single large cells (called muscle fibers) that form by cell fusion and contain multiple nuclei. Each muscle fiber contains many myofibrils, which are bundles of actin and myosin filaments organized into a

Table 1 Chest wall musculature that effects shoulder motion: anatomy and function

Chest wall muscles	Attachments		Innervation	Main Action
	Proximal	Distal		
Pectoralis major	*Clavicular head:* Medial clavicle	Upper humerus	Pectoral nv. C5, C6	Adducts and medially rotates humerus Draws scapula anterior and inferior Clavicular h.: flexes humerus Sternocostal h.: extends humerus from flexed position
	Sternocostal head: Manubrium, sternum Upper six costal cartilages	Upper humerus	C7, C8, T1	
Pectoralis minor	3rd–5th ribs medially	Coracoid Scapula	Medial pectoral nv. C8, T1	Stabilizes scapula Draws scapula inferior and anterior
Subclavius	1st rib-costal junction	Mid-clavicle	Nv to subclavius C5, C6	Anchors, depresses clavicle
Serratus anterior	1st–8th rib, anterior-laterally	Scapula, medial border	Long thoracic nv. C5, C6, C7	Depresses scapula Holds scapula against thoracic wall Rotates scapula
Intercostal	Rib—superior border	Rib—inferior border	Intercostal nv.	Stabilize ribs during expiration

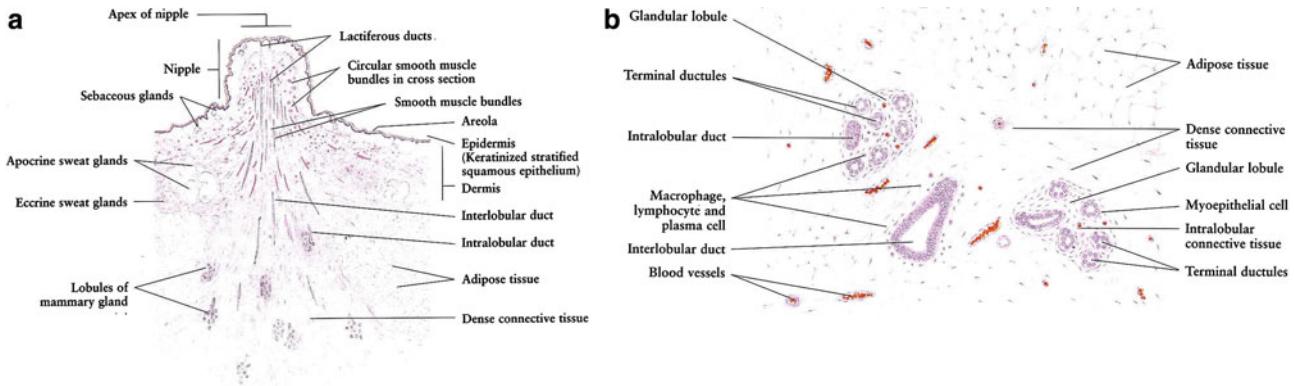

Fig. 3 **a** This figure shows a resting mammary gland, in which the glandular tissues are not developed. The lobules are composed of only ducts, dense connective tissue, and adipose tissue. (reprinted with permission from Zhang 1999) **b** In the resting mammary gland, the glandular tissue is not active, as it would beduring pregnancy or lactation (reprinted with permission from Zhang 1999)

chain of repeating units called sarcomeres. Individual muscle fibers are surrounded by endomysium, that carries numerous capillaries to supply blood to the muscle fibers. See "Musculoskeletal System: Growing Endochondral Bone, Mature Osseous, Muscle (Striated), and Soft Tissue Mesenchyme" Musculoskeletal.

3 Physiology and Pathology

3.1 Physiology

These changes are well described by Zhang (1999) as follows: "During pregnancy, the mammary glands undergo extensive histological changes in preparation for lactation. These changes are primarily manifested in two aspects: the formation of secretory acini and the relative decrease of connective tissue and adipose tissue".

"Under the influence of several hormones, such as estrogens, progesterone, prolactic, and human placental lactogen, the epithelium of the terminal ductules proliferates to form numerous secretory glandular acini. These are spherical in shape and composed of a layer of cuboidal or columnar epithelial cells resting on a basement membrane. Stellate myoepithelial cells are found between the acinar epithelial cells and the basement membrane."

"At the end of pregnancy and after parturition, the glandular tissues reach their highest development and begin to secrete milk. Figure 4a shows a lactating mammary gland with its glandular tissue at the state of maximum development. The glandular acini are lined by a cuboidal epithelium, and some epithelial cells have secretory vacuoles within their cytoplasm. The myoepithelial cells are located

between epithelial cells and basement membrane, and their contraction pushes milk toward the excretory ducts. The acinar lumina are dilated and filled with secretion of milk."

3.2 Biology

The pathogenesis of radiation-induced muscle injury has been studied only to a limited extent in animal models. In rat thighs, there was an increase in release of amino acids 4–6 h after a single dose of 15 Gy, suggesting acute protein breakdown (Schwenen et al. 1989). In rabbits, 24 h after a single dose of 11–13 Gy to the pectoralis muscle interfibrillar edema, myofilament disruption, and endothelial swelling were present on electron microscopy. At 1 week and 1 month, there were areas of myofiber necrosis, focal atrophy, fiber hypertrophy, mesenchymal cell proliferation, and fibrinoid necrosis of the vessels. Significant vascular changes were present and confined to the microvasculature (Khan 1974). Similar findings of muscle fibrosis, vessel lesions, and inflammation were observed in muscles of pigs steadily worsening over 6 months after 40–80 Gy given in a single dose. Increased collagen and glycosaminoglicans contents were found in both fibrotic and perifibrotic muscle tissue. Cultures of fibroblasts from fibrotic tissue demonstrate that these continue to be metabolically more active for several months post-irradiation than fibroblasts from nonirradiated tissue (Remy et al. 1989; Wegrowski et al. 1988). Also, a two- to four-fold increase in transforming growth factor *Beta* (TGF-β) was found in a pig model within fibrotic tissue as early as 3 weeks after 35 Gy and was still increased 1 year later. The TGF-β was localized to myofibroblasts, mononuclear inflammatory cells, and endothelial cells as well as cells within the collagenous matrix (Martin 1993).

Adult skeletal muscle is a stable tissue with little turnover of nuclei. However, in response to injury, skeletal muscle has the ability to complete extensive and rapid regeneration (Charge and Rudnicki 2004). Repair occurs through differentiation of myogenic precursor cells or satellite cells. Satellite cells are present in all skeletal muscles in varying amounts. The initial phase of muscle repair is characterized by necrosis of the damaged tissue, followed by an inflammatory response, and subsequent activation of a muscle repair process. Muscle regeneration is regulated by numerous secreted factors including TGF β, which has inhibitory role. A recent study demonstrated that doses of gamma radiation $>/= 5$ Gy reduced satellite cell numbers by at least 70 % due in part to elevated apoptosis and the inhibition of cell cycle progression (Caiozzo et al. 2010).

These studies suggest that radiation causes injury to myofibers and muscle microvasculature, decreases satellite cells, increases TGF-β and other inhibitory mediators, leading to *less regenerative capacity and increased fibrosis*. The replacement of myofibers with fibrosis leads to a shorter and weaker muscle and impacts patient function.

3.3 Pathology

The major overt-radiation induced changes are those to skin, ranging from erythema to dry, then moist desquamation. The late changes are pigmentation, fibrosis, and telangiectasia. These physiopathologic changes are well documented and illustrated in the integument/skin chapter.

The alterations to the breast tissue described in biopsies and mastectomies, months to years post-radiation, with or without chemotherapy, include the following findings (example see Fig. 4b).

- The most consistent change is in the terminal duct-lobular unit, where atypical epithelial cells with large hyperchromatic nuclei and small nuclei are seen.
- Fat atrophy due to loss of adipocytes after standard radiation doses accounts for the initial improved cosmetic lift. However, with larger doses, post-irradiation lumps may occur which are due to fat necrosis. The histologic appearance is foam cells, foamy multinucleated giant cells and zones of fibrosis. Retraction and deformation can occur in areas of surgical lumpectomy sites when large fraction boost doses are administered (Clarke et al. 1983).
- Fibrosis varied with perilobular and intralobular distribution. Stromal fibrosis, atypical fibroblasts, and vascular lesions occur. The severe diffuse fibrosis of breast stroma, tends to encircle lobules and small ducts. The epithelium of each lobule and ductile is distorted by the fibrosis.
- Lactation can occur; however, the breast does not enlarge during pregnancy.
- Ductal cell atypia rimmed with bipolar nuclei of myoepithelium or epithelial cell nuclei may be large. The need to differentiate recurrent cancer from cell atypia is a challenge but monoacinar arrangements, anisocytosis, and anisonucleosis can usually determine benign diagnosis as correct. Small needle biopsy aspirations can be a challenge but true recurrence usually resembles the original carcinoma.
- The pathophysiology of radiation injury to skeletal muscle is characterized by early muscle injury and inflammation and late fibrosis mediated predominantly by vascular injury (See Chap. 35 Musculoskeletal).

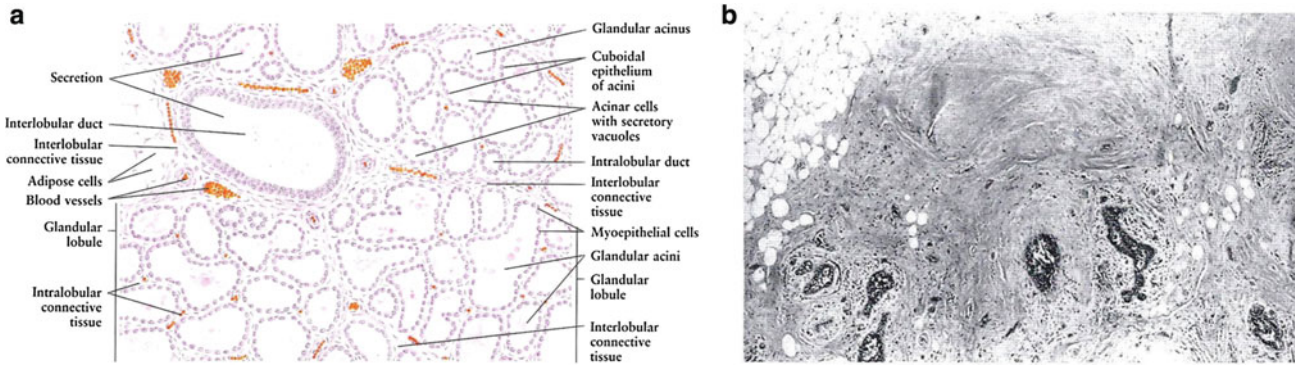

Fig. 4 **a** This figure shows a lactating mammary gland with its glandular tissue at the state of maximum development (reprinted with permission from Zhang 1999). **b** This photomicrograph of an irradiated female breast shows severe diffuse fibrosis of the breast stroma, especially encircling lobules and small ducts. The epithelium of each lobule and ductule is quite distorted by the fibrosis. This epithelium is atrophoid. but significant atypism is not observed. Much of the lobular epithelium is lost entirely. The fibrosis shows homogeneous hyalin change characteristic but not diagnostic of radiation-induced fibrosis. Several enlarged, hyperchromatic cells in the scar may be atypical fibroblasts but more likely are remaining altered lobular gland epithelium. Low power, H & E (with permissions from Fajardo 2001)

4 Clinical Syndromes (Endpoints)

Acute effects from fractionated radiation treatment to the breast involving the skin include erythema and moist dermatitis, and are illustrated in Fig. 5 in the skin/integument chapter. The late changes involving skin are relatively infrequent but can include fibrotic scarring and retraction of the breast, illustrated in Figs. 6 and 7 in the skin/integument chapter. A variety of endpoints can be used to grade the effects of therapy on the breast (Table 2).

4.1 Breast

4.1.1 Cosmesis (Late Breast Appearance)

The main goals of breast conservation therapy in early-stage breast cancer are to provide primary tumor control comparable to mastectomy and to preserve an acceptable cosmetic appearance of the breast. An unsatisfactory cosmetic outcome should be considered as a potential late toxicity. The rate of poor or fair cosmetic outcome in most series is 15–20 % or less (Pezner et al. 1992; Ryoo et al. 1989; De la Rochefordiere et al. 1992; Taylor et al. 1995; Wazer et al. 1992; Harris et al. 1979; Olivotto et al. 1989; Sneeuw et al. 1992). It has been demonstrated in many studies that surgical factors including the extent or volume of surgical resection (Taylor et al. 1995; Wazer et al. 1992) and scar orientation, (Taylor et al. 1995) have a large impact on cosmetic outcome (Pezner et al. 1992; Ryoo et al. 1989; De la Rochefordiere et al. 1992; Taylor et al. 1995; Wazer et al. 1992; Tuamokumo and Haffty 2003). The use of chemotherapy and patient factors such as breast size, older age, and race have also been associated with more frequent cosmetic failures (Pezner et al. 1992; Ryoo et al. 1989; De la Rochefordiere et al. 1992; Taylor et al. 1995; Wazer et al. 1992; Tuamokumo and Haffty 2003). However, several radiation treatment factors are associated with poorer cosmetic outcomes as well. It is important to consider these factors when planning radiation treatment to minimize the late toxicity rate.

Table 3 lists the cosmetic outcomes from single institution retrospective studies that have analyzed the impact of radiation techniques on subsequent cosmetic outcome. Wazer et al. from New England Medical center at Tufts demonstrated an increase in fair/poor cosmetic outcomes with larger chest wall separations (24 cm mean) and greater maximal dose inhomogeneity (13 % mean) at the central axis (Wazer et al. 1992). The use of a boost and a supraclavicular and/or axillary field were the other factors associated with a higher proportion of fair/poor cosmetic outcomes. In this study, an electron boost, but not an interstitial implant boost, was associated with the decline in cosmetic outcome. Patients in this study were treated with 6 MV photons, 81 patients with an implant boost, and it is not stated what proportion were treated to >2 fields.

The effect of radiation technique on the cosmetic result was demonstrated by the Joint Center for Radiation Therapy and Harvard Department of Radiation Therapy when it compared cosmetic results in two different cohorts of patients treated between 1970–1981 and 1981–1985 (De la Rochefordiere et al. 1992). In the earlier cohort, 85 % received a 3-field technique, 95 % an implant for boost, 33 % $\geq$ 50 Gy breast dose, and 85 % > 18 Gy boost dose. The institution had previously found that the use of >2 fields, an implant boost, boost dose >18 Gy, and a breast dose >50 Gy were associated with poorer cosmetic outcomes (Harris et al. 1979; Olivotto et al. 1989). Treatment techniques had changed during the latter time interval such that 55 % received a 3-field technique, 47 % an implant for

Table 2 Breast toxicity assessment: LENT SOMA

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal Hypersensation, Pruritus	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective				
Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Fibrosis[a]/Fat necrosis	Barely palpable increased density	Definite increased density and firmness	Very marked density, retraction, and fixation	
Telangiectasia	<1 cm^2	1–4 cm^2	>4 cm^2	
Lymphedema arm (circumference)	2–4 cm increase	>4–6 cm increase	>6 cm increase	Useless arm, angiosarcoma
Retraction/Atrophy[b]	10–25 %	>25–40 %	>40–75 %	Whole breast
Ulcer	Epidermal only, ≤1 cm^2	Dermal, >1 cm^2	Subcutaneous	Bone exposed, necrosis
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Edema			Medical intervention	Surgical intervention/ mastectomy
Lymphedema arm		Elevate arm, elastic stocking	Compression wrapping, intensive physiotherapy	Surgical intervention/ amputation
Atrophy				Surgical intervention/ mastectomy
Ulcer		Medical intervention	Surgical intervention, wound debridement	Surgical intervention/ mastectomy
Analytic				
Photographs	Assessment of skin changes as atrophy, retraction or fibrosis, ulcer			
Tape measure	Assessment of breast size and forearm diameter			
Mammogram	Assessment of skin thickness and breast density			
CT/MRI	Assessment of breast size, fat atrophy, fibrosis density			

[a] Compare exposed area to contralateral nonirradiated skin accordingly to defined parameters
[b] Volume loss due to surgery, with or without radiotherapy

Table 3 Physician assessed cosmetic results from breast conservation therapy (White and Joiner 2006 with permission)

Institution	*N*	F/U (years)	Excellent (%)	Good (%)	Fair (%)	Poor (%)	Radiation factors associated with poorer cosmesis
Tufts U[46]	234	4.2	41	47	9	3	Heterogeneous RT dose; boost; use of >2 fields
Harvard/ JCRT[44, 49]							Breast dose >50 Gy; use of >2 fields; boost dose >18 Gy; implant boost
<I981	504	8.9	58	28	10	4	
1982–1985	655	5.6	73	23	3.5	0.5	
Washington U[45]	458	4.4	38	44	15	4	Use of >2 fields; breast dose >50 Gy; no compensator filters

boost, 5 % ≥ 50 Gy breast dose, and 42 % > 18 Gy boost dose. The cosmetic results were better with the techniques used in the latter period (Table 3). When examined, there was no influence of the boost, number of fields treated, and/or the daily dose on cosmetic outcome in the latter cohort (De la Rochefordiere et al. 1992).

Washington University similarly found that the percentage of excellent/good cosmetic outcomes decreased

with the use of more than 2 fields ($P = 0.034$), and increasing radiation dose to the entire breast ($P = 0.024$). With increasing separations at the central axis, a relative deterioration occurred in excellent/good rations, especially with the use of lower energy, 4 MV photons. This is inferred to be from the dose inhomogeneity that occurs with the larger chest wall separation. The effect of dose homogeneity on cosmetic outcome is again demonstrated in this study by a significantly higher frequency of excellent/good cosmetic scores (82 %) that occurred with the use of compensating filters compared with no use of compensating filters (59 %) ($P = 0.002$). Daily fraction size (1.8 vs. 2.0 Gy), boost versus no boost, and the type of boost did not influence cosmetic outcome in this series (Taylor et al. 1995). Other studies have confirmed the influence of radiation therapy factors on cosmetic outcomes. For instance, Ryoo et al. (1989) reported that the use of a wedge in the breast tangents was a significant factor for obtaining a good cosmetic result.

The cosmetic failure rates reported in all of these studies reflect treating physician observation. Studies that include patient-rated cosmetic evaluations demonstrate fairly good concordance with physician-rated cosmesis and satisfaction with a range of cosmetic outcomes (Taylor et al. 1995; Sneeuw et al. 1992).

In an attempt to objectively measure cosmetic outcome, Pezner et al. developed a breast retraction assessment (BRA) that quantified the amount of retraction of the treated breast in comparison to the untreated one by measuring the lateral and vertical displacement of the nipple (Pezner et al. 1992). On multivariate analysis, in order of descending importance, patient age >60, extensive breast reaction, patient weight >150 pounds, and upper quadrant primary site were the most significant factors related to breast retraction after breast conserving surgery and radiotherapy (BCT). None of the radiotherapy (RT) parameters studied were associated with breast retraction. Subset analysis related that the volume of the boost had some relation to retraction, but did not reach statistical significance.

Cosmetic outcome was assessed in a subset of 101 women accrued to the Milan III trial that randomized women with breast cancers ≤2 cm in size to quadrantectomy (QUAD) or quadrantectomy plus breast irradiation (QUART) (Ververs et al. 2001; Veronesi et al. 2001; Sacchini et al. 1995). Radiation consisted of 50 Gy whole breast dose followed by a "scar" boost of 10 Gy, all delivered with 2 Gy fractionation. Interestingly, there were no statistically significant differences in cosmetic outcome (scored either objectively based on nipple displacement/symmetry or subjectively by physicians and patients) between the QUAD versus QUART groups (Sacchini et al. 1995). The negative findings from this study are in conflict with many other studies. These differences might be due to the small sample size or the extent of the surgery. For example, the negative cosmetic effects of a QUAD (versus a lesser degree of surgery) might make the potential effects of radiation less evident.

The effect of the boost on the cosmetic result was evaluated in two randomized trials. In EORTC 22881/10882 (Vreilng et al. 1999), 5,569 patients with stage I and II breast cancer who had received lumpectomy, axillary dissection, and breast radiation up to 50 Gy over 25 fractions were randomized between a boost of 16 Gy or no boost if the lumpectomy resection margins were negative. Cosmetic outcome in each arm was assessed by two methods postoperatively and at 3 years: by a five-physical panel evaluating photographs in a sample of 713 patients (Table 4) and by the percentage BRA relative to a reference length in a sample of 1,141 patients. Postoperatively, there was no significant difference in cosmetic assessment between the two arms. However, by 3 years, the patients in the boost arm had significantly lower rate of excellent/good cosmetic outcome and nearly double the rate of fair outcomes (13 % no boost vs 25.8 % boost) ($P = 0.0001$). Very few patients in either arm had a poor result at either time period. By the panel assessment, the boost group had significantly worse median scores for all the items evaluated—appearance of the surgical scar, breast size, breast shape, nipple position, and areola shape. Interestingly, despite the observations of the panel, the difference in the percentage BRA was small, less than 1 % between the borderline statistical significance ($P = 0.04$). In the Lyon trial, patients with early breast carcinoma (≤3 cm) treated by local excision (tumorectomy or quadrantectomy), axillary dissection, and conventional 50-Gy irradiation were randomized to either a boost of 10 Gy electrons, or no boost. There were no significant differences in either the physician-evaluated or patient self-assessment of cosmetic outcome.

In a prospective randomized trial, the use of IMRT was associated with a better late cosmetic outcome (Table 5; Donovan et al. 2007). Almost all of these patients had RT to the breast alone, without the nodes. Similarly, IMRT has been demonstrated in a randomized trial to reduce acute effects as well; e.g. rate of moist desquamation reduced from ≈45 % without IMRT to ≈30 % with IMRT (Pignol et al. 2008).

In summary, several patient and treatment factors can contribute to a poor cosmetic outcome following breast conservation therapy with RT. The radiation factors that influence the cosmetic outcome in most series are the use of a boost, greater than 2 fields (i.e., the addition of a supraclavicular, axillary, or internal mammary field), the total dose, and dose heterogeneity in the breast fields. Newer radiation therapy planning methods such as 3-dimensional conformal therapy or intensity-modulated radiation therapy can produce more homogeneous dose distributions through the breast.

Table 4 The impact of tumor bed boost on cosmetic outcomes in randomized trials

	EORTC 22881/10882 ($n = 713$)				Lyon trial Romestaing et al. (1997)			
	Post-op		3 year Follow-up		2 year by physician ($n = 702$)		2 year by patients ($n = 600$)	
Score (%)	No boost	Boost (16 Gy)	No boost	Boost (16 Gy)	No boost	Boost (10 Gy)	No boost	Boost (10 Gy)
Excellent	37.4	34.8	41.7	32.7	85		90	
Good	47.3	45.0	43.9	38.2				
Fair	13.7	18.8	13.1	25.8	Not stated	Not stated	Not stated	Not stated
Poor	1.6	1.4	1.4	3.3	0		0	

Table 5 Proportion of patients showing change in breast appearance after randomization to 2D (control group) or IMRT (test group)[a]

	Standard 2D	IMRT
1 year		
Percent with no effects	64.1	74.2
Percent with mild effects	28.2	21
Percent with marked effects	7.6	4.8
2 year		
Percent with no effects	56.6	65.1
Percent with mild effects	38	30.2
Percent with marked effects	5.4	4.7
5 year		
Percent with no effects	41.8	60.2
Percent with mild effects	44.3	29.7
Percent with marked effects	13.9	10.2

[a] Adapted from Donovan et al. (2007)

The negative cosmetic impact of the boost needs to be taken in the context of the increased rate of local control achieved when the boost is added; a meaningful benefit especially in some patient subsets. Nevertheless, care should be taken that the boost is delivered using techniques that minimize morbidity. Careful image-guided localization of the cavity will help reduce excess breast tissue being taken to higher doses unnecessarily.

4.1.2 Chronic Breast Pain

A survey of 127 breast cancer survivors, on average 3 years post-treatment, revealed that 27 % reported chronic pain (Carpenter et al. 1998); rated as mild in 90 % of patients. The sites of pain affected were breast 86 %, ipsilateral arm 69 %, and ipsilateral axilla 81 %. Pain in all three sites was reported in 58 %. The prevalence of pain was 27 % after lumpectomy with RT, and 23 % after mastectomy alone.

The impact of irradiation on breast pain has been reported form two randomized studies. In a prospective randomized trial at Princess Margaret Hospital of tamoxifen alone versus tamoxifen plus breast RT, in women aged ≥50 who have had a lumpectomy, the addition of radiation did not adversely affect breast pain up to 12 months post-treatment (Ryan et al. 2003).

In a large prospective study conducted in Ontario, Canada, women with lymph node negative breast carcinoma who had undergone lumpectomy and axillary lymph node dissection were randomized to either breast irradiation or no further treatment. Within the first few months or randomization, the irradiated patients had a lesser quality of life (QOL) and more breast pain, than did the control group, with the maximum difference at about 3–6 months post-randomization. The differences declined over time, and became undetectable by 2 years (Whelan et al. 2000). Similarly, there was no difference in long-term patient-reported QOL metrics in the randomized trial of ± IMRT (Donovan et al. 2007).

In concert, these data suggest that long-term breast pain can occur, but that it is not a prominent clinical problem for most patients.

4.1.3 Lactation

There are several studies that access the ability of the breast to lactate following breast conservation therapy with lumpectomy plus RT (Table 6). In general, normal lactation is not possible (e.g., reduced frequency or volume of lactation).

A cohort study compared the breast feeding outcomes in 83 female survivors of Hodgkin's lymphoma (treated with mediastinal RT to a median dose of 41 Gy, range 27–46 Gy) to their 70 female sibling controls. Both groups had 141 live births and 94 attempts at breastfeeding. In the irradiated group, 57/94 (61 %) of these attempted breast-feedings were successful versus 74/94 (79 %), $p = 0.04$. There were no meaningful differences noted in their analysis related to various factors including age at the time of RT, age at the time of pregnancy, nor RT dose. There were 30 patients ≪21 years of age at the time of their initial diagnosis. They had 49 live births, 35 attempts at breast-feeding, and of these 66 % (23/35) were successful. On a per-person (rather than per-birth basis), 22/30 patients attempted to breast feed, and 68 % (15/22) were successful

Table 6 Reports of lactation in irradiated breasts (following breast conservation with tumor excision and breast RT for early-stage breast cancer)

Author	Report type	Tx year	Patient age	T stage	ALND	Dose[c] (Gy)	Boost[d] (Gy)	RNI	Chemo	Interval between RT and pregnancy (year)	Breast enlargement during pregnancy	Colostrum present	Breast milk start day postpartum	Lactation duration (months)	Lactation rate
Findlay et al. (1988)	Case	1979	35	NS	Yes	48.6	20	No	No	4	NS	No	3	2.5	NA
Rodger et al. (1989)	Case	1983	30	T1a	Yes	42–45	20	Yes[g]	NS	3	NS	NS	NS	NS	1/2[a]
Green (1989)	Case	1988	32	T2	Yes	48.6	No	No	NS	19 mo	No	No	5	1	NA
Higgins and Haffty (1994)	Retrospective review	1965–1989	25–41	I–II	Yes	50–54	10–11	No	1 pt	28–75 mo	NS	NS	NS	1–7	4/11[a]
Tralins (1995)	ASTRO survey	1995	30–39	T1–2	NS	40–50.4	10–22	NS	3 pts	3[b]	No[e]	Yes[f]	7[h]	NS	18/53[a]

ALND axillary lymph node dissection, *L* lumpectomy, *NCI* national cancer institute, *NA* not applicable, *NS* not stated, *Q* quadrantectomy, *RNI* regional nodal irradiation

[a] Number of patients pregnant and delivered

[b] Mean value of these 18 people

[c] All fractionation are 1.8–2.0 Gy/Fx except in Rodger study, 2.1–2.5 Gy/Fx was used

[d] Boost are treated with electron or Ir192

[e] Reported in 5 patients among these 18 patients

[f] Reported in 1 patient among these 18 patients

[g] Upper internal mammary nodes; 42–45 (2.1–2.5/fx)

[h] Reported in 1 patient among these 18 patients

Table 7 Rates of patient-reported shoulder symptoms following breast cancer treatment

Author (year)	*N*	Surgery[a]	RT	Symptom Reported	Rate of symptoms in patients undergoing mastectomy (%)	Rate of symptoms in patients undergoing breast conservation therapy (%)	*P*[f]
Ernst et al. (2002)	148	MRM[b] 106 BCT[c] 42	All (no RT axilla)	Pain[d] >3 Strength[d] <6	27 14	24 9	ns
Nesvold et al. (2008)	263	MRM 186 BCT 77	All (23 % RT Axilla)	Pain[e] 3–5 Shoulder stiffness[e] 3–5	58 32	33 12	0.001 0.001
Kärki et al. (2005)	96	MRM 64 BCT 32	63.5 %	Neck-shoulder pain Shoulder movement restriction	42.2 17	37.5 5	– –

[a] All had axillary node dissection
[b] Modified radical mastectomy
[c] Breast conserving surgery and radiation
[d] Visual analogue scale 0–10
[e] Likert Scale 1–5
[f] Comparing the mastectomy and breast conservation patients

at least once. Of these, there were eight girls aged 14–16 at diagnosis. All of them attempted breastfeeding, and 6/8 were successful (McCullough et al. 2010).

The apparent greater success at breast feeding in the Hodgkin's survivors (compared to the breast cancer patients) may be related to the lack of breast surgery, the often-used lower doses of RT, and the fact that the entire breast is not usually irradiated.

4.2 Chest Wall and Associated Muscle

4.2.1 Shoulder Symptoms/Mobility

Patient-reported shoulder-associated complaints (e.g. pain and stiffness) are common clinical syndromes following breast cancer therapy. Table 7 summarized several studies comparing outcomes following therapy with mastectomy versus breast conservation. Globally, the outcomes with breast conservation (that almost always included RT) were similar or better than those with mastectomy.

Similarly, Table 8 summarizes some studies comparing outcomes based on objective measures of shoulder mobility, in patients undergoing mastectomy versus breast conservation therapy. In the breast conservation patients, breast RT was delivered in almost all cases, and axillary RT was delivered in only a minority of patients. Across the board, the outcomes appear superior with breast conservation versus mastectomy.

The addition of RT clearly can have negative effects on shoulder mobility. Table 9 summarizes several studies comparing outcomes, both patient-reported and objective measures, in patients undergoing surgery with or without RT. The addition of RT is associated with a higher rate of impairment.

The extent of the RT field is also important, as can be inferred from the data summarized in Table 10. The studies listed compare outcomes, both patient-reported and objective measures, in patients undergoing surgery with or without RT, with variable *extents* of the RT field. The rates of impairment appear typically higher in the patients receiving RT to the *breast and axilla* versus those undergoing RT to the breast alone (where the impairment rates are similar to those patients undergoing surgery without RT).

The outcomes appear to be also dependent on the surgical extent. Table 11 summarizes studies comparing outcomes in patients undergoing axillary nodal dissection versus sentinel node biopsy. Note the superior functional outcomes in those undergoing the lesser surgery. However, other clinical factors may alternatively account for these differences (e.g., different rates of additional therapies delivered in these groups).

Standard tangent breast fields typically include portions of the pectoralis major, pectoralis minor, and serratus anterior muscles, as well as adjacent tissues. Isolating the exact component of radiation in the genesis of these syndromes is challenging given that multiple factors influence their development such as surgical procedure and patient comorbidities. This is exemplified by a study of 57 unilaterally irradiated patients with breast cancer who underwent MRI and EMG of muscles involved with shoulder movement (pectoralis major and minor, upper trapezius, serratous anterior, and rhomboid muscles) on the affected and unaffected side. A questionnaire regarding shoulder function,

Table 8 Rates of measured reduction in shoulder range of motion (ROM) following breast cancer treatment

Author (year)	*N*	Surgery[a]	Rate of RT usage in BCT patients (axillary irradiation usage)	Measure	Rate of symptoms in patients undergoing mastectomy (%)	Rate of symptoms in patients undergoing breast conservation therapy (%)	*P*[d]
Ernst et al. (2002)	148	MRM[b] 102 BCT[c] 46	All (no RT axilla)	ROM >20°	15	3	ns
Nesvold et al. (2008)	263	MRM 186 BCT 77	All (23 % RT axilla)	ROM >25° Flexion Abduction	24 38	7 18	0.01 0.01
Gosselink et al. (2003)	76	MRM 31 BCT 45	84 % (16 % RT axilla)	ROM >25° Flexion Abduction	87 90	58 53	0.001 0.001
Voogd (2003)	332	MRM 118 BCT 213	64 % (no RT axilla)	Abduction >20°	14	7	0.03
Sugden et al. (1998)	141	MRM 27 BCT 80	All (35 % RT axilla)	Any ° ROM Pre-RT Post-RT	44 79	9 35	0.001 0.001

[a] All had axillary node dissection
[b] Modified radical mastectomy
[c] Breast conserving surgery and radiation
[d] Comparing the mastectomy and breast conservation patients

Table 9 Incidence of impaired shoulder mobility after irradiation (White and Joiner 2006 with permission)

Institution (author)	*N*	Surgery	Nodal RT (%)	Measure	Surgery (%)	Surgery + RT (%)
Netherlands Cancer Institute (Bijker)	691	Mastectomy	70	Patient self-report	3.4	8[a]
						18.9[b]
University of Oxford (Sugedn)	39	Mastectomy	35	Measured ROM[c]	71[d]	81[d]
	102	Lumpectomy			31[e]	59[e]
Aarhus University Hospital (Hojris)	84	Mastectomy	100	Measured ROM	2	16
Odense University (Ryttov)	57	Mastectomy	23	Measured ROM	6.8	38

[a] Axillary sampling
[b] Axillary clearance
[c] Range of Motion
[d] Mastectomy patients
[e] Lumpectomy patients

the shoulder pain and disability index (SPADI), was used to evaluate shoulder muscle activity following treatment (Shamley et al. 2007). Ninety-four percent of cases received RT after either mastectomy (23 %) or breast conserving surgery (71 %); the axilla was irradiated in 21.6 %. Roughly 15–40 % experienced pain or dysfunction over the 6 year follow-up period. The three items most associated with pain were: reaching up to a shelf, lying on the involved side, and pushing an object with the involved arm. MRI evaluation revealed that only the pectoralis major and pectoralis minor demonstrated a decrease in muscle size on the affected size. Loss of EMG activity was seen for all muscles evaluated on the affected side, but it was most significant in the upper trapezius, serratus anterior, and rhomboid. The most symptomatic patients were noted to have loss of activity for the upper trapezius and rhomboid; both of which are outside the radiation and surgical fields. These are theorized to be secondary muscle changes that persist and affect patient's function. Similarly, other studies have demonstrated that late shoulder symptoms on the affected side can be associated with other nontreatment variables such as body mass index (BMI) (Nesvold et al. 2008) and the presence of diabetes or cardiovascular disease (Engel et al. 2003).

There is marked variation in the reported rates of dysfunction. This likely relates to a variety of factors including the variable endpoints considered, variable lengths of follow-up, and differences in radiation/surgical treatments applied. The variation is illustrated by two systemic reviews of the literature that have focused on late morbidity after

Table 10 Rates of reduction in shoulder range of mobility (ROM): with or without radiotherapy (RT)

Author (year)	*N*	Surgery[a]	Measure	Rate in patients without RT	Rate in patients with RT (extent of RT as noted)	*P*[b]
Johansson et al. (2001)	61	26 MRM 35 BCS	Reduced ROM >10°	23 %	79 % with RT to the axilla 19 % with RT to the breast alone	<0.001 ns
Hojris (2000)	84	84 MRM	ROM <175°	15 %	52 % (with nodal RT)	<0.01
Sugden et al. (1998)	107	39 MRM 102 BCS	Any reduction in ROM	MRM 71 % BCT 31 %	81 % 59 %	<0.01
Liljegren et al. (1997)	381	BCS	Survey: arm symptoms	16 %	23 % (RT to breast only)	NS
Tengrup et al. (2003)	370	BCS	Survey: shoulder stiffness	No AND 3 % AND 46 %	17 % 52 %(RT to breast only)	0.3
Tengrup (2000)	110	BCS	Reduced ROM >15°	30 %	57 %(RT to Breast only)	–

AND axillary node dissection
[a] All had axillary node dissection
[b] Comparing the RT and no-RT patients

Table 11 Shoulder morbidity following axillary node dissection (AND) versus sentinel node biopsy (SNB)

Author (year)	*N*	Measure	Rate (or measurement) in patients undergoing axillary node dissection	Rate (or measurement) in patients undergoing sentinel node biopsy	*P*[a]
Peintinger et al. (2003)	56	Questionnaire- pain at 1 week Average ROM -flexion -Abduction	68 % 143.8° 146°	36 % 158.9° 154.6°	0.012 0.03
Leidenius et al. (2003)	85	Reduce ROM flexion/abduction	86 %	45 %	0.002
Purushotham et al. (2005)	298	Loss of ROM flexion at 3 month	13°	6.7°	0.04
Haid et al. (2002)	197	Questionnaire- reported reduced ROM at 18 month	43.5 %	8.8 %	0.001
Burak et al. (2002)	96	Questionnaire- any arm symptom at 15 month	87.5 %	41.7 %	–

[a] Comparing patients undergoing axillary node dissection versus sentinel node biopsy

treatment of breast cancer and specifically rates of shoulder/arm impairment and pain. Rietman et al. identified six studies that assessed late morbidity of breast cancer treatment in relationship to the effect on activities of daily living (ADL) and QOL. The prevalence of chest wall/upper extremity morbidity was highly variable: impaired range of motion (ROM) ranged from 2 to 51 %, decreased muscle strength 17 to 33 %, and pain 12 to 51 % (Rietman et al. 2003). The relationship between the presence of symptoms and reduced QOL was noted to be poorly understood. Similarly, Lee et al. reviewed 32 relevant studies that reported upper limb consequences and effects on QOL, and also found wide variation in morbidity prevalence. Shoulder restriction was reported between <1 and 67 %, shoulder/arm pain between 9 and 68 %, and arm weakness between 9 and 28 % (Lee et al. 2008). Quality of life was generally high in the reviewed studies. In concert, these many studies suggest that these issues represent a clinically meaningful source of morbidity for large numbers of patients.

4.2.2 QOL

Several studies evaluating patient-reported shoulder symptoms have also examined the extent that symptoms disrupt patients' daily activities and QOL. A large study involved 990 cases from the Munich Cancer Registry, of which 88 % returned patient surveys (EORTC QOL validated form QL3-C30), demonstrated that the complaint of reduced ROM on the treated side persisted 5 years after treatment: 47 % at year 1, 44 % at year 2, 40 % at year 3, and 38 % at years 4 and 5. Consistently over the 5 years, QOL was significantly ($p < 0.001$) lower for patients with arm difficulties. For those whose arm problems dissipated, QOL significantly improved ($p < 0.01$). A multivariate logistic regression analysis ($N = 886$) revealed significant effects of extent of axillary surgery, comorbidities, age, employment, and the clinic where the patient was treated. Those with more than 10 removed lymph nodes, diabetes or cardiovascular disease, those still working, and those treated in certain clinics were more likely to suffer arm complications.

Interestingly, adjuvant therapy such as radiation was *not* predictive for arm complications (Engel et al. 2003).

5 Radiation Tolerance

5.1 Dose Time Fractionation

5.1.1 Breast Fibrosis

Skin thickening or fibrosis of the breast can occur after radiation for breast cancer. An analysis was done of 294 patients treated with BCT (including breast radiation with standard fractionation to 50 Gy) at MD Anderson Cancer Center from 1990 to 1992 (Meric et al. 2002). Some fibrosis was noted to develop in 29 %, but only 3.7 % experienced grade 2 (moderate) and 0.3 % grade 3 (impaired ROM) fibrosis (Meric et al. 2002). Similar to the findings associated with cosmetic failure, breast fibrosis developed more commonly in patients treated with additional radiation fields (38 vs. 21 %, $P = 0.001$) and in patients who received a boost (33 vs. 22 %, $P = 0.04$).

The influence of total dose and fraction size on the development of subsequent breast fibrosis is demonstrated by a study form the University of Hamburg that evaluated long-term radiation sequelae using LENT-SOMA criteria (LENT-SOMA 1995) in three groups of women who had undergone BCT with a minimum of 6 years follow-up. The rates of grade 2–3 breast fibrosis were 58 % following 60 Gy with 2.5 Gy fractions (1983–1987, $n = 45$); 51 % following 55 Gy with 2.5 Gy fractions (1988–1993, $n = 345$); and 20 % following 55 Gy in 2 Gy fractions (1993–1995, $n = 200$) (Fehlauer et al. 2003).

The effect of hypofractionation on the incidence and latency for developing subcutaneous fibrosis was studied by Bentzen et al. Two groups of breast cancer patients treated with post-mastectomy irradiation between 1978 and 1982 were compared: 163 receiving a minimum target dose of 36.6 Gy to mid-axilla in 12 fractions of 3.05 Gy delivered twice weekly versus a sample of 66 women treated with a total dose of 40.92 Gy to mid-axilla in 22 fractions of 2.04 Gy delivered 5 fractions per week. The incidence of fibrosis increased with time during the first 4 years of follow-up, with 90 % of the cases being manifest by 3.2 years. A longer latency was demonstrated for the most severe fibrosis at 4.4 years, in comparison to grade one fibrosis that typically developed within 2 years. The incidence of moderate to severe fibrosis was nearly double in the hypofractionated versus more conventional fraction schedule (96 vs. 45 %), (Bentzen et al. 1989b).

Certain patient populations may be at increased risk for developing exaggerated fibrotic reactions following radiation. Patients with certain collagen vascular diseases (CVDs) may represent such a subset and are discussed later. Breast cancer patients who are heterozygous for the ataxia telangiectasia mutation (ATM) have been reported to have more severe fibrosis following radiation (Jannuzzi et al. 2002).

5.1.2 Shoulder Mobility

A measured reduction in shoulder ROM was more frequent with hypofractionated radiotherapy after mastectomy in patients treated from 1978 to 1982 in Aarhus, Denmark (Bentzen et al. 1989a). Maximum shoulder abduction and flexion angles were more frequently reduced in the patient cohort treated with 3–4.5 Gy/fraction two times per week than in those who received 1.8 Gy/day five times per week. Other factors associated with decrease movement on linear regression analysis included age >60 years, presence of subcutaneous fibrosis, and nonadherence to an exercise program. The length of time to expression of 90 % of the ultimate frequency of moderate-severe shoulder impairments was estimated at 3.9 years. The use of more modest hypofractionated regimens on the United Kingdom randomized standardization of breast radiotherapy (START) Trials A and B, was not associated with higher rates of patient-reported shoulder symptoms (Table 12), (Hopwood et al. 2010). Lymphatic radiation was delivered to 23 % of patients enrolled on START A, and to 10 % of those on START B. There was no significant difference of reported symptoms in all comparisons of the different fractionated regimens. Care should be taken in interpreting these findings since larger fraction sizes are typically associated with greater late effects, and the interval between RT and the clinical manifestation of symptoms can be prolonged (especially, if the dose per fraction is not that high). High doses per fraction are not recommended in patients undergoing nodal irradiation.

5.2 Summary Dose Time Fractionation

Whole breast doses of 45–50 Gy delivered at 1.8–2.0 Gy/fraction is generally very well tolerated with an acceptable cosmetic outcome. These doses are also well tolerated by the shoulder and associated regional muscle as well. The addition of a tumor bed boost (e.g. 10–16 Gy) negatively impacts the cosmetic outcomes (but also improves tumor recurrence rates).

Modest hypofractionation (e.g. 40–42 Gy in 12–16 fractions) is also well tolerated by the breast, but the experience with the shoulder region is less extensive. More aggressive hypofractionation (e.g. >3 Gy/fraction) appears to be less well tolerated by the normal tissues in the region of the shoulder.

Table 12 Kaplan Meier estimates of 5-year rate of patient-reported shoulder/arm symptoms on START A and B trials (%) (with permissions from Hopwood et al. 2010)

	START A			START B	
Total Dose *Fractionation*	50 Gy 25 fractions	41.6 Gy 12 fractions	39 Gy 12 fractions	50 Gy 25 fractions	40 Gy 15 fractions
Pain in shoulder/arm	30.9	30.2	32.5	32	32
Shoulder stiffness	19.8	16	18.1	19.3	18.3
Difficulty in raising or moving arm sideways	15	14.1	15	17	15.9

Table 13 Acute skin toxicity from concurrent radiation and chemotherapy for breast cancer (adapted from White and Joiner 2006 with permission)

Author	Regimen evaluated	% Grade 3 toxicity
Ellerbroeck	Paclitaxel every 3 weeks	0[a] (0/24)
Hanna	Paclitaxel every 3 weeks	33[a] (7/20)
Formenti	Paclitaxel twice weekly	7[a] (3/44)
Bellon	Paclitaxel every 3 weeks	10[a] (3/29)
	Docataxel every 3 weeks	40[a] (6/15)
Isaac	CMF every 3 weeks	1.5[a] (3/220)
Fiets	CMF (classic) every 21 days	41[b] (21/51)
	AC every 21 days	70[b] (43/61)

[a] RTOG acute toxicity
[b] Common toxicity criteria version 2

6 Chemotherapy Tolerance

Concurrent chemotherapy with breast radiation has also been associated with worse acute skin toxicity (Ellerbroek et al. 2003; Hanna et al. 2002; Formenti et al. 2003; Bellon et al. 2000; Issac et al. 2002; Fiets et al. 2003). Select series are shown in Table 13 suggesting a higher rate of grade three skin toxicity with combined modality therapy, particularly anthracycline-based chemotherapy (Formenti et al. 2003; Fiets et al. 2003). Conflicting results are observed with concomitant CMF and paclitaxel chemotherapy. Caution is advised in delivering chemotherapy together with breast radiation, given the potential for wore acute toxicity and no consistent evidence that it offers a benefit in terms of survival and/or local regional recurrence rates over sequential therapy.

7 Special Topics

7.1 Lymphedema

Lymphedema of the arm can be caused by an interruption of the normal filtration process between capillaries, interstitial tissue, and lymphatic vessels. Under normal circumstances, capillary pressures force fluid into the interstitial and reabsorption pressures pull most of the fluid back into the capillary at the venous side. The remainder of the filtered fluid and protein are removed by lymphatic vessels. Without a dysfunctional lymphatic system, protein, cells, and non-reabsorbed fluid remain in the intestinal tissue. The stasis of fluid in the subcutaneous tissues of the arm leads to increased weight and girth of the extremity. Patients with arm edema secondary to breast cancer therapy can experience difficulty in performing skills at home or work because of functional impairment, psychological distress as a result of the change of body image, and chronic pain, leading to significantly reduced QOL (Tobin et al. 1993; Maunsell et al. 1993; Ververs et al. 2001). The primary treatment factors contributing to arm edema are the extent of axillary node dissection (AND) and nodal irradiation. Other clinical factors that have been associated with an increased risk of lymphedema include infection (Petrek et al. 2001) and obesity (Werner et al. 1991).

Until recently, AND was generally a standard part of the surgical management of breast cancer regardless of tumor size or nodal involvement. The incidence of subsequent lymphedema in several studies is shown in Table 14 and averages about 13 %. Studies with longer follow-up tend to show a greater incidence of arm edema. Increased rates of lymphedema have been reported with more extensive dissection (Larson et al. 1986; Kissin et al. 1986); greater number of nodes removed (Kiel and Rademacker 1996; Pezner et al. 1986; Herd-Smith et al. 2001), and splitting pectorals muscle (Pezner et al. 1986). Sentinel lymph node biopsy has resulted in significantly less morbidity with estimates of subsequent lymphedema being <1–3 % (Guiliano et al. 2000; Veronesi et al. 2003).

The addition of supraclavicular and/or axillary radiation following a dissection is associated with a relatively high incidence of lymphedema; from 9 to 58 % in some series (Table 15). Increased rates of lymphedema have been reported in the randomized trials from British Columbia and the Danish Breast Cancer Cooperative Group (DBCG) 82 B and 82 C that reported a survival advantage with the addition of chest wall and comprehensive nodal RT following mastectomy. In the British Columbia trial, symptomatic lymphedema was reported in 9 % of irradiated versus 3 % in the nonirradiated patients (Ragaz et al. 1997). Hojris reported lymphedema in 14 % of irradiated versus 3 % in

Table 14 Incidence of arm lymphedema after axillary dissection (White and Joiner 2006 with permission)

Institution (author)	*N*	Measure	Nodal RT (%)	Lymphedema (%)
Johns Hopkins (Lin)	283	Arm circumference >2 cm	6	16
Memorial Sloan Kettering (Peterek)	263	Arm circumference >2 cm	0	13
Wessex Radiotherapy (Ivens)	126	Arm circumference, water displacement >200 cc	0	10

Table 15 Incidence of arm lymphedema after axillary dissection and nodal irradiation (White and Joiner 2006 with permission)

Institution (author)	Years	*N*	Surgery	Measure	AND (%)	AND + RT(%)
Royal Marsden (Kissin et al)	1986	200	BCS[a] 35 %	Limb volume >200 cc	0[b]	9.3[b]
					7.4[c]	38.3[c]
Odense University (Ryttov)	1998	57	Mastectomy	Arm circumference >2.5 cm	11	46
Umea and Lund University (Segerstrom)	1992	136	Mastectomy	Volume displacement >150 cc	21	58
Netherlands Cancer Institute (Bijker)	1999	691	Mastectomy	None given	6	28
Aarhus University (Hojris)	2000	84	Mastectomy	Arm circumference/limb volume >200 cc	3	14
MD Anderson Cancer Center (Meric et al)	2002	294	BCS[d]	Arm circumference >3 cm	10	18
Massachusetts General Hosp. (Powell)	2003	727[e]	BCS[d]	Arm circumference "frequently" >2 cm	1.8	8.9

[a] BCS, breast conserving surgery
[b] Axillary sampling
[c] Axillary clearance
[d] All patients received breast irradiation
[e] No axillary dissection done in 14 % of population

Table 16 Incidence of arm lymphedema following breast conserving surgery, axillary node dissection, and breast irradiation (White and Joiner 2006 with permission)

Institution (author)	*N*	Measure	AND[a] (%)	Nodal RT (%)	Lymphedema (%)
Memorial Sloan Kettering (Werner)	282	Arm circumference >2.5 cm	100	24	12.1
Northwestern University (Kiel)	183	Arm circumference >2.0 cm	82	0.01	17.5
City of Hope (Pezner)	37	Arm circumference >2.5 cm	86	0	14
Centro per lo Studio e la Prevenzione Onocologica (Herd-Smith)	601	Arm circumference >5 % difference	100	0	17.9

[a] Axillary node dissection

the nonirradiated patients, in 84 women who were treated on the DBCG trials at a single institution (Table 15).

The extent of dissection prior to nodal irradiation appears to impact the rate of subsequent edema (Kissin et al. 1986). For instance, the risk of symptomatic edema in patients treated at JCRT/Harvard was 4 % after RT alone without dissection, 6 % after level I/II dissection plus axillary radiation, versus 36 % after a complete AND with axillary RT (Larson et al. 1986). The incidence of arm edema following nodal irradiation in an undissected axilla ranges from 4 to 8 % (Larson et al. 1986; Kissin et al. 1986).

Breast irradiation alone after lumpectomy and AND seems to have a negligible effect on the incidence of lymphedema. The average incidence of lymphedema in the studies listed in Table 16 is 15 %, which is similar to what is reported in the studies in Table 14 with AND alone. The randomized trial from the Uppsala-Orebro assessed cancer recurrence following lumpectomy ± breast irradiation in 381 women (Liljegren et al. 1997). Complete arm circumference data were available from 273 patients (117 in the RT group and 155 in the non-RT group). The addition of breast irradiation was not associated with an increase in arm edema or any other arm symptoms (i.e., pain, numbness, impaired shoulder mobility). The number of nodes dissected was associated with the rate of arm morbidity. At 3–12 months following treatment, arm symptoms were reported in 54 % of women who had ≥10 lymph nodes recovered in the axillary specimen versus 34 % women with <10 recovered. The rate

of arm symptoms declined with time such that by 13–36 months, the rate of arm symptoms was 33 and 20 % for the ≥10 versus <10 node group, respectively.

Radiation technique may influence the risk of lymphedema. Large fraction size and the inadvertent overlapping of fields have been associated with an increased incidence of arm edema (Johansson et al. 2002). Johansson et al. reported on 150 patients treated with RT in the mid-1960s following radical mastectomy. The patients were divided into three groups based on their fractionation: 4 Gy × 11 fractions delivered over 21 days; 4 Gy × 11 fractions delivered over 15 days; and 3 Gy × 14–15 fractions delivered over 20 days. With a follow-up of >30 years in surviving patients, the incidence of lymphedema was 70 and 69 % from the two 4 Gy fractionation schedules versus 35 % in the 3 Gy fractionation schedule ($P < 0.0001$). The patients in the 3 Gy fractionation group were treated with much smaller supraclavicular and internal mammary fields that may also have contributed to their lower rates of arm edema.

In the 1998–1999 patterns of case study of post-mastectomy irradiation, the fractionation was ≤ 2 Gy in 97, and 93 % were prescribed a total dose between 45 and 50.4 Gy using 6 MV photons (White 2004). However, only 15 % of the patients had CT-based treatment planning. A heterogeneous dose distribution can potentially lead to the unintentional delivery of larger fraction sizes and larger total doses. For instance, a 15–20 % hot spot in an anterior supraclavicular field prescribed to receive 50.4 Gy in 28 fractions at depth could lead to 58–60 Gy being delivered with 2.2–2.3 Gy fractions. This is compounded with the use of an additional posterior axillary field that was used in 40 % of the patients in the PCS post-mastectomy study (White et al. 2004). This field was dosed most frequently to mid-axilla in the PCS study using 6 MV photons. When this field is used and dose prescribed at mid-axilla, it is important to watch the cumulative dose in the superfial tissues anteriorly, as the fractionation at this site with the combined supraclavicular field and exit from the posterior axillary field can become significantly higher than intended. Omitting the posterior axillary field has been associated with lower rates of lymphedema in some retrospective studies. There was a 3 % rate of lymphedema reported in 82 node-positive patients treated at the University of Michigan with supraclavicular irradiation only after level I/II axillary dissection (Pierce et al. 1995).

7.2 Brachial Plexopathy

Brachial plexopathy after radiation therapy is uncommon and typically seen only with regional nodal irradiation. This is typically manifest as slowly progressive paresthesis and weakness, less commonly with pain, starting 6 months to many years post-RT (Fathers et al. 2002; Olsen et al. 1993; Johansson et al. 2000). The mechanism of radiation-induced brachial plexopathy is not well understood, but it is suspected that fibrosis of tissue around peripheral nerves leads to small vessels injury and ischemia. Pathologic studies have shown loss of myelin, fibrosis and thickening of the neurolemma sheath, and obliteration of the vasonevum.

The incidence of brachial plexopathy is generally reported to be very low. Pierce et al. from the Harvard group reported 20 (1.2 %) of 1,624 patients developed brachial plexopathy. The median time to occurrence was 10 months (range 1.5–77 months) and in 17 (85 %), the symptoms had completely resolved by 1–2 years. Three women had severe, progressive symptoms for an overall rate of permanent brachial plexopathy of approximately 0.2 % (Pierce et al. 1992). Supraclavicular/axillary radiation, axillary dose, and the use of chemotherapy were significantly associated with brachial plexopathy. Of the 1,117 patients treated with supraclavicular/axillary field, 1.8 % developed brachial plexopathy, compared to none of the 507 patients treated to the breast alone ($P < 0.009$). Of those women who received nodal irradiation, higher rates of brachial plexopathy were seen with axillary doses >versus <50 Gy (5.6 % versus 1.3 % respectively, $P = 0.004$), and the use of chemotherapy (4.5 % versus 0.6 % with no chemotherapy, $P < 0.001$). Other retrospective series of BCT from single institutions also report very low rates of brachial plexopathy with breast-only irradiation (Meric et al. 2002; Kini et al. 1998; Fowble et al. 1991).

Brachial plexopathy as a late morbidity from supraclavicular/axillary irradiation has been examined in older post-mastectomy series. In these studies, its incidence is associated with increasing fraction size and total dose (Table 17), similar to what is seen for late fibrosis. In the series from Hamburg University (Bajrovic et al. 2004), the 60 Gy in 3 Gy fractions prescribed at a depth of 0.5 cm is estimated to have delivered a brachial plexus dose (at depth of 3 cm) of about 53 Gy at 2.6 Gy/fraction. The overall rate of brachial plexopathy was 14 %, but the risks appeared to progress over time with the rates of grade ≥3 plexopathy 2 % after 5 years, 5.5 % after 10 years, 11.8 % after 15 years, and 19.1 % after 19 years (Bajrovic et al. 2004). In the report from Odense University of Olsen et al. of patients treated according to the DBCG 77 protocol, 19 % had mild symptoms of sensory disturbances and/or weakness, but an additional 16 % had severe disabling brachial plexopathy symptoms (Olsen N 1993). A very high rate of plexopathy was seen in the patients treated from 1963 to 1965 at the Umea University Hospital (Johansson et al. 2000) where the prescription dose was 40 Gy in 11 fractions, but only 2 or 3 fields were treated per day so that the "effective fraction size" was higher. Overlap occurred between the axillary and supraclavicular fields so that the given dose to the brachial plexus was 54–75 Gy delivered over a complex combination of 1.8, 3.4, and 5.2 Gy fractions. The mean time

Table 17 Hypofractionated supraclavicular/axillary irradiation and brachial plexopathy (White and Joiner 2006 with permission)

Institution (author)	*N*	F/U (years)	Prescribed total dose (Gy)	Fraction size Gy)	Fractions/ week	Energy	Brachial plexopathy (%)
Hamburg (Bajrovic)	140	8	60	3.0	4	Co-60	14
Odense (Olsen)	79	8	36.6	3.05	2	8-16 MV	35
Umea (Johansson)	71	12	40	4	5	Co^{60}	63

for onset of brachial plexopathy was 4.2 years. Symptoms were seen to be progressive over as long as 34 years. Of the 17 % of women alive at 34 years follow-up, 92 % had paralysis on their arm. A 5 % rate of vocal cord paralysis that had onset at a mean of 19 years follow-up was also seen in this study. All of these occurred in left-sided lesions suggesting injury to the recurrent laryngeal nerve (Johansson et al. 2000).

Subsequent post-mastectomy studies have demonstrated lower rates of brachial plexopathy following nodal irradiation. One hundred and twenty-eight women irradiated on the DBCG 82B and 82C post-mastectomy studies were evaluated with thorough neurological exams to detect neuropathy. The dose to the supraclavicular and axillary nodes was 50 Gy in 25 fractions on this study. Mild brachial plexopathy was noted in 9 % and disabling symptoms in 5 %. There was a higher incidence of plexopathy following radiation in patients who also received chemotherapy ($P = 0.01$) and were younger than 47 years (0.04). Interestingly, Hojris et al. evaluated 84 patients for the presence of late morbidity that had been treated at his institution on the DBCG 82B and 82C trials. Paresthesias and weakness of the arm were more common in the irradiated patients than in the nonirradiated patients. Subjective complaints of paresthesia and weakness occurred in 7 and 28 %, respectively, of the irradiated patients, and in none and 19 %, respectively, of the nonirradiated patients. Objective examination revealed that 21 % had paresthesias and 14 % weakness in the irradiated group, and 7 and 2 %, respectively, in the nonirradiated group. No patient had more than mild, grade I weakness measured (Hojris et al. 2000).

During the planning for supraclavicular or axillary nodal irradiation at our institution, the axillary vessels are contoured as a structure within the axilla to be a surrogate for the brachial plexus. It is our policy to not match over this structure to minimize the potential for inadvertent overlaps. The area of the contoured vessels is monitored to ensure that there are no hotspots in or around the structure that would give an unintentional higher dose.

7.3 Collagen Vascular Diseases

These are a heterogeneous group of diseases that have been considered as a relative contraindication for breast conserving therapy with radiation because of sporadic reports of severe acute and late-treatment-related toxicity (Robertson et al. 1991; Varga et al. 1991). A study from Yale University identified 36 cases of CVD (17 rheumatoid arthritis (RA), 5 systemic or discoid lupus (S or DL), 4 scleroderma (SCD), 4 Raynaud's, 2 Sjogren's, and 4 dermatomyositis/polymyositis) among the 1,677 patients in their database who had undergone breast radiation and matched each case to two control patients of similar age, tumor, and treatment factors (Chen et al. 2001). The breast was irradiated to a median dose of 48 Gy followed by a boost to the lumpectomy site to a total median dose of 64 Gy. There was no significant difference in acute toxicity for the CVD group overall compared to the controls. When analyzed by specific CVD, only the SCD subset was associated with an increased risk of acute toxicity. A significantly greater incidence of late toxicity was found between the CVD (17 %) versus control groups (3 %) ($P = 0.0095$). Again, this was limited to the 4 SCD patients when this was analyzed by specific CVD. The late toxicities noted in 3 SCD patients were fibrosis-necrosis, ulceration-necrosis, and cord paralysis-dense fibrosis. The authors concluded that patients with SCD have higher rates of complications after breast irradiation, but that other CVD should not be considered contraindications.

Three other retrospective series have examined the relationship between CVD and radiation-induced complications. Two hundred nine patients with CVD with a variety of malignancies underwent irradiation to a median dose of 45 Gy (13–81 Gy) at Massachusetts General Hospital from 1960 to 1985 (Morris and Powell 1997). Most patients, 131 (60 %) had RA and the other 78 had on-RA CVD (28 patients had S or DL, 17 polymyositis/dermatomyositis, 16 SCD, 8 ankylosing spondylitis, and 4 mixed connective tissue disorder). The patients in the RA group did not have higher rates of acute or late radiation toxicities. The non-RA CVD did not have higher acute toxicity rates, but had a significantly greater percentage of late complications, 21 versus 6 % at 5 years ($P = 0.0002$).

Another series from the University of Iowa studied 61 patients with CVD who had been irradiated for various malignancies to matched-control groups of 61 irradiated patients without CVD (Ross et al. 1993). Of the patients with CVD, 39 patients had RA, 13 had S or DL, 4 had SCD, 4 had dermatomyositis, and 1 had polymyositis. Those with systemic lupus had a nonsignificantly higher rate of acute

toxicity compared to the control group (36 versus 18 %, P = n.s.). Patients with RA had a nonsignificant increase in late complications when compared to the control group (24 versus 5 %, P = n.s.). Among the late toxicities observed in the RA group were perforated sigmoid colon, small bowel obstruction, soft tissue necrosis, radiation pneumonitis, and fatal constrictive pericarditis. Patients with CVD treated with palliative doses of RT (<40 Gy) had acute and late complication rates equivalent to the controls. Finally, another recent retrospective study from the University of Louisville compared acute and late toxicity from radiation from various malignancies in 38 patients with documented CVD to 38 matched-control cases (Phan et al. 2003). There was not a significantly higher incidence of acute or late toxicity when the two groups were compared. However, the few SCD patients in this study had a higher rate of grade III acute and late complication following irradiation.

Breast cancer patients with CVD should be made aware of the potential for exaggerated acute and late toxicity related to radiation treatment, but should not necessarily be considered ineligible breast conservation with radiation. From three retrospective studies so far, it appears that patients with SCD and other non-RA CVD may be at the highest risk for severe toxicities such that breast radiation in this group should be approached with caution.

7.4 Pediatric

The breast development prior to adolescent pubertal onset is extremely vulnerable to modest radiation doses has and can result in the inability of breast to develop and respond to hormonal stimulus.

7.5 Gynecomastia

Prostate cancer patients placed on estrogen therapy can develop breast enlargement. Modest doses of radiation (2 Gy × 3 fractions) can inhibit breast tissue proliferation prior to hormonal treatment.

7.6 Neutron Therapy

Neutron Therapy can be especially damaging due to its high LET qualities. Neutrons are preferentially absorbed in tissues with a high fat content. Catarell found that neutron therapy can cause complete atrophy of the normal female breast (Catterall et al. 1987).

8 Prevention and Management

8.1 Breast

8.1.1 Topical Agents

Numerous studies address topical skin agents during breast radiation (Table 18). The skin-damaging effects of radiation were noted early on in the evolution of radiation therapy, and topical agents were considered many decades ago (Collins and Collins 1935). We herein focus on studies primarily in breast cancer patients published since 1990. The intention of most of these studies has been prevention of, instead of treatment for, acute radiation skin toxicity.

A Canadian study reported that routine skin washing was associated with a lesser degree of acute skin toxicity ($p < 0.04$), and less frequent moist desquamation (14 versus 33 %, $p < 0.03$) in a randomized trial involving 100 patients with breast cancer (Roy et al. 2001). Nonsignificant differences were reported for the rates dry desquamation (56 % with washing versus 74 % without washing. On univariate analysis, washing, chemotherapy, concomitant chemotherapy schedule, weight >165 lb, and dosimetric hotspots were all predictors of worse acute skin toxicity. On multivariate analysis, concomitant chemotherapy schedule, either >165 lb, and dosimetric hotspots remained the strongest predictors of increased skin toxicity. Nonwashing was weakly associated ($P = 0.06$).

A Norwegian study evaluated the effects of Bepanthen (dexpanthenol) cream during RT in 86 patients (80 % with breast cancer and the remainder with laryngeal cancer) with each patient serving as their own control (Lokkevik et al. 1996). Patients applied the Bepanthen cream twice daily beginning with the first day of treatment to *half* the RT field and none to the other half. The evaluators were kept blinded. Three patients discontinued the Bepanthen cream because of "untoward or allergic" reactions. There was a statistically significant reduction in "low grade" desquamation with the use of the cream. The authors concluded that there was no overall significant effect of the ointment. Chamomile cream and almond ointment have also been studied in breast cancer patients in a similar fashion using the patient as her own control. Neither agent had a significant overall effect, but the almond ointment did reduce grade II toxicity (Maiche et al. 1991).

An interesting study reported a significant reduction in high-grade skin toxicity with the use of hyaluronic acid 0.2 % cream (Ialugen) compared to placebo in a population of predominantly head and neck cancer patients (Liguori et al. 1997). A double-blind randomized trial was performed

Table 18 Prospective trials in breast cancer patients evaluating topical agents for reduction of acute radiation skin reaction (White and Joiner 2006 with permission)

Author	*N*	Topical agents	Study design	Toxicity scoring	Results	*P*
Roy	100	Washing versus no washing	Randomized	RTOG	Washing: less skin reaction, less moist desquamation	0.03
Lokkevik	86	Bepanthen versus placebo	Randomized double blind	Institution[a]	Less desquamation	
Ligouri	130	Hyalurenic acid versus placebo[b]	Randomized	Institution	Reduced skin toxicity wks 3–7	<0.001
Maiche	50	Chamomile cream versus almond oil	Pt own control	Institution	No significant difference in maximal toxicity score	NS
Maiche	50	Sucralfate cream versus placebo	Pt own control, physician blinded	Institution	Reduced grade II toxicity with faster recovery time	0.05
Williams	194	Aloe vera versus placebo	Randomized double blind	Modified RTOG	No difference maximal radiation reaction or weekly scores	NS
Williams	106	Aloe vera versus observation	Randomized double blind	Modified RTOG	No difference maximal radiation reaction or weekly scores	NS
					No difference erythema, moist desquamation	<0.001
Heggie	208	Aloe vera versus aqueous cream	Randomized double blind	Institution	Aloe vera: more dry desquamation, more pain	0.003
Olsen	77	Aloe vera versus soap	Randomized	RTOG	Aloe vera may delay onset skin reactions	NS
Bostrom	49	MMF[c] (steroid) versus emollient cream	Randomized double blind	Institution	MMF: < maximal erythema < burning < itching	0.011 0.069 0.087
Schmuth	36	0.1 % Methyl prednisone versus 0.5 % dexpanthenol versus control	Randomized double blind	Institution	Reduced mean toxicity severity with steroids	<0.005
Potera	21	0.2 % Hydrocortisone versus placebo[c]	Pt own control	Institution	No significant difference	NS
Fisher	172	Biafine versus best supportive car	Randomized	RTOG	No difference in maximal skin toxicity	NS
Fenig	74	Biafine versus Lipiderm versus control	Randomized	RTOG	No difference in maximal skin toxicity	NS
Szumacher	60	Biafine	Prospective single arm	RTOG	Less severe toxicity than expected when giving chemotherapy concomitantly	
Pommier	245	Biafine versus Calendula	Randomized	RTOG	Calendula: < grade 2–3 toxicity < pain	0.001 0.003

[a] Institution developed and used its own toxicity scoring scale
[b] Small percentage of breast cancer patients
[c] Mometasone furoate cream (Elocon®)

in 134 patients (68 % had head and neck cancer, 22 % breast cancer, and 10 % pelvic cancer) with the agents applied twice daily (1–2 h after treatment and evening) for 10 weeks. No concomitant medications were allowed. The hyaluronic acid groups had significantly delayed onset of skin reactions, overall less severity in toxicity, and faster resolution of reactions than the placebo group.

Aloe vera has been used by various institutions for radiation-induced skin toxicity (Williams et al. 1996; Heggie et al. 2002; Olsen et al. 2001). Aloe vera is an extract derived from the tropical cactus genus, Aloe. It is available over the counter in a variety of preparations and used generally for other types of dermatitis such as sunburn. The North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic collaboratively conducted a randomized, prospective trial evaluating aloe vera gel as a prophylactic agent for acute skin toxicity in breast cancer patients receiving either intact breast or chest wall irradiation (Williams et al. 1996). Two separate studies were conducted: the first was a randomized double-blind comparison of aloe vera gel versus placebo gel, and the second was aloe vera gel versus observation. Gel application was BID beginning within the first 3 days of RT and

continued for 2 weeks. The study allowed treatment with other topical agents once a skin reaction was demonstrated. Patients with marked erythema and pruritus were to use 1 % hydrocortisone cream. No significant differences were found between the two arms in either study, leading the authors to conclude that aloe vera was unable to decrease radiation-induced dermatitis. No mention was made of the agents used for the "treatment" of dermatitis during the study and no analysis was performed to evaluate if this may have confounded the study's results. The scores of health care providers and patients were highly correlated. Patients typically judged their dermatitis to be *more severe* than did their health care provider (in 36 % of the patients), versus less severe than the physician in only 7 % of the patients ($P < 0.0001$).

Another randomized trial found some benefit from aloe vera gel in reducing erythema associated with radiation but inferior to an aqueous cream for relief of dry desquamation and pain (Heggie et al. 2002). In this study, 225 patients after lumpectomy for early-stage cancer were randomized in a double-blinded fashion to use aqueous cream or 98 % aloe vera gel on their skin during breast radiation (each applied three times daily beginning with RT and continued for 2 weeks post-treatment). The cumulative probability of pain (26 versus 16 %, $P = 0.03$) and dry desquamation (70 versus 41 %, $P \leq 0.001$) was *greater* in the aloe vera arm compared to aqueous cream. The cumulative probability for pruritus trended higher in the aloe vera arm but did not reach statistical significance. However, the aloe vera arm had a *lower* rate of grade $\geq$2 erythema than the aqueous cream arm ($P = 0.06$). Subjects in either arm with a bra cup $\geq$ size D-cup had more severe erythema than those patients with smaller breast sizes.

Finally, a third study compared aloe vera gel plus mild soap to mild soap alone in a randomized blinded manner in a heterogeneous group of cancer patients receiving RT (Olsen et al. 2001). They reported that for patients who had not shown skin reactions by 27 Gy, those patients using aloe vera had a significant delay in the onset of skin reactions ($P = 0.013$). This led the authors to speculate that aloe vera is protective for radiation dermatitis in some people.

Topical steroids have also been commonly used for the management of acute radiation skin reactions for breast cancer patients (Bostrom et al. 2001; Schmuth et al. 2002; Potera et al. 1982). A small double-blind randomized study from Sweden compared mometasone furoate (MMF) (Elocon) with an emollient cream in 50 breast cancer patients (Bostrom et al. 2001). The agents were applied once daily, 3 times a week until 24 Gy, and then once daily until 3 weeks post-treatment. Patients using the steroid cream had statistically lower maximal erythema scores, $P = 0.011$, and non-significant trends toward less itching and burning symptoms.

Another smaller double-blind randomized trial compared 0.1 % methylprednisolone (Advantan) to 0.5 % dexpanthenol (Bepanthen) in 31 breast cancer patients receiving breast radiation after lumpectomy (Schmuth et al. 2002). There were less severe skin reactions, and better skin-specific quality of life (QOL) scores, in the steroid group.

Biafine is a water-based emulsion for dermal wound healing that has been used for the management of acute radiation skin reactions (Fisher et al. 2000; Szumacher et al. 2001; Fenig et al. 2001; Pommier et al. 2004). The RTOG conducted a randomized phase III trial comparing Biafine to the best supportive care for preventing or reducing acute skin toxicity in 172 women receiving breast radiation after lumpectomy (Fisher et al. 2000). There was no statistical difference in maximum toxicity, time to development of $\geq$ grade 2 toxicity, or resolution of toxicity between the two arms. Large-breasted women (D-cup or larger) had a higher frequency of $\geq$ grade 2 toxicity, overall, and in this subgroup, Biafine was associated with statistically less toxicity at 6 weeks post-RT ($P = 0.002$).

A phase II study evaluated Biafine for 60 breast cancer patients receiving concomitant breast radiation with CMF chemotherapy (Szumacher et al. 2001). Eighty-three percent had grade 2 toxicity and 2 % grade 3. The authors concluded that this was less than what would probably occur with no topical therapy in this clinical scenario.

A small prospective study from Israel evaluated acute skin toxicity in 74 women receiving breast radiation after lumpectomy randomly assigned to Biafine, Lipiderm, or observation (Fenig et al. 2001). Lipiderm is a moisturizing cream popular in Israel. Patients could have additional topical therapies for radiation skin reaction if clinically warranted. There was no significant difference between the three arms for the rates of grades 3–4 reactions.

Finally, Biafine was compared to calendula in 254 breast cancer patients undergoing radiation following lumpectomy or mastectomy in a Phase III randomized study from Lyon, France (Pommier et al. 2004). Calendula is fabricated from a plant of the marigold family and is used for the topical treatment of irritant dermatitis, skin lesions, and superficial burns (Pommier). The radiation to the intact breast was 52 Gy in 2 Gy fractions with 5 MV photons and a 10 Gy tumor bed boost with electrons. After mastectomy, the chest wall received 46 Gy with electrons. The ointment was applied at the beginning of RT, twice daily until completion. No other prophylactic agent was allowed, but treatment of $>$ grade 2 toxicity with other topical agents was permitted. Acute skin toxicity was evaluated in four regions: breast or chest wall, inframammary fold when present, axilla, and within the supraclavicular field. There was a lower incidence of grades 2–3 acute skin toxicity with the use of Calendula compared to Biafine, 41 versus 63 %, respectively ($P < 0.001$). Grade 3 toxicity was observed in 7 % who used Calendula, and in 20 % who used Biafine ($P = 0.034$). When these results were examined by treated

region, the benefits regarding acute toxicity were primarily in the inframammary fold, axilla, and the supraclavicular field. There were no significant reductions in acute skin toxicity over the breast, chest wall, or internal mammary regions. The mean maximal pain score was less with Calendula versus Biafine ($P = 0.03$). Multivariate analysis suggested that radiation-induced skin reactions were associated with a BMI $\geq$25 ($P < 0.001$) and type of ointment used ($P > 0.001$). For patients undergoing lumpectomy, chemotherapy prior to RT ($P < 0.001$), BMI $\geq$ 25 ($P < 0.001$), and ointment used ($P = 0.001$) were risk factors associated with skin toxicity. The authors conclude that Calendula should be proposed as preventative treatment for patients undergoing radiation for breast cancer.

In summary, the multiple studies above that examined primarily prophylaxis for acute skin toxicity by a topical agent demonstrated some reduction in toxicity with hyaluronic acid and calendula application. Washing the irradiated skin was also associated with less severe skin reactions. In general, topical steroids reduced symptoms, particularly erythema and pruritis. Aqueous cream application reduced the occurrence of dry desquamation in comparison to aloe vera.

In clinical practice, breast cancer patients are typically placed on a light moisturizer (clean and moist) during their first week of treatment to be used twice daily and continued until 4 weeks post-radiation. If patients cannot tolerate this product, they are given Biafine or some other comparable moisturizer. A switch is made to a thicker oil-based product (typically Aquaphor) as necessary later in the treatment course depending on the severity of reactions that develop. Patients are asked *not* to apply the moisturizer during the 1–2h before each radiation treatment to minimize a potential bolus effect. A steroid cream (e.g., Synalaar, Lidex) is prescribed for those patients who develop significant pruritus and/or a raised bumpy follicular rash associated with their skin erythema. Patients are encouraged to take acetaminophen, ibuprofen, or other over-the-counter nonsteroid pain relievers as directed for breast discomfort. For that small percentage of patients who develop pain that does not respond to the measures above, a narcotic analgesic is prescribed (e.g., Ultracet or Tylenol with codeine). We find the most common need for narcotics is to help patients sleep more comfortably. It is our observation that patients experience two different types of breast discomfort during radiation. The first type is associated with the skin reaction and is localized to the most severe skin changes. This is the discomfort for which analgesics are most often prescribed. The second type is sharp shooting pains in the breast, lasting only seconds, that tend to occur in the latter half of treatment that are unrelated to the severity of the skin reaction. Patients refer to these as "zingers", or "electric shocks". These become less frequent following the completion of treatment and resolve over the next several weeks to months.

On average, >80 % of acute skin toxicity during breast radiation is grade 1–2 with moist desquamation confined to the skin fold areas such as the axilla or the inframammary fold. The incidence of grade 3 acute skin toxicity in the studies detailed above averaged about 11 % (range 0–40 %). When moist desquamation does occur, it is recommended that the RT is held or, if possible, the affected area of the skin is blocked from the field, particularly when irradiating for breast conservation. Moist desquamation is associated with an increased risk of late telangiectasia development that can contribute to cosmetic failure.

There is limited information regarding the optimal method for managing radiation-induced moist desquamation, and the principles of wound healing for other types of injuries have generally been applied. Many follow the philosophy that wound healing is more rapid in a moist environment, and accordingly hydrocolloid (HC) dressings have been used for radiation-induced moist desquamation. HC dressings are pliable sheets made of material such as pectin or gelatin with a polyurethane backing. Studies have demonstrated their benefit in a wide range of injuries including pressure sores, leg ulcers, donor sites, and minor burns (Mallet et al. 1999; Dobrzanski et al. 1990). The HC dressing absorbs wound exudate and forms a gel that keeps the wound surface moist and has also been shown to be an effective barrier for bacteria. They are best for low to moderate exudate wounds. There are limited data examining their efficacy in radiation-induced moist desquamation. One study compared a Tegaderm type dressing to a conventional dressing (hydrous lanolin gauze) in 16 patients and found shorter overall healing times in patients using the Tegaderm type of dressing (Shell et al. 1986). Other studies have suggested that occlusive HC dressings reduce healing time of moist desquamation (Margolin et al. 1990). An interesting study from Hong Kong randomly assigned 42 patients, with mostly head and neck cancers and moist desquamation, to a HC dressing or application of gentian violet (Mak et al. 2000). There was no significant different in the overall healing time between the two therapies. However, patients were more satisfied and comfortable with the HC dressings than the gentian violet ($P = 0.0002$), despite increased discomfort with dressing changes.

When moist desquamation occurs from breast radiation, our clinic uses HC dressings. The challenge is to get these dressings to conform and stick to areas such as the axillary, inframammary, or supraclavicular folds. Frequently, a secondary dressing such as dry gauze or an ABD is placed over the HC dressing and then gauze mesh tubes (Stockinette) or gauze bandage (kerlex) is fitted around the thorax to keep

Table 19 Randomized control trials of rehabilitation intervention for improved shoulder function

Author (year)	*N*	Intervention	Control	Outcome
Lauridsen et al. (2005)	139	PT at 6–8 weeks post-op	PT at 26 weeks post-op	Improved shoulder function at 6 months with early PT
Box et al. (2002)	65	2 year PT management care plan	Observation	Less patient-reported arm symptoms and less loss of shoulder ROM
Kilbreath et al. (2006)	22	PT, resistance strength training	Pamphlet	Less patient-reported arm complaints, less loss of shoulder ROM

everything in place. The dressing is removed for treatment. After treatment, the nursing staff gently cleans and debrides as much necrotic material as possible within the desquamating area with normal saline and reapplies the dressing. Patients change the dressings again at home as necessary depending on the amount of exudate. It has been our experience, as well as others (Porock and Kristjanson 1999), that patients with tender, dry desquamation are more comfortable with the application of a HC dressing.

Avoidance of moist desquamation is a major goal of the skin care strategy during radiation therapy for breast cancer. In review of the studies above, larger BMI, patient size, and/or breast size, and skin folds were consistent predictors of more severe skin reactions. It is crucial that this be considered at the time of simulation and that patients be positioned to minimize skin folds in areas with a high incidence of moist desquamation (e.g. inframmary, axillary, and supraclavicular). This can be challenging for larger and/or ptotic breasts that tend to hang laterally on the chest wall or inferiorly on the abdominal wall. A breast ring and cup that are fitted around/over the breast have been advocated to reduce skin folds in this setting. These have been shown to have some bolus effect and thus can also worsen acute skin toxicity. Prone positioning is often a good way to reduce skin folds, and increase dose homogeneity, in women with larger and/or ptotic breasts.

8.1.2 Oral Agents

Several studies suggest that oral pentoxifylline (trental; 400 mg orally three times per day), often given with vitamin E, can help to reduce *late* soft tissue fibrosis post-RT of the breast and/or surrounding soft tissues (Okunieff et al. 2004; Magnusson et al. 2009; Haddad et al. 2005; Delanian et al. 2003), and perhaps *acute* reactions as well (Shoma et al. 2010). However, there are negative trials for these agents as well, for example in their ability to improve arm edema (Gothard et al. 2004). Since these oral agents are usually very well tolerated, a trial of pentoxifylline and vitamin E is a very reasonable intervention in patients with fibrosis post-RT affecting the breast and/or adjacent soft tissues.

8.2 Chest Wall and Associated Muscle

Rehabilitation interventions have been the mainstay of treatment of shoulder morbidity following breast cancer treatment. Randomized control trials have demonstrated improved shoulder symptoms after surgery with a rehabilitative service such as physical therapy or exercise (Table 19). This is supported by multiple other prospective studies of PT intervention suggesting either overall improvement or hastened recovery of shoulder function (Wingate et al. 1989; Gutman et al. 1990; Bentzen et al. 1989a). The impact of physical therapy on loss of shoulder function that occurs as a result of RT is less well studied. Lee et al., reported a randomized control trial of pectoral stretching consisting of gentle ROM exercises versus control, with ROM being maintained from pre- to post-RT equally well in either group (Lee et al. 2007). In a randomized trial of PT delivered at 6–8 weeks versus 26 weeks post-MRM, the early PT was associated with a better outcome at 6 months post-op (Lauridsen et al. 2005). Among the patients undergoing MRM + RT, the benefits of PT were less evident. However, this observation is difficult to interpret since sequencing of RT was not controlled for and could have been delivered either before, during or after the PT.

8.3 Lymphedema

Complete decongestive therapy (CDT) is often recommended for management of lymphedema (International Society of Lymphology Executive Committee 1998; Brennan and Miller 1998). The goal of CDT is to reduce arm edema to a minimum level, maintain the results, and prevent infections. It has four main components: (1) manual lymph drainage, (2) skin and nail care, (3) compression bandaging and/or garments, and (4) therapeutic exercise. In a prospective trial of 20 breast cancer patients with lymphedema, CDT was associated with a median decrease in girth of 1.5 cm and median volume reduction of 138 cc. During follow-up at 6 and 12 months, there was a mild increase in

girth and volume but stabilized at less than 1 cm and 100 cc below study entry (Mondry et al. 2004). Other studies have demonstrated symptomatic and objective measures of response to CDT (Erickson et al. 2001).

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Lung

Christopher R. Kelsey, Zeljko Vujaskovic, Isabel Lauren Jackson, Richard F. Riedel, and Lawrence B. Marks

Contents

Abstract

- The lungs are particularly sensitive to RT, and are often the primary dose-limiting structure during thoracic therapy.
- The alveolar/capillary units and pneumocytes within the alveoli appear to be particularly sensitive to RT.
- Hypoxia may be important in the underlying physiology of RT-associated lung injury.
- The cytokine transforming growth factor-beta (TGF-β), plays an important role in the development of RT-induced fibrosis.
- The histopathological changes observed in the lung after RT are broadly characterized as *diffuse alveolar damage*.
- The interaction between pre-treatment PFTs and the risk of symptomatic lung injury is complex. Similarly, the link between changes in PFTs and the development of symptoms is uncertain.
- The incidence of symptomatic lung injury increases with increase in most dosimetric parameters. The mean lung dose (MLD) and V20 have been the most-often considered parameters. MLD might be a preferable metric since it considers the entire 3D dose distribution.
- Radiation to the lower lobes appears to be more often associated with clinical symptoms than is radiation to the upper lobes. This might be related to incidental cardiac

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irradiation. In pre-clinical models, there appears to be a complex interaction between lung and heart irradiation.
- TGF-β has been suggested in several studies to predict for RT-induced lung injury, but the data are still somewhat inconsistent.
- Oral prednisone (Salinas and Winterbauer 1995), typically 40–60 mg daily for 1–2 weeks with a slow taper, is usually effective in treating pneumonitis. There are no widely accepted treatments for fibrosis.
- A number of chemotherapeutic agents have been suggested to be associated with a range of pulmonary toxicities.

1 Introduction

Radiation therapy (RT) is an important treatment modality for multiple thoracic malignancies, including breast, lung, and esophageal cancer, as well as malignant lymphomas involving the mediastinum. The thoracic cavity contains the heart, great vessels, esophagus, and lungs, surrounded by the musculoskeletal constituents of the chest wall. The lungs are particularly sensitive to RT, and are consequentially a dose-limiting structure when planning therapy.

The lungs are complex organs, consisting of the large central airways such as the trachea and mainstem bronchi, the smaller conducting airways, a complex vascular network, and the alveolar sacs where gas exchange occurs. Irradiation of the trachea and proximal bronchi can lead to mucosal irritation, clinically manifesting as a dry cough. However, late complications of the conducting airways (e.g., fistula or stenosis) are unusual with conventional doses of RT. The proximal vascular network is generally considered to be relatively insensitive to the effects of RT. The primary toxicity from lung irradiation is related to the alveolar/capillary complex.

The processes that ultimately culminate in clinically apparent alveolar injury are complex but thought to begin with reactive oxygen and nitrogen species (ROS/RNS). In addition to being directly toxic to cells, ROS/RNS instigate a host of molecular cascades which alter the cytokine milieu leading to chronic inflammation, tissue damage, and remodeling. Edema and extravasation of proteinaceous material into the alveoli can be appreciated within a few weeks after RT as increased density on radiographs (Skoczylas et al. 2000). If the volume of inflammed lung is large, pulmonary symptoms can develop 1–6 months after RT. Within 3 months after completing RT (and maybe sooner), there is a reduction in pulmonary function tests secondary to thickening of the intraalveolar septum (edema and fibrosis) and loss of alveoli. The RT-induced microenvironment of chronic inflammation, hypoxia, and fibrosis appears to be self-sustaining leading to progressive decline in pulmonary function. Our understanding of the cellular and biochemical changes that occur in the lung after RT continues to evolve (Brush et al. 2007; Fleckenstein et al. 2007; Tsoutsou and Koukourakis 2006) (see Sect. 3).

Concern for RT-induced lung injury must be taken in the context of the cancer that is being targeted. For example, a small volume of the anterior ipsilateral lung is typically included within tangent fields used to treat patients with breast cancer. Most patients with breast cancer have ample lung reserve, especially relative to the small volume of lung within the RT fields. Therefore, the incidence of clinical symptoms is low. Typical pneumonitis rates are in the range of 1–5 %, with severe injury being even less common.

Conversely, patients irradiated for lung cancer usually have a history of tobacco use, and usually have poor baseline lung function. Primary lung tumors typically invade into, and replace, normal lung. Further, the primary lung tumor or enlarged hilar/mediastinal lymph nodes can compress central airways/vessels that can decrease overall cardiopulmonary function. In these instances, the damaging effects of RT on the lung are often, at least partially, off-set by RT-induced reductions in tumor mass that may increase lung function. For such patients, the resultant change in lung function after thoracic RT is typically a balance between the radiotoxic effects on the normal lung and improvement in lung function resulting from tumor shrinkage.

A variety of dose/volume parameters have been linked to pulmonary injury and provide rationale clinical guidelines (see Sect. 5). However, predictive models for RT-induced lung injury are suboptimal. Further, only limited progress has been made in developing compounds that prevent and/or mitigate the detrimental effects of RT. In this chapter, we will review many facets of RT-induced lung injury and provide dose/volume recommendations for the clinician. Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Gross Anatomy

The lungs are paired organs, each contained in its own pleural sac within the thoracic cavity. Both lungs are subdivided into anatomically distinct lobes. The right lung normally has three lobes separated by two fissures. The horizontal fissure separates the upper and middle lobes while the oblique fissure separates the lower lobe from the middle and upper lobes. The left lung normally has two lobes (upper and lower) divided by an oblique fissure. The lobes can be further subdivided into segments. The lingula (Latin-little tongue) is part of the upper lobe and is composed of a superior and inferior segments (Fig. 2).

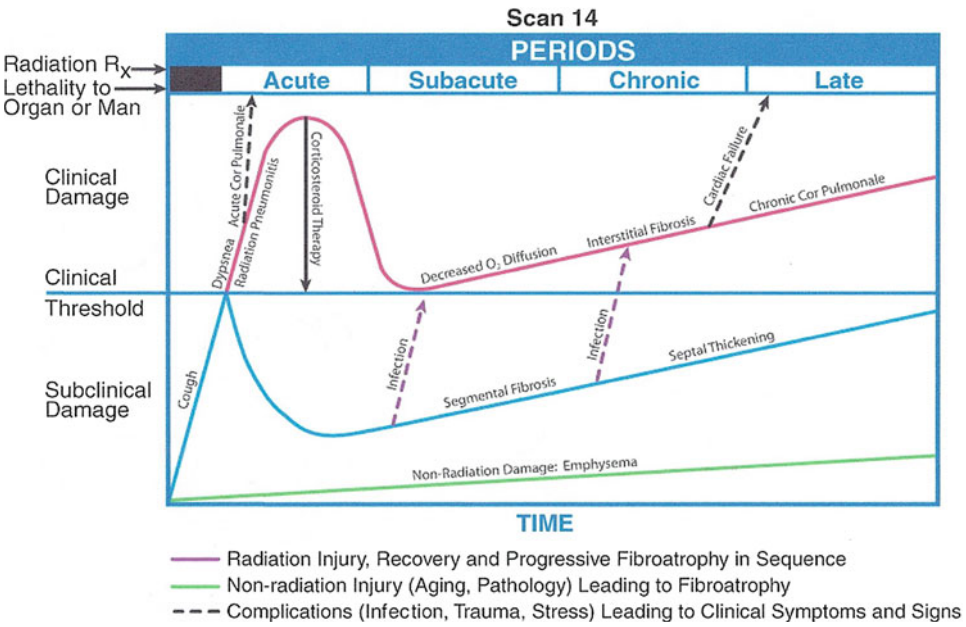

Fig. 1 Biocontinuum of adverse early and late effects are shown of the lung (with permission from Rubin and Casarett 1968)

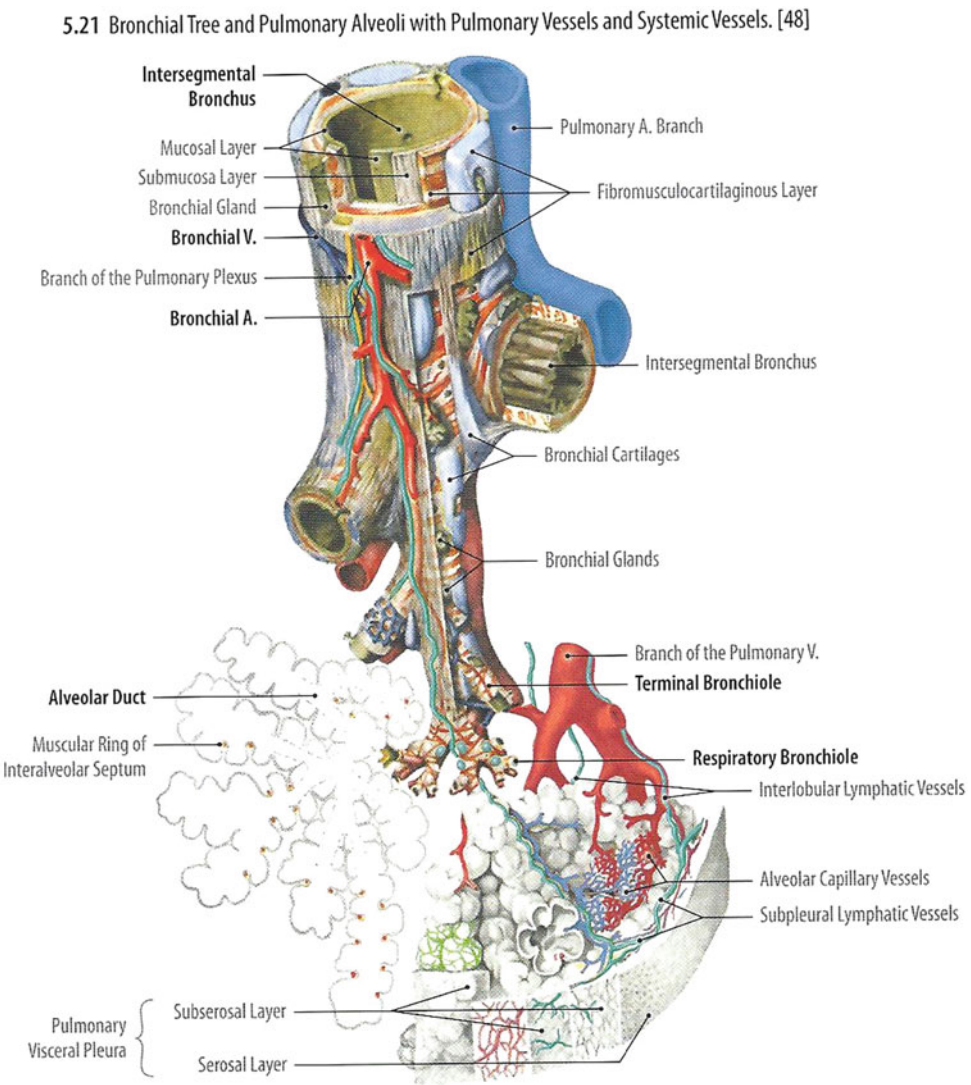

Fig. 2 Gross anatomy of the lung (with permission from Tillman)

The architecture of the lung can be considered as subunits arranged in both parallel and series. Centrally, the structure is "in series" as the large vessels and airways in the mediastinum and hilum support all of the distal vessels and airways to which they are connected. Fibrosis/stenosis of a central vessel or bronchus will render the downstream alveoli nonfunctional. Conversely, in the periphery, the smaller alveolar/capillary units function relatively independently (i.e., "in parallel"). Resection or injury to a region of lung will not compromise function of adjacent regions. The alveolar/capillary units appear far more sensitive to the effects of RT than the central conducting airways and vessels. Therefore, most RT-induced injury is referable to these "peripheral" structures and the lung is classically considered a "parallel" organ regarding RT-induced effects.

2.2 Histology and the Functional Subunit

The functional unit of the lung is the pulmonary lobule which consists of a terminal bronchiole and the lung parenchyma distal to it (i.e., alveolar/capillary unit) (Fig. 3a, b). The terminal bronchiole is the final conducting branch of the tracheobronchial tree not involved in gaseous exchange. Terminal bronchioles branch into transitional airways (respiratory bronchioles and alveolar ducts) which contribute to gaseous exchange. The transitional airways terminate in alveolar sacs which open into the alveoli.

The principal function of the lungs is to facilitate gas exchange between alveoli and adjoining capillaries. Gas exchange is most efficient when the thickness of intervening tissues is minimal. Adjacent alveoli share a common wall, termed the interalveolar septum, which contains capillaries and a fine connective tissue framework. Within the interalveolar septum, the adjacent basal lamina of the alveolar epithelium and endothelium are often fused providing a thin barrier between the erythrocytes in the capillaries and the alveolar air space ($\sim$0.5 μm). The capillaries wrap around the alveoli creating a prodigious surface area for diffusion (50–100 m^2).

Several cell types are present in the pulmonary lobule. Type 1 pneumocytes are flat epithelial cells with minimal cytoplasm and few organelles that form a complete, thin (0.2 μm), lining of the alveoli. Type II pneumocytes are as numerous as type I pneumocytes but only cover 2–5% of the alveolar surface. They are round cells with larger nuclei, and contain prominent lamellar bodies (cytosomes) which contain dipalmitoyl phosphatidylcholine (surfactant), which reduces surface tension within the alveoli. Type II pneumocytes can differentiate into type I pneumocytes in response to damage to the alveolar lining. Alveolar macrophages (dust cells) derive from circulating monocytes and phagocytose microorganisms and other particulate matter that is deposited in the alveoli.

3 Biology, Physiology, and Pathophysiology

3.1 Biology: Molecular Mechanisms of RT-Induced Lung Injury

Radiation injury of the lung is categorized as two distinct phases: acute inflammatory (pneumonitis) and late fibroproliferative. The progression of radiation injury is well established in both mice and humans. In humans, the pneumonitis phase peaks between 2–3 months after radiation exposure. This phase is characterized by a dense inflammatory cell infiltrate, exudation of proteinaceous material, and edema. The chronic fibroproliferative phase occurs months to years after exposure and is characterized by diffuse interstitial fibrosis, focal scarring, and impaired ventilation.

The lung is considered to be a late responding tissue, as the time between exposure and symptomatic injury can last months to years, presumably as a result of innate tissue kinetics. During the asymptomatic latency period, radiographic changes can be observed (Skoczylas et al. 2000; Brush et al. 2007; Fleckenstein et al. 2007). Although the period of time between exposure and symptomatic injury may appear to be quiet, there is a firestorm of events occurring at the molecular and cellular level that is just beginning to be better understood.

At the time of the initial irradiation, exposed cells rapidly spread the "danger signal" to neighboring cells as far away as 1 mm (Tsoutsou and Koukourakis 2006; Pusey 1905). This results in an orchestrated response of tissue-specific cells, the vascular endothelium, and inflammatory mediators in order to resolve the injury (Skoczylas et al. 2000; Fleckenstein et al. 2007; Tsoutsou and Koukourakis 2006; Bernier et al. 2004).

The intercellular conversation is initiated at the moment of irradiation when injury to the cell membrane, DNA, cytoplasmic bodies, and other cell components occurs, resulting in an immediate release of cytokine mRNA. The identification of a "perpetual cytokine cascade" (Fleckenstein et al. 2007) caused a major paradigm shift from the classical "target cell theory" (α/β) to one that posits a dynamic molecular crosstalk among numerous cells in normal tissue (the lung has more than 40 cell types (Evans and Leucutia 1925)) that propagates the injurious process (Fig. 4).

The cytokine and chemokine reaction observed by Rubin and colleagues clearly demonstrated the absence of a molecular and cellular latent period prior to observed histologic changes. These findings suggest that radiation

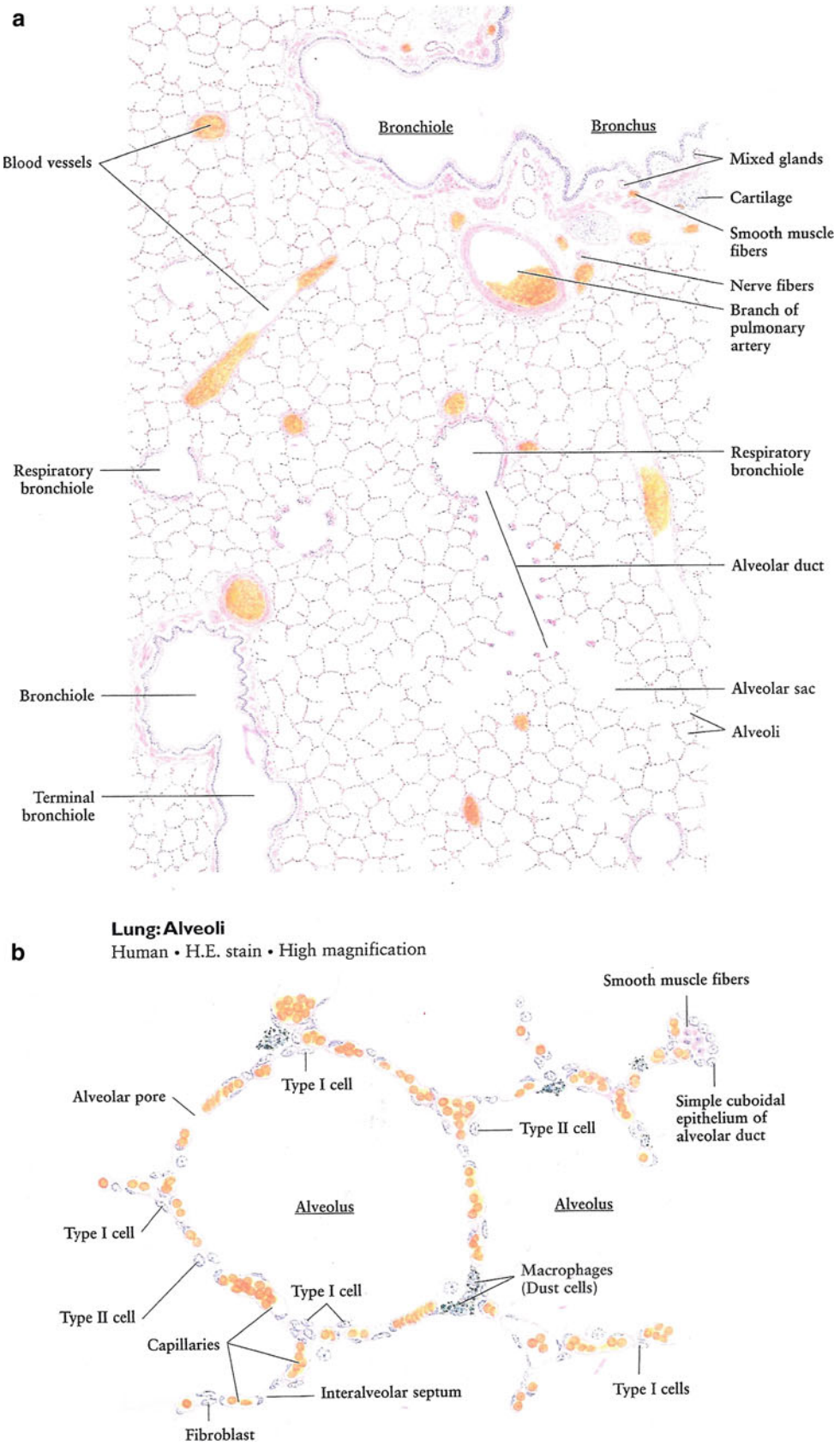

Fig. 3 Lung histology. **a** Low magnification, **b** high magnification (with permission from Zhang)

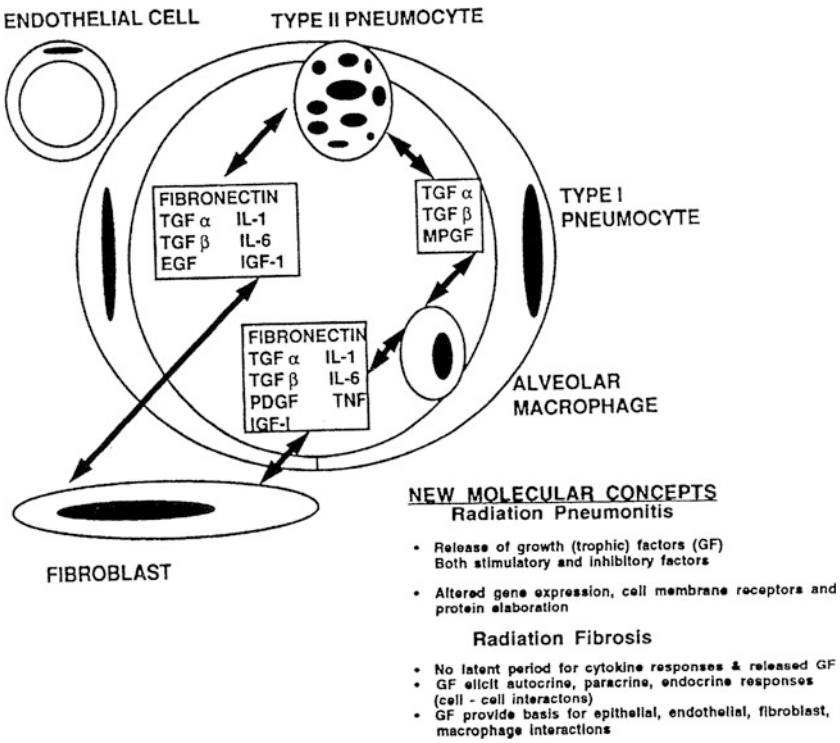

Fig. 4 Cytokine cascade associated with lung injury. Cell–cell interactions and control of gene expression by growth factors among alveolar cells is shown (with permission from McDonald et al. 1995, IJROBP LENT SOMA)

initiates a downstream sequence of spatial and temporal events that eventually express themselves as clinical manifestations months later.

Coincident with the release of inflammatory cytokines is the development of oxidative stress. Free radical species can participate in a host of cellular signaling events. Indeed, many of the signaling pathways implicated in radiation injury, such as the TGF-β pathway, are sensitive to changes in cellular redox status (Tyler and Blackman 1922; Groover et al. 1922). The transient nature of ionizing radiation suggests that a mechanism of amplification of ROS/RNS occurs after radiation. Proposed mechanisms include activation of oxidant-generating enzymes, such as NADPH oxidases, mitochondrial leakage, and the respiratory burst from activated inflammatory mediators recruited to the site of injury. The role of NADPH oxidases is supported by the fact that TGF-β is activated by radiation and that in turn, TGF-β can activate the NADPH oxidase isoform, Nox4. Newer data coming to light recently have shown a critical role for Nox4 in TGF-β mediated apoptosis (Hines 1922) and downstream Smad signaling (Davis 1924).

In the lung, chronic oxidative stress has been observed using markers for DNA oxidation (Skoczylas et al. 2000) and lipid peroxidation (Groover et al. 1922; Fleckenstein et al. 2007). Oxidative stress can contribute to a number of changes within injured tissue including endothelial cell activation, increased vascular permeability and edema, lipid peroxidation, inflammation, and fibrosis (Skoczylas et al. 2000; Bernier et al. 2004; Johnston et al. 1996; Rubin et al. 1995). The end result is a cyclic progression of oxidative stress and activation of growth factors, transcription factors, and cytokines, all of which can contribute to lung injury.

It is hypothesized that the imbalance between oxidant-generating enzymes and antioxidant capacity is a primary cause of hypoperfusion following radiation (Skoczylas et al. 2000; Vujaskovic et al. 2001). Fleckenstein et al. demonstrated that tissue perfusion begins to decrease 3 days after radiation exposure, resolves for approximately 2 weeks, and then progressively decreases throughout the time of disease progression (Skoczylas et al. 2000). In parallel, the lung tissue becomes increasingly hypoxic (Skoczylas et al. 2000). The late decrease in tissue oxygenation is likely a result of fibrous obliteration of capillaries and decreased gas exchange due to increased alveolar wall thickness and edema/congestion within the alveolar space. The early drop in perfusion cannot be explained by these events and is more likely a result of vasoconstriction, although this is not confirmed. The activation of NADPH oxidase after radiation increases superoxide production, which may suppress vasodilation by oxidizing key enzymes within the NO signaling pathway or through rapid reaction with NO itself to form peroxynitrite. Both of these reactions can interfere with NO signaling leading to vasoconstriction, a transient loss in tissue perfusion, and tissue hypoxia. Tissue hypoxia, a fundamental feature underlying the development of lung injury, develops several weeks after lung irradiation and progresses with time, presumably as a result of injury to the pulmonary vascular and decreased perfusion (Skoczylas et al. 2000; Bernier et al.

2004). Changes in pulmonary perfusion have been observed within months following high doses of radiation in humans (Bentzen 2006; Mikkelsen and Wardman 2003) and within weeks in rodent models (Skoczylas et al. 2000; Rubin et al. 1995; Jackson et al. 2006). In studies by Fleckenstein et al. (Skoczylas et al. 2000), the transient decrease in perfusion was associated with increased edema and elevated expression of hypoxia-inducible factor-1 alpha (HIF-1α) and TGF-β. In that study, the vascular perfusion changes were noted before the development of histologically apparent and functional disease.

The same study showed that tissue hypoxia and perfusion changes coincide with the accumulation and activation of macrophages within the residual alveolar space and interstitium, as well as enhanced cytokine and growth factor production. This could, in part, contribute to the presence of cytokines in the irradiated tissue weeks to months after exposure (Skoczylas et al. 2000). Jackson et al. (Johnston et al. 1996) found that in vitro TGF-β production by macrophages could be induced by hypoxia (0.5% O_2), prior to the onset of VEGF production. In that study, incubation with a superoxide dismutase mimetic led to decreased TGF-β and VEGF production (Johnston et al. 1996). Thus, it appears that ROS signaling plays a key role in macrophage-associated expression of the above cytokines under hypoxic conditions.

The pro-inflammatory/pro-fibrogenic cytokine transforming growth factor-beta (TGF-β) has been most extensively studied in regard to its role in the development of radiation-induced lung injury (Fleckenstein et al. 2007; Novakova-Jiresova et al. 2007; Kang et al. 2003; Feletou et al. 1995). TGF-β is secreted as an inactive polypeptide by a number of cells including macrophages, fibroblasts, and epithelial cells of the lung. The inactive precursor is sequestered in the extracellular matrix with its latency-associated peptide (LAP), which has been suggested to be the "sensory" portion of the protein (Marks et al. 1997; Theuws et al. 2000; Peterson et al. 1992; Dor et al. 2001; Li et al. 2001). The LAP is sensitive to free radicals, changes in cellular pH, and integrins, all of which can induce activation of TGF-β which readily binds the TGF-β type II receptor to stimulate the Smad second messenger signaling pathway (Bartholdi et al. 1997). Activation of TGF-β and subsequent translocation of Smad2/3 protein into the nucleus of the responding cell leads to transcription of genes involved in fibroproliferation and tissue repair (Li et al. 2007; van Hinsbergh et al. 2001). An increase in TGF-β protein can be observed within 24 hours following radiation exposure (Skoczylas et al. 2000; Dor et al. 2001; Anscher et al. 1998, 2006). Epperly et al. (Rodemann et al. 1996) found a biphasic TGF-β surge associated with the early and delayed radiation response in mice after 20 Gy whole lung irradiation. The establishment of TGF-β as a mediator of radiation-induced lung injury has led to a number of studies evaluating circulating serum TGF-β levels as a potential biomarker for increased risk of lung injury as well as pre-clinical testing of inhibitors of TGF-β and/or its signaling pathway. These studies have used either neutralizing antibodies or adenoviral vectors to demonstrate significantly reduced histological and functional damage in rodent models of lung injury following radiation exposure. Reduced lung damage was also associated with decreased cytokine activity, fewer macrophages, and less oxidative stress (Kang et al. 2003; Barcellos-Hoff 1996; Rahimi and Leof 2007).

In summary, our knowledge of the mechanisms of radiation injury has vastly improved over the past 30 years. It is now established that chronic oxidative stress and continuous production of cytokines, particularly TGF-β, play a significant role in sustaining inflammation and fibroproliferation in irradiated lung during the progression of disease. Symptomatic and histologically relevant lung injury is preceded by cytokine production and communication, inflammatory cell infiltration, changes in blood flow and perfusion, and increased vascular permeability (Bernier et al. 2004; Roberts 1999; Barcellos-Hoff 1993; Barcellos-Hoff et al. 1994; Stone et al. 2003, Vujaskovic et al. 2000). Although great progress has been made in identifying the mechanisms underlying radiation-induced lung injury, more comprehensive studies are needed to link the events occurring at the molecular level to cellular and tissue pathology.

Despite these laboratory findings, the results in the clinic are less encouraging. To date, the observed associations between changes in a variety of biological markers and clinical pneumonitis have been inconsistent (Table 1).

3.2 Pathophysiology (Cellular Dynamics and the Radiation Response)

3.2.1 Animal Models

The ultrastructural changes in lung were documented by Penney et al. in a mouse model. These are documented for a wide range of single doses from 5 to 13 Gy over a period of months (1 h–60 weeks) (Table 2) (Penney 1087). Examples of corresponding histologic images are shown in Fig. 5a, b.

The Biocontinuum 'roller coaster' curve for radiation pneumonitis hypothesized by Rubin and Casarett was confirmed in an elegant series of studies in mice using breathing rates by Travis et al. (1980). The increased breathing rates at 16–36 weeks are associated with radiation pneumonitis and then becomes elevated again at 52 weeks associated with fibrosis. Utilizing a split dose exposure, the early pneumonitis phase was not expressed, however, the late occurrence of pulmonary fibrosis appeared between 6–12 months. This was confirmed in similar studies by Siemann et al. (1982) who utilized different fractionation

Table 1 Proposed biological markers of lung injury

Marker	Author (n)	Increased when?	Predictive for RP?
Interleukins			
IL-1α	Chen et al. (2002), Peterson et al. (1992)	Before, during, after RT	Yes
IL-6	Chen et al. (2002), Peterson et al. (1992)	Before, during, after RT	Yes
IL-6	Zhao et al. (2007), Ewan et al. (2002)	Post-RT	Weakly
IL-6	Hart et al. (2005), Comroe (1965)	Before RT	No
IL-8	Hart et al. (2005), Comroe (1965)	Before RT[a]	Yes
Growth factors			
TGF-β1	Fu et al. (2001), Wiegman et al. (2003)	End of RT (relative to pre-RT)	Yes
TGF-β1	Anscher et al. (1994), Boersma et al. (1996)	End of RT (relative to pre-RT)	Yes
TGF-β1	Evans et al. (2006), Kyas et al. (2007)	End of RT (relative to pre-RT)	Yes
TGF-β1	Novakova-Jiresova et al. (2004), Denham and Hauer-Jensen (2002)	Mid-RT (relative to Pre-RT)	Weakly
TGF-β1	Chen et al. (2002), Peterson et al. (1992)	Before, during, after RT	No
TGF-β1	De Jaeger et al. (2004), Monson et al. (1998)	Any time	No
TGF-β1	Zhao et al. (2007), Ewan et al. (2002)	Pre- RT	No
TGF-β1	Hart et al. (2005), Comroe (1965)	Before RT	No
b FGF	Chen et al. (2002), Peterson et al. (1992)	Before, during, after RT	No
Others			
ACE	Zhao et al. (2007), Ewan et al. (2002)	Pre- and Post-RT	Yes
TM	Hauer-Jensen et al. (2004), Mikkelsen and Wardman (2003)	During RT	Yes
MCP-1	Chen et al. (2002), Peterson et al. (1992)	Before, during, after RT	No
E/L selectin	Chen et al. (2002), Peterson et al. (1992)	Before, during, after RT	No

IL interleukin, *TGF* transforming growth factor, *bFGF* basic fibroblast growth factor, *MCP* monocyte chemotactic protein, *ACE* angiotensin-converting enzyme, *TM* thrombomodulin

[a] Lower levels of IL-8

Table 2 Changes in the lung after radiation therapy (Adapted from Clinical Oncology 8th edition)

		Dose (Gy)			
Event	Time	0	5	9	13
Type II cell degranulation; surfactant release	1 h–7 days	–	–	–	+
Loss of basal laminar proteoglycans	1 h–7 days	–	±	+	++
Loss of alveolar macrophages	7 days	–	–	±	+
Surfactant recovery	4 weeks	–	–	–	+
Replacement of laminar proteoglycans	4–12 weeks	–	±	±	+
Radiation pneumonitis	12–30 weeks	–	–	–	+
Peak in soluble fibronectin	12–30 weeks	–	±	±	++
Fibrosis	30–60 weeks	–	±	+	+
Peak in insoluble fibronectin	30–60 weeks	–	+	+	++
Increased laminin	12–60 weeks	–	±	+	++

Modified from Penney DP: Ultrastructural organization of the distal lung and potential target cells of ionizing radiation. Paper presented at: International Conference on New Biology of Lung and Lung Injury and Their Implications for Oncology; 1987; Porvoo, Finland

schedules in mice and confirmed the appearance of a late fibrotic stage without an early pneumonitic phase. There observations support the concept of differing underlying mechanisms for pneumonitis and fibrosis.

The importance of host response is well-recognized clinically. A number of investigators have compared the variation in pulmonary response comparing a radioresistant strain (C_3H) with a radiosensitive strain ($C_{57}BL$) to radiation (Jackson et al. 2010; Williams et al. 2010). The basis

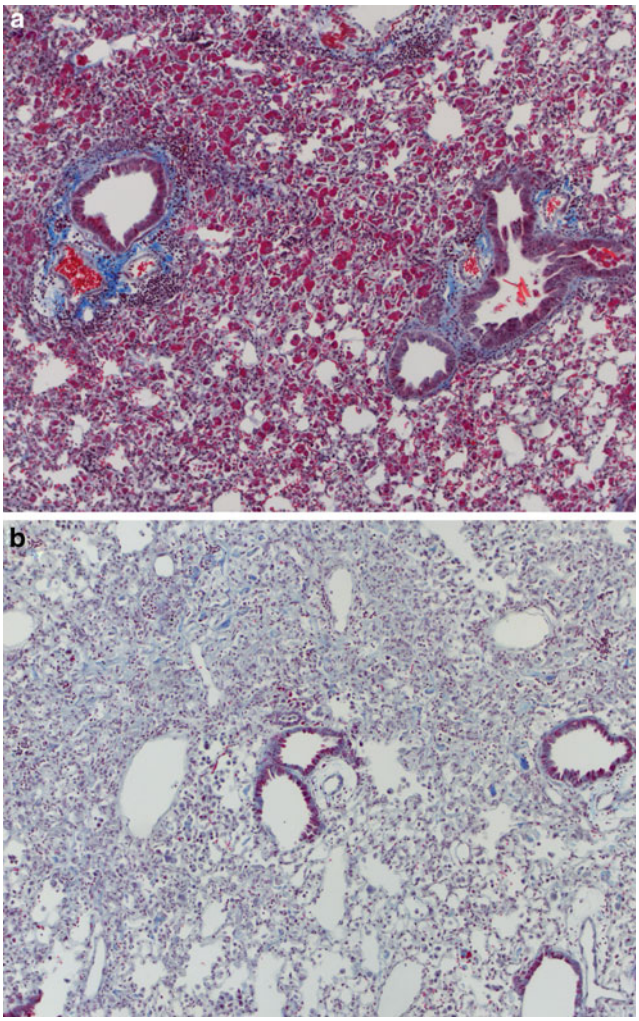

Fig. 5 **a** Radiation pneumonitis: pneumonitis in a C57L/J mouse 14 weeks after thoracic irradiation with a single dose of 10 Gy. Alveolar inflammation and perivascular lymphocytic cuffing can be seen. **b** Radiation fibrosis in a C57BL/6J mouse 24 weeks after thoracic irradiation with a single dose of 12.5 Gy. Both are Masson's trichrome stain of paraffin embedded tissues

for the variation could be explained by differences in the elicited cytokine cascade to similar doses. Utilizing knock out mice for 1 CAM expression compared to wild type mice, Hallahan demonstrated a lower incidence of lung injury due to blocking the 1 CAM-1 pathway (Hallahan et al. 2002). Similarly in TGF_{β} knock out mice, the induction of radiation-induced fibrosis in both skin and lung is inhibited (Martin et al. 2000).

3.2.2 Clinical Observations

The lungs are complex organs containing conducting airways, a complex vascular network, and the alveolar/capillary units where gas exchange occurs. The trachea and proximal airways are lined with pseudostratified ciliated columnar epithelial cells with admixed mucus producing goblet cells. Since these cells have a relatively rapid turnover rate, the mucosa can become acutely denuded during RT. Mild dry cough and/or sore throat during RT is likely related to RT-induced changes in the epithelial lining and decreased clearance of intratracheal debris. Due to the rapid cellular turnover, the depleted mucosa is typically replenished promptly after completing RT and the associated symptoms are transient.

The supporting vascular and other connective tissues are comprised primarily of quiescent "mature" cells with a relatively slow mitotic rate. Although no clinical/pathologic findings are typically observed acutely in these tissues during thoracic RT, late normal tissue injury is possible. For example, bronchial stenosis has been observed following high-dose external beam RT (Miller et al. 2005) as well as brachytherapy (Speiser and Spratling 1993). Similarly, we have seen a case of diffuse pulmonary hypoperfusion after high-dose external beam RT, apparently due to fibrosis of central vascular structures. Months to years following RT, a fibrotic reaction develops within irradiated lung parenchyma. Whether this is a direct effect of RT on the cells comprising the supporting connective tissues, or due to an RT response in other cells, is unclear. While this fibrotic reaction is generally considered to be progressive and irreversible, there is limited experimental data suggesting that this process can be modified and perhaps even reversed (Delanian et al. 1994, 1999).

The more peripheral vascular structures, such as the alveolar capillaries, appear to be more sensitive to RT than the central vasculature. With even modest doses of RT, reductions in regional perfusion, apparently due to sclerosis of these small vessels, has been observed. The extent of reduction in regional lung perfusion has been associated with the degree of change in global lung function as assessed by pulmonary function tests (Fan et al. 2001; Theuws et al. 1998).

A reduction in regional ventilation is also observed after RT, apparently corresponding to a fibrotic/inflammatory reaction within the distal airways. However, the decline in ventilation after RT appears to be less than the corresponding decline in perfusion. Since optimal respiratory function requires both adequate ventilation and perfusion, RT-induced reductions in either will result in ventilation/perfusion mismatch with corresponding decline in overall pulmonary function. That ventilatory and perfusion changes occur in parallel suggests that normal physiologic compensatory mechanisms within both the ventilatory and circulatory systems are contributing to the changes noted after RT.

The histopathological changes observed in the lung after RT are broadly characterized as *diffuse alveolar damage*. Acutely, increased vascular permeability leads to edema of the interalveolar septa and extravasation of proteinaceous

material into the alveoli. Type I pneumocytes are depleted and type II pneumocytes proliferate to restore the integrity of the alveolar epithelium. However, type II pneumocytes are also known to be damaged by RT, leading to the release of surfactant into the alveolar lumen. Increased levels of alveolar surfactant can be seen within hours of RT and can persist for 2–6 weeks (Fleckenstein et al. 2007).

3.2.2.1 Airway Diameter and Airway Resistance

Resistance to airflow within the tracheobronchial tree increases the work of breathing. Assuming laminar flow, the pressure required to produce a given flow rate in a tube is inversely proportional to the *fourth* power of the radius. This is known as Poiseuille's law and can be expressed as:

$\Delta P/V = \text{resistance} = 8\ nl/\pi r^4$ where ΔP refers to the pressure difference between the two ends of a tube, V is the volume of flow per time period, n is the coefficient of viscosity, l is the length of the tube, and r is the radius of the tube (Comroe 1965). Because the length of the tracheobronchial tree is constant, and the viscosity of air is nearly constant, resistance to airflow is almost entirely dependent on the radius of the airways. Even modest reductions may be sufficient to cause pulmonary symptoms. For example, when the radius of a tube is *decreased* by a modest 10%, the resistance to airflow is *increased* by 46%.

Symptomatic narrowing of the tracheobronchial tree is not a common clinical problem after conventional-dose EBRT. However, this has been reported following brachytherapy (Speiser and Spratling 1993) and with higher than conventional doses of external beam RT ($\geq$70 Gy) (Miller et al. 2005; Kelsey et al. 2006). Whether asymptomatic narrowing of the bronchi occurs after conventional doses (60–70 Gy) is not known.

3.2.2.2 Gas Exchange

The rate at which a gas diffuses between the alveoli and capillaries is proportional to the partial pressure gradient of that gas and the available surface area, but inversely proportional to the thickness of the intervening tissues. Disease processes that affect any of these parameters have the potential to limit gaseous exchange. Decreased lung compliance from pulmonary fibrosis or increased airway resistance from bronchial stenosis can decrease the partial pressure of oxygen in the alveoli. Further, RT results in edema of the intraalveolar septa and extravasation of proteinaceous material into the alveoli, both of which negatively affects gas exchange. Later, deposition of scar tissue within the interalveolar septi will impede gas exchange while destruction of alveoli decreases the surface area available for gas exchange.

3.2.2.3 Ventilation and Perfusion

In healthy individuals, alveolar ventilation (V) and pulmonary capillary perfusion (Q) are closely matched for optimal efficiency. For example, if there is decreased alveolar ventilation to a portion of the lung, alveolar and interstitial P_{02} will decrease. Local arterioles respond by constricting, diverting blood to better ventilated portions of the lung. On the other hand, if alveolar P_{02} rises above normal, local arterioles dilate to maximize oxygen transport. In similar manner, local ventilation is regulated (albeit to a lesser degree than perfusion) in response to local levels of CO_2 to optimize the V/Q ratio and maximize the efficiency of gas exchange in the lung.

RT negatively affects both ventilation and perfusion, with perfusion being affected to a greater degree than ventilation (Allavena et al. 1992; Bell et al. 1988). RT reduces the number of perfused alveoli, with a corresponding increase in the alveolar dead-space (i.e., ventilated but under- or nonperfused alveoli). This increased dead-space and reduced functional units leads to a reduction in gas exchange that can cause dyspnea.

4 Clinical Syndromes (Endpoints)

Scoring lung toxicity is difficult for many reasons. For example, a variety of endpoints can be appraised including symptoms, radiographic abnormalities, and pulmonary function tests. These endpoints can be somewhat arbitrarily segregated as reflecting focal versus global, and clinical versus subclinical, changes (Table 3). The SOMA LENT system provides a reasonable way to categorize and grade these various toxicities (Table 4). Each of these endpoints are discussed separately. In broad terms, symptoms occur in approximately 1–40% of patients who receive thoracic RT, depending on the volume of lung irradiated and the dose that is given. Radiologic changes occur in almost all patients if a sensitive imaging tool is used. Changes in PFT's following RT are common and reflect the competing effects of RT-induced functional loss and recovery of function with tumor regression (for patients with gross intrathoracic lesions).

4.1 Symptoms

Radiation pneumonitis, typically manifested as shortness of breath, dry cough, and occasionally fever, occurring 1–6 months after treatment (Tsoutsou and Koukourakis 2006), appears to result from an acute inflammatory process within the alveolar spaces. While the radiologic changes associated with this inflammatory reaction are generally limited to the irradiated regions of the lung (Mah et al. 1987; Marks et al. 2000), radiologic changes have been occasionally observed to extend beyond the irradiated field (Gibson et al. 1988; Roberts et al. 1993). Furthermore,

Table 3 Categorization of representative endpoints for RT-induced lung injury

	Focal	Global
Clinical	Symptomatic bronchial stenosis	Symptoms (dyspnea, cough)
Subclinical	Radiologic abnormalities (computed tomography, perfusion/ventilation scans)	Pulmonary function tests; Exercise testing

Table 4 LENT SOMA System for Grading Lung Injury

	Grade 1	Grade 2	Grade 3	Grade 4
Lung				
Subjective				
Cough	Occasional	Intermittent	Persistent	Refractory
Dyspnea	Breathless on intense exertion	Breathless on mild exertion	Breathless at rest, limits all activities	Prevents any physical activity
Chest pain/ discomfort	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective				
Pulmonary fibrosis	Radiological abnormality	Patchy dense abnormalities on radiograph	Dense confluent radiographic changes limited to radiation field	Dense fibrosis, severe scarring ,and major retraction of normal lung
Lung function	10–25% reduction of respiration volume and/or diffusion capacity	>25–50% reduction of respiration volume and/or diffusion capacity	>50–75% reduction of respiration volume and/or diffusion capacity	>75% reduction of respiration volume and/or diffusion capacity
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Cough		Non-narcotic	Narcotic, intermittent corticosteroids	Respirator, continuous corticosteroids
Dyspnea		Occasional O_2	Continuous O_2	
Analytic				
PFT	Decrease to >75–90% of preTx value	Decrease to >50–75% of preTx value	Decrease to >25–50% of preTx value	Decrease to ≤25% of preTx value
DLCO	Decrease to >75–90% of preTx value	Decrease to >50–75% of preTx value	Decrease to >25–50% of preTx value	Decrease to ≤25% of preTx value
% O_2/CO_2 saturation	>70% O_2, ≤50% CO_2	>60% O_2, ≤60% CO_2	>50% O_2, ≤70% CO_2	≤50% O_2, >70% CO_2
CT/MRI	Assessment of lung volume and zones of fibrosis			
Perfusion scan	Assessment of pulmonary blood flow and alveolar filling			
Lung lavage	Assessment of cells and cytokines			

bronchoalveolar lavage (BAL) following unilateral irradiation reveals increased lymphocytes from both the irradiated and unirradiated lung (Gibson et al. 1988; Roberts et al. 1993; Martin et al. 1999). These observations suggest that radiation pneumonitis may be type of hypersensitivity pneumonitis (bilateral lymphocytic alveolitis) (Abratt and Morgan 2002). Further, the lymphocytes retrieved with BAL are activated T-lymphocytes (Martin et al. 1999), suggesting that immunologic processes are participating in the radiation reaction. The observation that pneumonitis typically responds well to oral prednisone (Salinas and Winterbauer 1995) also supports the inflammatory/immunologic nature of radiation pneumonitis.

In patients with symptomatic pneumonitis, physical exam is often normal, although rales or a friction rub can sometimes be appreciated. Radiological studies are often, but not always, abnormal. Thus, pneumonitis is a *clinical* diagnosis. Radiographic abnormalities without symptoms usually do not warrant intervention. Indeed, asymptomatic patients frequency has radiologic findings similar to those seen in symptomatic patients. Thus symptoms and radiologic findings do not necessarily parallel each other.

Further, since abnormalities on CT and CXR are very common following RT, reported studies that consider asymptomatic radiologic findings as 'an event' likely overestimate the rate of 'clinical toxicity'.

Differentiating radiation pneumonitis from other etiologies (e.g., tumor progression, infection, pulmonary emboli, heart disease) can be challenging (Kocak et al. 2005). Ideally, one should be reasonably sure that symptoms suggestive of pneumonitis are not due to these other conditions before therapy is initiated. A short course of antibiotics is occasionally useful if there is concern for infection, with a rapid institution of steroids if symptoms do not respond.

The culminating event in RT-induced lung injury is replacement of normal lung parenchyma with fibrosis, which is often appreciated on radiographic studies but is usually asymptomatic (Marks et al. 2000). However, if the baseline pulmonary reserve of a patient is limited and/or the region of fibrosis is extensive, symptoms can develop. In this circumstance, dyspnea can be progressive and difficult to manage, often requiring long-term steroids, oxygen, and/or rehabilitation. The severity of radiographic abnormalities is not always well-correlated with the presence or severity of pulmonary symptoms (Marks et al. 2000). The time course for the development of RT-associated lung symptoms is shown in Fig. 6a, b.

In patients treated with high doses of radiation (e.g., ≥70 Gy), unusual pulmonary complications, such as bronchial stenosis, bronchopleural fistula, and fatal hemoptysis have been reported (Miller et al. 2005; Socinski et al. 2004).

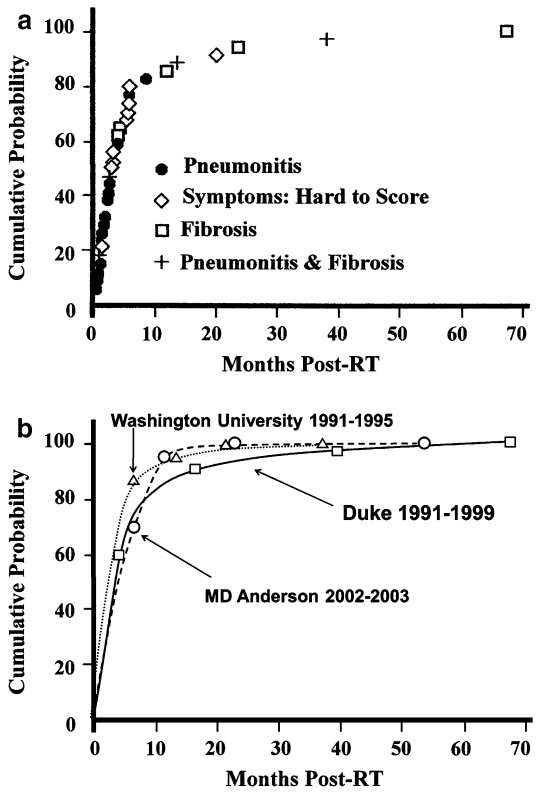

Fig. 6 Time course for the development of RT-associated lung symptoms. **a** Data from Duke with patients individually noted as having "pneumonitis", "fibrosis", as well as cases where the diagnosis was somewhat uncertain due to concurrent illnesses (e.g. infection). **b** Data from several different centers as shown. (Adapted from Marks et al. 2000)

4.2 Imaging

Multiple radiological studies have been used to assess regional lung injury. The most widely studied include chest X-ray and CT (which evaluate structure and tissue density), and single photon emission computed tomography (SPECT) (which can evaluate the functional endpoints of ventilation and perfusion). The sensitivity of these radiological modalities varies, and thus, the incidence of lung injury depends on the modality utilized. Furthermore, radiological changes are common in patients with lung cancer (who receive relatively large doses to large volumes of lung), and less common in patients with breast cancer or lymphoma (where the doses/volumes are lower). In general, 3D imaging modalities are more sensitive than 2D modalities (CT is more sensitive than CXR), and SPECT-based ventilation/perfusion imaging is more sensitive than either CXR or CT. Comparisons between studies are challenging since the patient populations and RT doses used are variable. Nevertheless, these generalizations appear to be true in studies that have considered multiple imaging modalities (Jackson et al. 2006).

4.2.1 Chest X-ray

The most common finding on plain radiographs after thoracic RT is increased density (radiopacity). This may be secondary to increased interstitial edema and/or alveolar consolidation acutely and pulmonary fibrosis at later time points. Other common findings are nonanatomic margination (corresponding to the RT field edge), volume loss with midline shift, and pleural thickening. Radiographic changes develop shortly after completion of RT, peak at approximately 6 months (Skoczylas et al. 2000; Monson et al. 1998; Lind et al 2000), and typically stabilize by 12 months. However, continued follow-up may show either further progression or even regression in a small number of patients (Skoczylas et al. 2000).

4.2.2 Computed Tomography

The abnormalities noted with CT and chest X-ray are similar. However, CT appears to be more sensitive, in part because paramediastinal abnormalities may be obscured by the cardiac or aortic silhouette on chest X-ray. The typical acute findings are often described as early ground-glass opacities and patchy infiltrates (Fig. 7a). Late findings

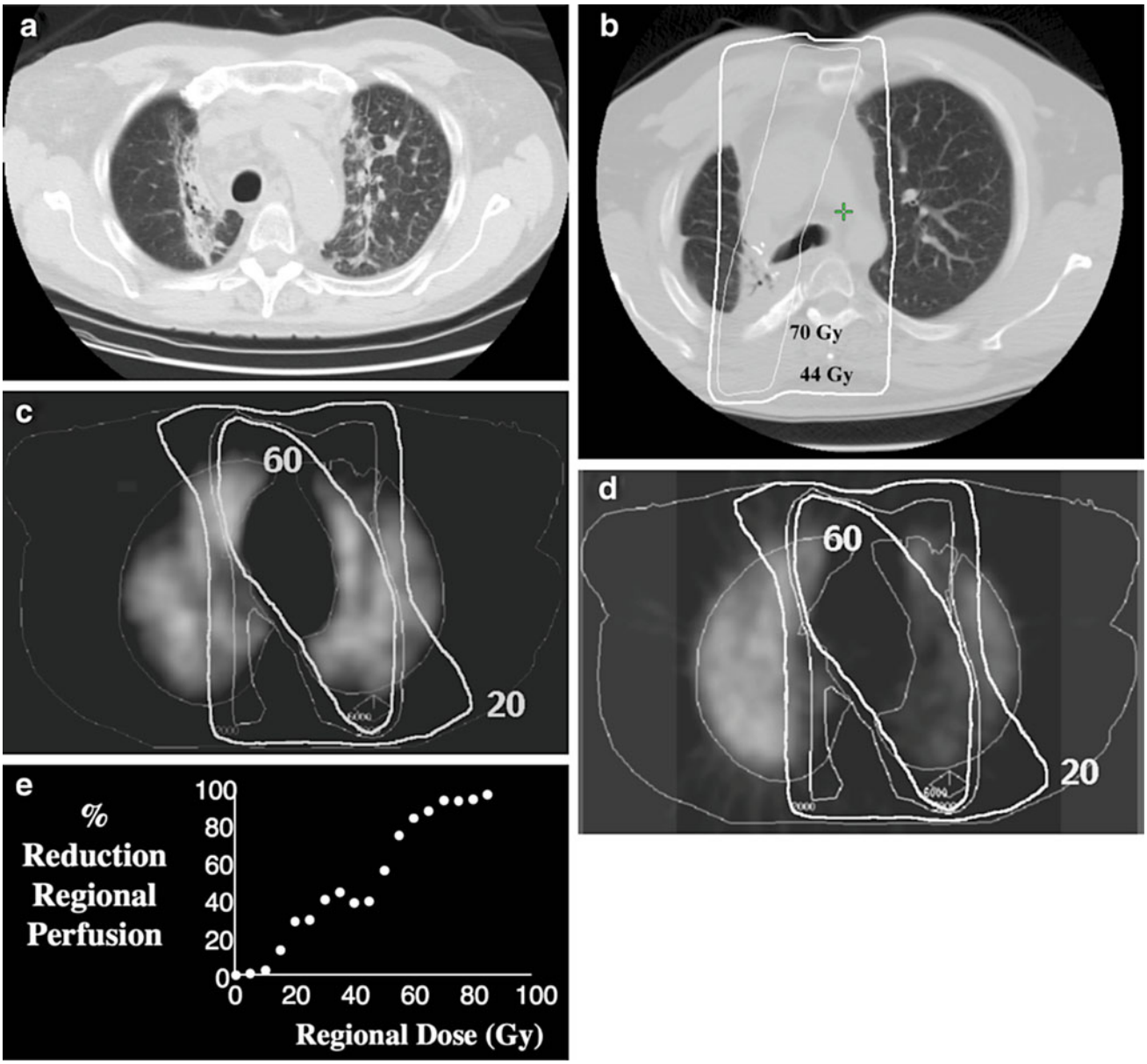

Fig. 7 CT image of a patient 3 months post-RT to the mediastinum for lung cancer. Characteristic increased interstitial markings are seen in the medial lung bilaterally, essentially demarcating the volume of lung that received ≥40 Gy (**a**). CT image about 2 years post-RT illustrating late fibrotic changes with volume loss. Representative overlying isodose curves shown (**b**). Transverse SPECT lung perfusion images obtained pre-RT (**c**) and post-RT (**d**) in a single patient irradiated for lung cancer. Representative isodose lines are shown. Note the reduction in regional perfusion post-RT. By considering the CT density or perfusion in each pixel independently, and pooling pixels into dose bins, one can create a dose response curve; example panel (**e**)

typically include fibrotic changes with consolidation and volume loss (Fig. 7b). It can sometimes be difficult to differentiate mass-like fibrosis from persistent/recurrent tumor (Koenig et al. 2002). Registration of the planning CT scan (and hence the 3D dose distribution) to the post-RT CT, demonstrates that there are CT-defined increases in tissue density, which are dose-dependent, and largely seen in lung regions receiving ≥40 Gy (Theuws et al. 1998; Kocak and Marks 2005) (Fig. 7e).

Other abnormalities include traction bronchiectasis, diminished pulmonary vascularity, as well as narrowing of the proximal bronchi. Traction bronchiectasis develops from tethering of the bronchial wall by RT-induced fibrosis. Decrease in pulmonary vasculature has been demonstrated outside of the RT field. This maybe secondary to irradiation of central tumors with injury to proximal vessels and/or bronchi (Bell et al. 1988). However, in our studies using SPECT to assess changes in regional perfusion post-RT, we

have not typically seen reduced perfusion in unirradiated lung, suggesting that perfusion through larger central vessels is preserved after conventional doses of RT. Symptomatic bronchial stenosis is not commonly observed after conventional doses of RT. With dose escalation, bronchial stenosis has been observed in both symptomatic (Miller et al. 2005) and asymptomatic patients (Kelsey et al. 2006).

4.2.3 Single Photon Emission Computed Tomography

Nuclear medicine imaging of regional perfusion and/or ventilation can also be used to assess regional lung function. Imaging can be planer or 3D (via SPECT). The latter is more sensitive than the former (Bell et al. 1988), analogous to the utility of CT over CXR. Example pre- and post-RT SPECT perfusion images are shown in Fig. 7c, d. Registration of the planning CT scan to pre-and post-RT SPECT scans allows one to quantitatively relate regional RT doses to changes in regional perfusion (Fig. 7e). RT-induced changes in ventilation and perfusion appear to be more common than corresponding changes on CT (Theuws et al. 1998).

Dose-dependent reductions in perfusion are seen as early as 6 weeks after RT (Theuws et al. 2000; Woel et al. 2002), and peaking by approximately 6 months (Woel et al. 2002). Whether recovery occurs with time is unclear. Following modest doses of RT for breast cancer and lymphoma, investigators at the Netherlands Cancer Institute (NKI) report up to 50% recovery by 18 months (Theuws et al. 2000; Boersma et al. 1996). At Duke, we have not seen such recovery, but our study population was predominantly patients with lung cancer receiving higher doses of RT (Woel et al. 2002).

Since the alveolar network is structured in parallel, it is reasonable to hypothesize that changes in global lung function will be related to the extent and severity of regional injury. This is similar to what has been done by surgeons who have tried to relate the percent decline in pulmonary function with the percent of alveoli that are resected (Beckles et al. 2003). We and investigators at the NKI have attempted to relate the sum of the changes in regional perfusion (also termed the integrated response) to changes in pulmonary symptoms and PFTs, with mixed success. While there is a strong correlation between the sum of regional injuries and changes in global function, the correlation coefficients are weak, suggesting that there may be numerous other factors affecting global pulmonary function (Fan et al. 2001; Theuws et al. 1998). The correlation coefficients are higher for the patients with breast and lymphoma than for the patients with lung cancer.

4.2.4 Other Modalities

Magnetic resonance imaging (MRI) has not been widely used to evaluate RT-induced lung toxicity. A preliminary study demonstrated T1 and T2 changes within normal lung parenchyma as early as 17 days after RT. These changes increased over several months before beginning to resolve (Yankelevitz et al. 1994). Another study demonstrated distinct perfusion changes associated with radiation pneumonitis (greater enhancement with both first-pass and redistribution phases) and fibrosis (decreased enhancement with first-pass but greater enhancement with the distribution phase) (Ogasawara et al. 2002). Further MRI investigations may be warranted.

Like MRI, there are few studies evaluating RT-induced lung injury using positron emission tomography (PET). Increased uptake in the lungs of patients with radiation pneumonitis has been reported (Hassaballa et al. 2005; Lin et al. 2000). Another study demonstrated an apparent linear dose response (Guerrero et al. 2007). As expected, there was marked inter-patient variation suggesting an underlying biological susceptibility to injury.

4.3 Pulmonary Function Tests

PFTs objectively assess multiple pulmonary parameters including lung volumes, the amount and rate of air flow (spirometry), and the ability of the lung to transfer gas at the alveolar level. Diffusing capacity of the lung for carbon monoxide (DLCO) is likely the best parameter to assess lung function after RT, since the ultimate role of the lungs is to facilitate gas exchange. Loss of alveolar surface area and thickening of the intraalveolar septi are the primary causes for reductions in DLCO. Thus, both acute (edema, extravasation of material into the alveoli) and chronic (fibrosis, loss of alveoli) injury can affect DLCO. The forced expiratory volume in 1 s (FEV1) is another useful parameter and often interpreted in the context of the FEV1/FVC ratio (FVC = forced vital capacity). A decreased FEV1 with a normal FEV1/FVC ratio is most consistent with a restrictive process, such as fibrosis. A decreased FEV1 and FEV1/FVC ratio is more consistent with an obstructive process.

Assessing the impact of RT on PFTs in patients with lung cancer is challenging. Many patients with lung cancer have baseline pulmonary dysfunction from smoking, such as chronic obstructive pulmonary disease, and some patients continue to smoke after RT with continued accelerated diminutive effects on function. Also, pulmonary function may transiently improve as large central tumors regress. Finally, there is limited data on long-term PFT changes

Table 5 Prospective studies evaluating PFTs in patients with lung cancer

Study	*n*	% Decline in FEV1 after RT (months)				
		3	6	12	18	36
Miller et al. (2003)	13		111	0		14
Borst et al. (2005)	34	5			8.8	13.4
Choi and Kanarek (1994)	45[a]		19	19[b]		
Abratt and Willcox (1995)	42		2	+3		
		% Decline in DLCO after RT (months)				
		3	6	12	18	36
Miller et al. (2003)	13		8	10		17
Borst et al. (2005)[c]	34	8[b]			14[b]	20[b]
Choi and Kanarek (1994)	45[a]			27		
Abratt and Willcox (1995)	42		13	14		

[a] 45 of patients with baseline FEV1 ≥50% without significant ventilation or perfusion shift to contralateral lung
[b] Estimated from graphs provided
[c] Transfer factor for carbon monoxide corrected for hemoglobin level and alveolar volume

since most patients with lung cancer succumb to their disease within 1–2 years.

With these caveats, most studies show a decline in pulmonary function after RT. Reductions in FEV1 are appreciated approximately 3–6 months post-RT (Table 5), sometimes followed by partial/complete recovery at ≈12 months. This transient decline may be coincident with the acute inflammatory reaction associated with pneumonitis. DLCO typically is reduced to a greater degree than FEV1 (Table 5), and many studies appears to show less recovery at ≈12 months than FEV1. Most studies show a decline in both FEV1 and FVC (Borst et al. 2005; Miller et al. 2003), such that the FEV1/FVC ratio remains in the normal range (Myers et al. 2005), consistent with a restrictive process. In the few patients with long-term changes in PFTs systematically studied beyond one year, there appears to be long-term continued diminution in PFTs 2–8 years post-RT (Miller et al. 2003).

Multiple studies, primarily in children, have confirmed that pulmonary function tests are abnormal after whole lung irradiation (Benoist et al. 1982; Ellis et al. 1992; Littman et al. 1976; Miller et al. 1986; Weiner et al. 2006). In general, these studies demonstrate decreased lung volumes (vital capacity, total lung capacity), impaired air flow (forced expiratory volume in 1 second), and perhaps diminished diffusing capacity (DLCO). Multiple factors likely play a role, including impaired chest wall growth, a reduction in the number of functioning alveolar units, and fibrotic changes within the lung. Whether function improves over time (Ellis et al. 1992) or continues to deteriorate (Weiner et al. 2006) is unclear.

5 Radiation Tolerance and Predicting Radiation-Induced Lung Injury

5.1 Whole Lung Irradiation

Irradiation of both lungs occurs in multiple clinical contexts. This includes total body irradiation (TBI) as part of the preparative regimen for stem cell transplants, hemibody irradiation in the setting of diffuse symptomatic metastatic disease, and whole lung irradiation for pulmonary metastases from various malignancies (not commonly done recently). Clinical experience in these settings has permitted the tolerance of whole lung irradiation to be estimated.

5.1.1 Single Fraction (Total Body RT and Hemibody RT)

With single fraction whole lung irradiation, the risk of interstitial pneumonitis is primarily dependent on total dose and dose rate. For low-dose rate TBI (5–10 cGy/min), assuming lung density corrections, an early study concluded that the threshold dose for pneumonitis is approximately 9 Gy, the TD_5 (dose resulting in a 5% complication rate) is approximately 10 Gy, with a TD_{50} (dose resulting in a 50% complication rate) of 11–12 Gy (Keane et al. 1981). When higher dose rates are utilized, principally for hemibody irradiation, the dose response curve is shifted to the left. In this circumstance, the threshold dose was estimated to be approximately 7 Gy, with a TD_5 of 8 Gy and a TD_{50} of approximately 9.3 Gy (Keane et al. 1981). In a more recent, comprehensive review, the TD_5 (with cyclophosphamide)

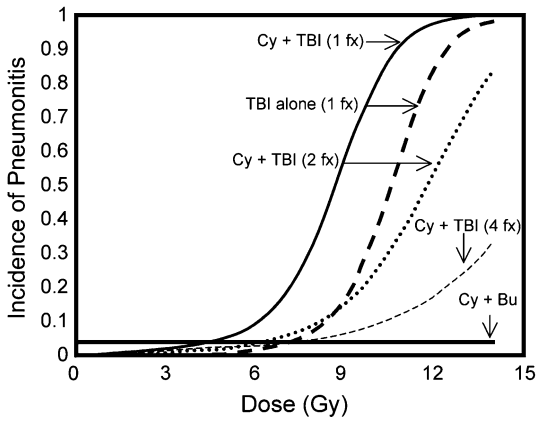

Fig. 8 The risk of pneumonitis following whole lung RT as part of TBI. The addition of chemotherapy appears to move the dose response curve to the *left*, and fractionating the RT moves the dose response curve to the *right* (Adopted from QUANTEC, Marks et al. 2010, IJROBP)

was estimated to be much lower, approximately 5 Gy for low-dose rate TBI (Sampath et al. 2005). Both studies demonstrated that the dose response curve for whole lung irradiation is steep such that a difference of only 1–2 Gy increases the risk of pneumonitis significantly (Fig. 8) The development of pneumonitis after whole lung irradiation is an ominous sign, proving fatal in up to 80% of patients (Fryer et al. 1978). The difference in mortality for similar doses between TBI and HBI dose response appears to have been due to the low-dose rate protraction for TBI. Decreasing the dose rate from 0.5 to 0.1 by per minute decreases the incidence of pneumonitis associated with whole lung irradiation during TBI. This was a byproduct of greater distance from the radiation source, required to produce a large field to encompass the whole body.

5.1.2 Multiple Fractions

Two randomized studies treated patients with osteogenic sarcoma with prophylactic, fractionated whole lung irradiation. A Mayo clinic trial treated patients with 15 Gy over 2 weeks with concurrent actinomycin D (Rab et al. 1976). A European study treated patients with 17.5 Gy in 2 weeks without chemotherapy (Breur et al. 1978). Lung density corrections were not utilized in either study, and thus the true total physical doses delivered were likely in the neighborhood of 17 and 20 Gy in these two studies, respectively. No cases of pneumonitis were reported in either trial. A retrospective study of whole lung irradiation for a variety of tumor histologies, mostly pediatric, reported no cases of pneumonitis after doses ranging from 15–25 Gy (Newton and Spittle 1969). Furthermore, in several retrospective studies in which TBI was utilized in the preparative regimen prior to stem cell transplant, the risk of interstitial pneumonitis appeared to be lower with fractionation (Cosset et al. 1989; Pino et al. 1982; Shank et al. 1983). These studies suggest that fractionation increases lung tolerance. However, in two randomized studies comparing single fraction TBI with fractionated TBI, there was no difference in the risk of interstitial pneumonitis (virus + idiopathic) (Table 6). There were less cases of idiopathic pneumonitis with fractionation (Deeg et al. 1986; Girinsky et al. 2000).

Pulmonary toxicity after allogeneic stem cell transplantation, particularly after myeloablative conditioning, is relatively common. Pulmonary toxicity includes both infectious (bacterial, viral, or fungal) and non-infectious (interstitial pneumonia, adult respiratory distress syndrome, diffuse alveolar hemorrhage, bronchiolitis obliterans, etc.) etiologies. However, in immunocompromised transplant patients, it is often difficult to definitively differentiate one etiology from another (e.g., radiation pneumonitis versus bacterial pneumonia) and often requires invasive tests such as bronchoscopy.

Most, if not all, TBI protocols are now fractionated. Total doses are typically 10–14 Gy given in once or twice daily fractions, usually with the lungs attenuated to ~7–10 Gy. Patients also receive high-dose chemotherapy which appears to lower the threshold for pneumonitis. In the absence of chemotherapy, single doses of up to 6–8 Gy and fractionated doses of up to 25–28 Gy appear tolerable. Conversely, for patients undergoing TBI as part of a transplant regimen that includes chemotherapy, far lower doses are tolerated.

5.2 Partial Lung Irradiation: Conventional Fractionation

Most patients receiving thoracic RT receive fractionated partial lung irradiation. Determining tolerance doses and accurately predicting the risk of RT-associated pulmonary toxicity after partial lung irradiation is challenging. Multiple clinical (patient- and tumor-specific), biologic, and dosimetric parameters have been evaluated. Dosimetric parameters appear to be the most useful and will thus receive the most attention.

5.2.1 Clinical Parameters

In both retrospective and prospective studies, several clinical factors have been associated with an increased risk of developing symptomatic pneumonitis, including underlying lung disease (Monson et al. 1998; Rancati et al. 2003), decreased baseline pulmonary function (Monson et al. 1998; Robnett et al. 2000), low performance status (Monson et al. 1998; Robnett et al. 2000), female gender (Robnett et al. 2000), history of smoking (Monson et al. 1998), and not actively smoking. However, these findings have been inconsistent across studies, such that none of these parameters have been found to be a robust and reliable risk factor for the development of RT-induced lung injury.

Table 6 Randomized studies of TBI fractionation for hematological malignancies

Author	*n*	Dose/fractions	Dose rate	Chemotherapy	Pneumonitis rate
Girinsky et al. (2000)	147	10 Gy/1[a] 14.85 Gy/11[b]	12.5 cGy/min 25 cGy/min	CYC or MEL CYC or MEL	19% (6 mos) 14% (6 mos)
Deeg et al. (1986)	53	10 Gy/1 12 Gy/6	6 cGy/min 6 cGy/min	CYC CYC	26% (crude) 23% (crude)

TBI total body irradiation, *CYC* cyclophosphamide, *MEL* melphalan
[a] Lungs shielded to 8 Gy
[b] Lungs shielded to 9 Gy

Preclinical and clinical data suggest that irradiation of lower lung regions may be more clinically important than irradiation of upper lung regions. This may be secondary to nonuniform distribution of gas exchange throughout the lung and/or incidental heart dose. In mice, Travis et al. (1997) demonstrated that the lower lobes are more radiosensitive (increased respiratory rate, lethality) than the upper lobes. In another rodent study, the respiratory rate following thoracic RT was related to both the volume of lung *and* heart irradiated (van Luijk et al. 2005). Similarly, RT-induced changes in breathing rate were greater with left- versus right-sided RT in rats (Wiegman et al. 2003), suggesting that incidental dose to the heart may contribute to symptomatic RT-induced lung injury. Many (Graham et al. 1999; Hope et al. 2006; Seppenwoolde et al. 2004; Yorke et al. 2005), but not all (Robnett et al. 2000; Tsujino et al. 2003; Wang et al. 2006) clinical studies have shown increased rates of radiation pneumonitis with treatment of lower lobe tumors. As stated above, part of these effects may be related to incidental cardiac irradiation, as a greater volume of heart is the field with lower lobe targets.

It seems logical to assume that pre-RT pulmonary function would be an important factor in predicting RT-induced lung injury. In patients undergoing surgery, there is an association between the percent decline in PFTs and the percent of lung volume resected. Thus, pre-surgical pulmonary function is predictive of the patient's ability to tolerate surgery. For patients receiving RT, it has been more challenging to quantitatively relate pre-RT PFTs to the risk of subsequent RT-induced lung injury. One of the challenges for considering pulmonary function in the pre-RT assessment is that it may be compromised by the tumor itself, and that treatment may lead to improvements in pulmonary function with tumor shrinkage.

5.2.2 Biological Parameters

Many studies have also addressed the role of potential biologic predictors of RT-induced lung injury. These are markers found in the blood prior to, during, or after completing RT and are thought to reflect a predisposition for, or the ongoing evolution of, RT-induced lung injury. A host of cytokines have been implicated, including transforming growth factor-beta (TGF-β). This is a multifunctional regulator of cell growth and differentiation that stimulates connective tissue formation and decreases collagen degradation, which can result in fibrosis (Anscher et al. 1998). In patient subsets, TGF-β has been suggested to predict RT-induced lung injury (Anscher et al. 1994; Fu et al. 2001). However, further investigation will be necessary before biological predictors of lung injury can be used clinically because the present data regarding such cytokines are conflicting (Table 1).

Rare disorders (e.g., ataxia-telangiectasia), suggest that genetic differences, including single nucleotide polymorphisms (SNPs), may mediate RT sensitivity. A recent study demonstrated a reduced risk of radiation pneumonitis in lung cancer patients who harbored a polymorphism at position 869 within the TGF-β gene (Yuan et al. 2009). Further studies are ongoing.

5.2.3 Dosimetric Parameters

The risk of developing acute pneumonitis has been associated with a variety of dosimetric parameters (Kim et al 2005; Yorke et al 2002, Willner et al 2003, Oetzel et al 1995, Fay et al 2005) including the mean lung dose (MLD) and the percent of lung receiving doses in excess of a specified threshold dose, as summarized in the recent QUANTEC review (Marks et al. 2010) (Fig. 9a, b). These parameters are readily extractable from a dose–volume histogram (DVH) and/or treatment planning software. However, lung volumes vary with the breathing cycle and tumor response during RT may lead to increased lung exposure (with normal lung replacing space previously occupied by tumor). These factors are not easily accounted but should be kept in mind.

Strict dose/volume guidelines are difficult to define and implement clinically. Traditional DVHs assume that all regions of the lung contribute equally to pulmonary function, which is often an erroneous assumption since many patients have heterogenous regional lung function (e.g., from tumor or COPD). Furthermore, metrics such as the V20 or V30 (volume of lung receiving at least 20 or 30 Gy, respectively), consider only a single point on the cumulative DVH. It is apparent that two DVHs with markedly different shape may overlap at the same point (V20, for instance). MLD might be a preferable metric since it considers the

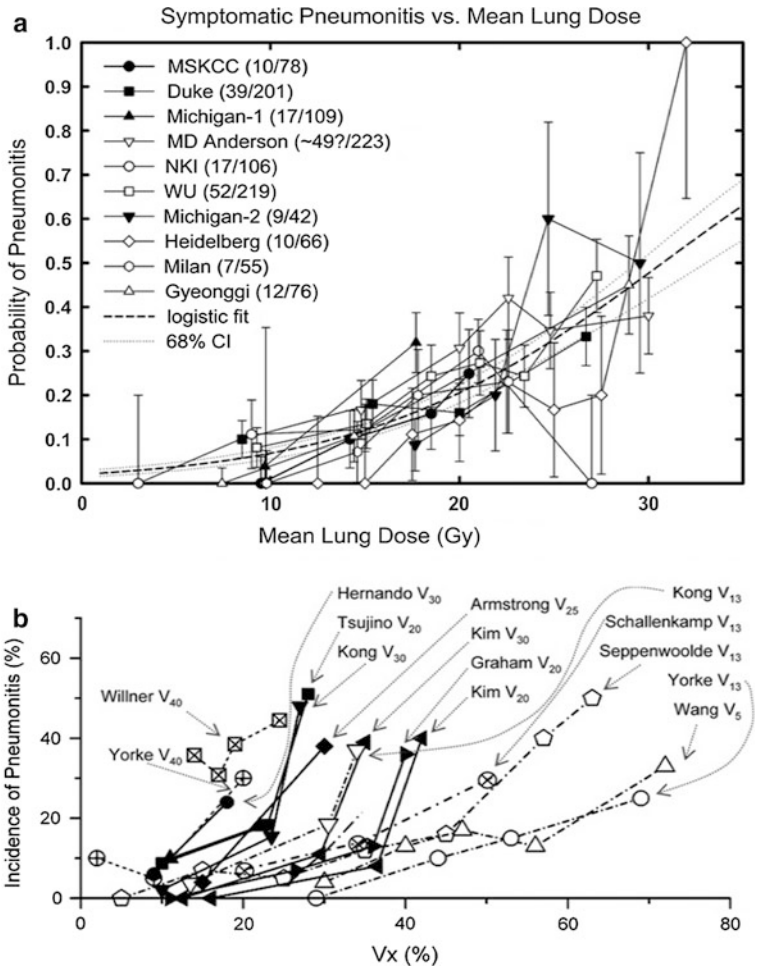

Fig. 9 Incidence of radiation pneumonitis versus mean lung dose (**a**) and the percent lung exposed to doses exceeding different thresholds [*Vx*] (**b**). *Vx* = percent of lung receiving ≥*x* Gy. (Adopted from QUANTEC, Marks et al. 2010, IJROBP)

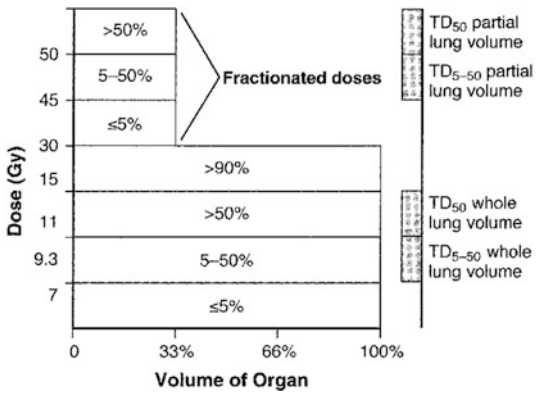

Fig. 10 A suggested manner to illustrate the relationship between DVH-based parameters and the risk for lung toxicity. The numbers in the rectangles are the estimated risks of injury with the corresponding dose (*left* *y*-axis) and volume (*x*-axis). The *right* *y*-axis indicates the tolerance dose ranges for the TD_5 and TD_{50} for whole organ (lungs) irradiation, as well as the TD_5 and TD_{50} for the partial organ volume (POV) irradiation. (with permission from Clinical Oncology 8th Edition)

entire 3D dose distribution. In practice, it may not be particularly useful to try to determine which parameter is truly "optimal" since there tends to be strong correlations between the different dosimetric parameters, at least with relatively uniform treatment techniques (Fan et al. 2001; Graham et al. 1999; Kong et al. 2006).

In most series, the majority of patients are treated with MLDs in the lower aspect of the range shown in Fig. 9a. Thus, even though the *incidence* of pneumonitis is less when the MLD is lower, the absolute number of patients with pneumonitis derived from the low-MLD group is relatively high. In this regard, MLD is not particularly sensitive (i.e., it does not predict a high fraction of the pneumonitis cases). An alternative manner to illustrate the approximate relationship between dose/volume/risk is shown in Fig. 10.

5.3 Partial Lung Irradiation: Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) facilitates conformal treatment of irregularly shaped and concave targets. This is especially useful for targets adjacent to critical structures. However, IMRT planning usually

delivers lower doses of radiation to larger volumes of surrounding normal tissue. The impact of large-volume/low-dose lung irradiation in the context of curative treatment of lung cancer is not known. The M.D. Anderson Cancer Center recently published the largest clinical experience using IMRT in 68 patients with lung cancer (Yom et al. 2007). In this report, the incidence of grade ≥3 radiation pneumonitis was significantly lower in those patients treated using IMRT versus their comparison group treated with conventional 3D-conformal RT (8 vs. 32% at 12 months, $p = 0.002$). In the IMRT group, patients with V5 values (volume of lung receiving more than 5 Gy) greater than 70% appeared to be at higher risk of pneumonitis. Other dosimetric parameters (MLD, V20) were not assessed for their association with pneumonitis. Investigators at Memorial Sloane Kettering Hospital noted a similarly low rate of clinical lung injury in patients with non-small cell cancer treated with IMRT (Sura et al. 2008). Additional experience is necessary to confirm the safety and efficacy of IMRT for lung cancer. Further, the dosimetric predictors of pneumonitis might be different with a limited number of conformal beams versus IMRT.

5.4 Partial Lung Irradiation: Hypofractionation

There is increasing interest in the use of stereotactic body radiation therapy (SBRT) for patients with medically inoperable stage I NSCLC and patients with oligometastases involving the lung. In contrast to the standard method of treating lung cancer (1.8–2 Gy daily fractions given over a period of 6–7 weeks) this unique approach uses only a few very large fractions given over 5–10 days. Currently used fractionation schemes of 18 Gy × 3, 12 Gy × 4, and 10 Gy × 5 appear to provide a reasonable therapeutic ratio for small lesions. These large daily doses are feasible because only small volumes are treated with conformal techniques, which minimizes dose to surrounding critical structures.

Within 6–12 months after SBRT, most patients develop increased tissue density on CT in the high-dose region (Hof et al. 2003; Kyas et al. 2007), which can be difficult to differentiate from persistent tumor. Symptoms consistent with radiation pneumonitis have occurred in 2–25% of patients (Stephans et al. 2009; Hoyer et al. 2006; Nagata et al. 2005; Timmerman et al. 2003). Serious, and sometimes lethal, pulmonary toxicity has associated with treatment of perihilar/central tumors (Song et al. 2009; Timmerman et al. 2006), especially with the 20 Gy × 3 regimen. Whether more protracted regimens (e.g., 10 Gy × 5) are safer for central tumors is not presently clear and dose-escalation studies are ongoing. PFT changes after SBRT appear to be minimal (Stephans et al. 2009). As experience with this radiation technique is being rapidly gained, our understanding of the effects of hypofractionated, high-dose RT to very small volumes of lung will become more broadly known in the near future.

Investigators at the University of Michigan have systematically studied the role of dose escalation for non-small cell lung cancer and their findings with conventional fractionation may have relevance to SBRT. The dose of RT was determined based on the predicted risk of grade 2 or higher radiation pneumonitis using Lyman's NTCP model (Lyman and Wolbarst 1987). In this manner, extremely high doses of RT (up to 102.9 Gy) were successfully delivered (Hayman et al. 2001) with ∼15% risk of radiation pneumonitis and no cases of grade 4–5 toxicity (Kong et al. 2006).

5.5 Recommended Dose/Volume Constraints

The lung is one of the most challenging organs to define dose/volume constraints. Many patients with lung cancer require large treatment fields due to tumor extent. The radiation oncologist does not always have the option to reduce the volume of lung irradiated. Further, there is marked inter-patient variation in pre-RT lung disease (e.g., COPD), and tumor-related pulmonary compromise. It may not be appropriate to force strict dose/volume constraints based on pre-RT pulmonary status, since poor pre-RT function maybe due to the tumor itself, and hence may actually improve with RT. Therefore, patients need to be counseled about the possible risks of lung injury and the uncertainty in defining individual risk. With these caveats in mind, there are nevertheless some broad guidelines that can be clinically useful (Table 7).

We recommend limiting the volume of lung receiving over 20 Gy (V20) to 30–35% (Graham et al. 1999) and limiting the MLD to 20–23 Gy (Hernando et al. 2001; Kwa et al. 1998). Recent data suggest that the volume of lung exposed to relatively low doses of RT (e.g., 5–15 Gy) may be more predictive for pneumonitis than V20–30 (Schallenkamp et al. 2007; Uno et al. 2006; Wang et al. 2006). This is particularly relevant when IMRT techniques are utilized or when patients with mesothelioma are treated after extrapleural pneumonectomy. However, further investigation is necessary to understand the biological and clinical ramifications of low-dose RT to large volumes of lung. Symptomatic bronchial stenosis has been observed with doses >70 Gy, thus care should be taken when irradiating central structures to high doses. Dose guidelines for

Table 7 Recommended dose–volume constraints[a]

Clinical scenario	V5 (%)	V20 (%)	Mean lung dose	Dose to central airways
Lung cancer (3D or IMRT)	<50–70	<30–35	<20–23 Gy	<70 Gy
Mesothelioma (IMRT after EPP)	<50–70	<4–10	<8 Gy	N/A

IMRT intensity-modulated radiation therapy, *EPP* extrapleural pneumonectomy

[a] Dose guidelines need to be considered and modified based on the clinical situation, competing risks, and other confounding issues that may affect the absolute risk and acceptance of risk

Table 8 Chemotherapy agents and reported pulmonary toxicities

Agent	Toxicity	Comments
Bleomycin (Toledo et al. 1982; Tryka et al. 1982; Maher and Daly 1993; White and Stover 1984; Einhorn et al. 1976; Rudders and Hensley 1973; Sleijfer 2001)	BOOP[a] Interstitial pneumonitis Fibrosis	Bleomycin is inactivated by bleomycin hydrolase, which has low activity in the lungs
Busulfan (Oliner et al. 1961; Feingold and Koss 1969; Hankins et al. 1978; Min and Gyorkey 1968)	Interstitial fibrosis	Mechanism unknown correlates with cumulative dose
Carmustine (Weinstein et al. 1986; Weiss et al. 1979)	Alveolitis Fibrosis	Reduced DLCO is sensitive marker of toxicity Toxicity appears to be dose-dependent.
Chlorambucil (Giles et al. 1990)	Interstitial pneumonitis Pulmonary fibrosis	Early cessation of drug is key
Cyclophosphamide (Malik et al. 1996)	Acute pneumonitis Chronic fibrosis	Risk appears increased with concomitant radiation and oxygen
Cytosine Arabinoside (Haupt et al. 1981)	Pulmonary edema	Increased capillary permeability
Docetaxel (Kouroussis et al. 2004; Esteban et al. 2008)	Shortness of breath Interstitial pneumonitis	High risk of pneumonitis when administered with RT or other chemotherapeutics
Etoposide (Dajczman et al. 1995; Gurjal et al. 1999; Kataoka et al. 1992)	Interstitial infiltrates Pulmonary fibrosis	Reported to exacerbate radiation pneumonitis via recall phenomenon
Fludarabine (Garg et al. 2002; Hurst et al. 1987; Kane et al. 1992)	Diffuse interstitial pneumonitis Pulmonary nodules	Reversible with drug discontinuation
Gemcitabine (Esteban et al. 2008; Barlesi et al. 2004; Ciotti et al. 1999; Czarnecki and Voss 2006; Dunsford et al. 1999; Gupta et al. 2002; Joerger et al. 2002; Pavlakis et al. 1997; Tempero and Brand 1998; Veltkamp et al. 2007)	Diffuse interstitial pneumonitis	Increased risk when administered with other chemotherapeutic agents
Methotrexate (Cannon 1997; Lateef et al. 2005; McKenna and Burrows 2000; Provenzano 2003)	Hypersensitivty pneumonitis	Seen even with low doses used in rheumatic disorders
Mitomycin (Buzdar et al. 1980; Chang et al. 1986; Linette et al. 1992; Luedke et al. 1985; Raderer et al. 1996)	Bronchospasm Acute pneumonitis Chronic fibrosis Pulmonary hemorrhage	Toxicity more common with concurrent vinca alkaloids May be dose-dependent
Paclitaxel (Stemmer et al. 1996)	Multi-organ failure in setting of high-dose paclitaxel	Rarely reported with standard dose
Procarabazine (Garbes et al. 1986; Lauta et al. 1987; Mahmood and Mudad 2002)	Interstitial pneumonitis	Usually reported as part of MOPP therapy
Vinca Alkaloids (Esteban et al. 2008; Raderer et al. 1996; Hoelzer et al. 1986; Konits et al. 1982)	Interstitial pneumonitis	Typically reported in combination of vinblastine and mitomycin C

[a] *BOOP* bronchiolitis obliterans organizing pneumonia

SBRT are in a state of rapid flux as the number of clinical reports appears to be rapidly increasing.

6 Chemotherapy

6.1 Combined Treatment

A number of chemotherapeutic agents have been shown to be associated with a range of pulmonary toxicities, including dyspnea, pulmonary edema, bronchospasm, acute and interstitial pneumonitis, and even pulmonary fibrosis. Toxicities are often dose-dependent and related to other factors such as concurrent administration of other chemotherapeutic drugs and/or RT. Although many toxicities are reversible with discontinuation of medication, some are permanent and may occur as part of late manifestations of treatment. As a result, a high index of suspicion is needed for patients who present with respiratory symptoms, particularly in those for whom the treatment is known to been associated with an increased risk of lung damage. Lung toxicity has been reported with a number of chemotherapeutic agents (Table 8) (Carver et al. 2007). It is important to note, however, that chemotherapy-induced lung toxicity is largely considered a diagnosis of exclusion after fully considering and exploring other differential diagnoses (i.e., typical and atypical infections, COPD exacerbation, pulmonary embolism, etc.).

The first recognition that chemotherapy could produce late effect fibrosis in lung without pneumonitis was a tragic event. In children with brain tumors, the administration of the nitrosoureas (BUDR) was continued and prolonged, judging toxicity hematologically. Eventually, 35% of brain tumor survivors died of lung fibrosis. Twelve percent died within three years of treatment, however, 24% died of progressive lung fibrosis being symptom free for 7–12 years.

Bleomycin, as an example, has been one of the most studied agents for chemotherapy-induced lung injury, and is a feared complication of treatment for germ cell tumors with an estimated occurence of $\sim$10% of patients (Jules-Elysee and White 1990). Although the exact mechanism is unknown, the pulmonary specific drug toxicity is felt to be in part due to the fact that the inactivating enzyme, bleomycin hydrolase, is less expressed in normal lung tissue compared to other normal tissues (Sikic 1986). Exposure to high FiO_2 has also been associated with exacerbation of bleomycin toxicity in animal models and humans (Gilson and Sahn 1985; Allen et al. 1981; Toledo et al. 1982; Tryka et al. 1982). Clinical manifestations include an acute hypersensitivity pneumonitis or a fibrosing alveolitis that may occur acutely, subacutely, or >6 months following exposure. Symptoms are nonspecific, as is the case in many presentations of chemotherapy-induced lung toxicity, and may include fever, cough, chest pain, dyspnea, tachypnea, hypoxemia, etc. Although treatment in the acute setting has traditionally consisted of prompt discontinuation of bleomycin and initiation of corticosteroids, reports are anecdotal and nonrandomized (Maher and Daly 1993; White and Stover 1984).

The interactions between chemotherapy and RT within the normal lung are still being deduced, although it has been observed that many chemotherapeutic drugs, including those without significant pulmonary toxicity, appear to potentiate the toxic effects of RT. For example, in a small series of 24 lung cancer patients treated with 40 Gy of RT with concurrent doxorubicin (10 mg/m^2), 13 (54%) developed radiation pneumonitis. Combinations of RT and chemotherapeutic agents with known pulmonary toxicity have generally been associated with higher rates of radiation pneumonitis, including mitomycin-C (Rancati et al. 2003) and bleomycin (Einhorn et al. 1976). The taxane docetaxel, with RT in the locally advanced setting and with gemcitabine in the metastatic setting (Kouroussis et al. 2004), has also been associated with high rates of pneumonitis. For example, in a Japanese phase II study (Onishi et al. 2003), lung cancer patients were treated with 60–66 Gy with concurrent weekly docetaxel (20 mg/m^2). The rate of grade 3–4 pneumonitis was 47%. Fortunately, the chemotherapeutic agents most commonly utilized with RT for lung cancer, such as cisplatin, carboplatin, paclitaxel, and etoposide, have not been consistently shown to increase the risk of pneumonitis (Robnett et al. 2000; Graham et al. 1999; Hope et al. 2006; Hernando et al. 2001). The impact of chemotherapy in the setting of TBI is shown in Fig. 8.

7 Special Topic

7.1 Abscopal Effects: Autoimmune Events

Contralateral pneumonitis following incidental ipsilateral lung irradiation for breast cancer utilizing tangential parallel fields was first reported in 1964. This was intensely studied by Morgan and Breit who lavaged the contralateral lung in a series of breast cancer patients post-irradiation. Although asymptomatic, the lavaged contralateral lung yielded an increase in lymphocytes and macrophages which was termed an autoimmune effect. Finklestein, Rubin and Williams observed a dramatic increase in the contralateral lung abnormalities following ipsilateral lung irradiation. Other investigators have confirmed abscopal out-of-field effects when confining radiation to the apex or base of lung attributed to cytokine cascades, inducing an inflammatory response in shielded lung segments. DNA damage in micronuclei are also evident in addition to lymph acidic infiltrates. The induction

of an acute respiratory distress syndrome (ARDS) in *out of field* lung, induced by *in field* radiation pneumonitis can be fatal. Bennett and Million reported that 8% (6/72) of lung cancer patients at necropsy had ARDSas did 3% of patients iiradiated for breast cancer, which had been attributed to bilateral radiation pneumonitis.

7.2 Malignant Pleural Mesothelioma

Local disease progression is the primary obstacle to cure for patients with pleural mesothelioma, even after aggressive surgery. Tumor can spread anywhere within the pleural space, including the fissures, diaphragmatic and pericardial surfaces, and the pleural recesses. RT techniques have historically been suboptimal to fully encompass sites at risk while respecting normal tissue tolerance. Recently, there has been growing interest in IMRT for these patients as it tends to be well suited for the delivery of the necessary concave dose distribution. In an initial report from MD Anderson, a low rate of lethal radiation pneumonitis was noted (1.6%, 1/62) (Stevens et al. 2005). A subsequent report from Harvard could not replicate the safety of this approach. Of 13 patients treated with IMRT, 6 experienced lethal radiation pneumonitis (46%, 6/13) (Allen et al. 2006). The MLD was 15 Gy for patients who developed pneumonitis (all lethal) versus 13 Gy for those who did not ($p = 0.07$). Similarly, the V20 was 18% for patients who developed pneumonitis versus 11% for those who did not ($p = 0.08$). In a reanalysis of the data from MD Anderson, fatal pulmonary toxicities (whether previously ascribed to RT or not) were noted to have occurred in 10% of patients. These events were more common in patients with higher V20 values (Rice et al. 2006). While IMRT may be particularly suited for the concave targets encountered with the postoperative treatment of mesothelioma, dose to the contralateral lung must be minimized. In this setting, we recommend limiting the V20 to 4–10% and the MLD to <8 Gy (Allen et al. 2006; Rice et al. 2006) (Table 7).

7.3 Functional Imaging

There is growing interest in utilizing functional imaging, such as SPECT, in the RT treatment planning process. In lung perfusion SPECT, injected radiolabeled microspheres are trapped in the small capillaries of the lung. The local concentration, in principle, is proportional to regional pulmonary blood flow. Lung function is nonuniform in most patients with lung cancer secondary to COPD. SPECT provides a three-dimensional map of functioning alveolar–capillary units.

When selecting beam orientations for a patient with an intrathoracic tumor, one can orient the beam such that it preferentially passes through hypoperfused regions of lung (Marks et al. 1995). Similarly, the quantitative functional information from SPECT can be used to define dose/volume constraints for IMRT planning (McGuire et al. 2006; Shioyama et al. 2007). These approaches assume that hypofunctional regions of lung are permanently nonfunctioning. However, if hypoperfusion is caused by an obstructing tumor, then it may be temporary and may *improve* with tumor shrinkage, and this should be taken into account in the RT planning process. In our experience, areas of hypoperfusion that are adjacent to large central lung lesions often demonstrate reperfusion on post-RT scans. Conversely, areas of hypoperfusion that are "apart" from the gross tumor do not demonstrate reperfusion post-RT. Thus, care must be taken when incorporating such functional information into the planning process.

7.4 Respiratory Motion

The most effective way to reduce the complications of pulmonary irradiation is to decrease the volume of lung that is exposed to the beam. It has been amply demonstrated that tumors within the lung may move with respiration. This is most commonly accounted for by adding a safety margin (the CTV → PTV expansion accounts for daily setup error and organ motion). Though this is an easy solution to the problem, it is clearly detrimental as it leads to increased normal tissue exposure.

Three strategies to account for respiratory motion are breath hold (often at deep inspiration, termed DIBH), respiratory gating (Mageras and Yorke 2004; Jiang 2006), and tracking. In DIBH, treatment planning and delivery is performed with the patient holding their breath in deep inspiration. DIBH requires a compliant patient with sufficient pulmonary function to hold their breath for a moderate length of time. DIBH has the added advantage of delivering treatment to an expanded lung, thus irradiating a smaller fraction of the lung for a given target size. Respiratory gating, on the other hand, allows the patient to breathe freely and the beam is turned on during a specified phase of the respiratory cycle and turned off when that phase has passed (Giraud et al. 2006). This technology requires a signal, usually an external marker acting as a surrogate for respiratory motion, to gate the linear accelerator. It is essential to have CT images corresponding to the desired phase of the respiratory cycle for treatment planning, often accomplished using 4D CT technology. Tracking refers to systems where the treatment beam adjusts, in real time, to movements of the intra-thoracic contents. This is most commonly performed using a CyberKnife (Accuray, Sunnyvale, CA) (Nuyttens et al. 2006), but has also been suggested to be possible with synchronized movement of

Table 9 Randomized trials of amifostine [a]

		Grade ≥2 pneumonitis	Fibrosis
Author *Affiliation*	*n*	Amifostine versus placebo	Amifostine versus placebo
Antonadou et al. (2001) *Greece*	146	9 versus 43%[a] ($p < 0.001$)	28 versus 53% ($p < 0.05$)
Antonadou et al. (2003) *Greece*	73	30 versus 67%[b] ($p = 0.009$)	29 versus 50% ($p = 0.16$)
Leong et al. (2003) *Singapore*	60	–	–
Komaki et al. (2004) *M.D. Anderson Cancer Center*	62	0 versus 16%[b] ($p = 0.02$)	–
Movsas et al. (2005) *RTOG 98-01*	243	8 versus 16.7%[b] ($p > 0.05$)	–

RT doses variable, 1.2 Gy b.i.d. to 69.6 Gy (Komaki et al. 2004; Movsas et al. 2005) or 2 Gy q.d. to 55–66 Gy (Antonadou et al. 2001, 2003; Leong et al. 2003); Chemotherapy usage variable, no chemotherapy (Antonadou et al. 2001), concurrent therapy (Antonadou et al. 2003; Komaki et al. 2004), and induction + concurrent (Movsas et al. 2005; Leong et al. 2003)

[a] Rates at 3 months follow-up

[b] Grade ≥3

Some of the data are estimated from data, figures, and tables provided in the citation

multi-leaf collimators (Keall et al. 2005). Respiratory gating and tracking are potentially less demanding on a patient compared with the breath-hold techniques.

8 Prevention

The therapeutic ratio is derived from differences between the tumor control probability (TCP) curve and the normal tissue complication probability (NTCP) curve. Shifting the NTCP curve away from the TCP curve will theoretically improve the therapeutic ratio, such that the same RT dose will be associated with a lower risk of injury or an escalated dose of RT can be administered with the same risk of injury.

Several pharmacologic agents have been employed to mitigate the acute and chronic consequences of incidental RT on normal lung tissue (shift the NTCP curve). Amifostine and pentoxifylline have shown the most promise and are discussed further here.

8.1 Amifostine

Amifostine (WR-2721; Ethyol, Medimmune Inc, Gaithersburg, MD), is a thio-organic pro-drug which is converted in vivo to the active free thiol (WR-1065) by vascular endothelial cell alkaline phosphatase. Amifostine is believed to scavenge harmful free radicals produced by the interaction of ionizing radiation and water molecules. Multiple randomized studies and a meta-analysis (Sasse et al. 2006) have tested the utility of amifostine in patients receiving RT for lung cancer with conflicting results (Table 9). The largest study was performed by the RTOG (Movsas et al. 2005). The incidence of grade ≥3 esophagitis, the primary endpoint of the study, was 30% with amifostine versus 34% without ($p = 0.9$). The incidence of grade ≥3 pulmonary toxicity was lower in patients receiving amifostine (9 vs. 16%), but this was not statistically significant. This study has been criticized since the drug was given *once* daily (4 days/week) and the RT was given *twice* daily (5 days/week), and thus 60% of the RT fractions were delivered *without* the protector. Conversely, there are several single-institutional randomized trials suggesting protection with amifostine, in which the drug was used during a larger fraction of radiation treatments (Table 9). Presently, given the acute toxicity associated with amifostine (nausea/vomiting, hypotension, infection, rash), and the mixed clinical results, amifostine is not currently utilized widely for patients receiving thoracic RT.

8.2 Pentoxifylline

Pentoxifylline (Trental, sanofi aventis, Bridgewater, NJ) is an ethyl xanthine derivative with immunomodulating and anti-inflammatory activity. It is primarily prescribed for patients with intermittent claudication secondary to its ability to improve erythrocyte flexibility. Preclinical studies of pentoxifylline are mixed. Koh et al. (1995) showed that pentoxifylline did not mitigate acute decline in lung perfusion after single fraction RT in rats. However, it did seem to facilitate late recovery in perfusion compared to rats receiving RT alone. In contrast, Stelzer et al. (1996) showed that rats receiving pentoxifylline maintained higher perfusion ratios than irradiated controls during weeks 3–5. However, the protection was transient and subsequent recovery from lung injury was inhibited at later times.

In a small study of 40 patients irradiated for lung or breast cancer, the addition of pentoxifylline appeared to reduce the incidence of lung injury (Ozturk et al. 2004). In particular, there were decreased perfusion defects, decreased chest X-ray abnormalities, and smaller decline in DLCO in patients receiving pentoxifylline. Additional study of this approach may be warranted.

9 Management

Evans and Leucutia stated in 1925 that "the treatment of the changes produced by radiation [in the lung] can only be symptomatic (Evans and Leucutia 1925)". This remains true today. Studies evaluating the optimal treatment of RT-induced lung injury are scarce and restricted to retrospective reports. Most recommendations are based on expert opinion.

9.1 Acute Pneumonitis

The traditional treatment for acute pneumonitis is oral steroids, typically prednisone. Symptomatic improvement after steroid therapy was first reported by Cosgriff and Kligerman (1951), who noted that although the acute symptoms rapidly abated, fibrosis eventually developed. There are no robust studies assessing the optimal corticosteroid or dosing schedule, though it has been observed that symptoms may recur with a rapid taper or when corticosteroids, prescribed for other reasons, are discontinued after completion of RT (Castellino et al. 1974). We recommend oral prednisone (Salinas and Winterbauer 1995), typically 40–60 mg daily for 1–2 weeks, followed by a slow taper (reducing $\sim$10 mg every 1–2 weeks). It must be remembered that there is a differential diagnosis for shortness of breath occurring after RT. This includes tumor progression, drug toxicity, cardiac disease, pulmonary embolus, anemia, and infection. Since steroids can exacerbate an infection, an initial short course of antibiotics may be considered. The majority of patients with pneumonitis recover. However, symptoms can be serious enough to require oxygen or hospitalization, and can be potentially fatal.

9.2 Chronic Fibrosis

It is generally assumed that established radiation fibrosis is irreversible. However, as our understanding of the physiology of radiation-induced fibrosis has increased, several pharmacologic agents have been evaluated and some have shown some promise in reversing subcutaneous fibrosis, which may be relevant to fibrosis in the lung. Such agents have included corticosteroids, pentoxifylline, alpha-tocopherol, hyperbaric oxygen, superoxide dismutase, angiotensin-converting enzymes, and combined pentoxifylline and alpha-tocopherol (Delanian and Lefaix 2007).

After promising results were obtained in a phase II study (Delanian et al. 1999), performed a randomized study in which 24 women with breast cancer and superficial RT-induced fibrosis were randomized to pentoxifylline (800 mg/day) and alpha-tocopherol (Vitamin E, 1000 U/day), pentoxifylline plus placebo, alpha-tocopherol plus placebo, or double placebo (Delanian et al. 2003). Treatment was continued for 6 months. There was a significant reduction in both fibrotic surface regression (60 vs. 43%, $p = 0.04$) and volume regression as based by ultrasound (73 vs. 51%, $p = 0.054$), comparing the combined treatment arm with the control arm. Neither pentoxifylline alone nor alpha-tocopherol alone was effective. Interestingly, there was a marked decrease in fibrosis in the double placebo arm. Another agent that has shown preliminary promise is liposomal superoxide dismutase. In a preclinical study (Lefaix et al. 1996), this agent has been shown to reverse RT-induced fibrosis with regeneration of normal tissue in the previously fibrotic region. A single arm clinical study has also been reported (Delanian et al. 1994). Patients ($n = 34$) with palpable radiation-induced fibrosis were treated with 3 weeks of liposomal Cu/Zn superoxide dismutase. All patients showed some clinical regression within weeks of initiation of treatment. Though promising, further study is necessary to confirm these findings. Currently there are no widely accepted treatments for lung fibrosis and management continues to be entirely supportive.

10 Future Directions

Progress regarding the predictors of RT-induced lung injury requires further understanding of the following.

Endpoint interaction

The study of RT-induced lung injury is confounded by the use of ambiguous endpoints. Many scoring systems combine radiologic, functional, and symptomatic criteria to define a "global score". Because each endpoint may have different dose–volume dependence, this approach may be counterproductive. Therefore, we recommend that further study of lung injury explicitly consider symptomatic, functional, and radiographic endpoints separately.

Impact of clinical factors

The impact of clinical factors (e.g., pre-RT functional status, tobacco use) and systemic agents (e.g., chemotherapy) on the risk of RP needs further study.

Table 10 Landmark studies of RT-induced lung injury

Author *Place, year*	Topic
Groover et al. (1922) *Washington, D.C., 1922*	Radiation pneumonitis first described
Davis (1924) *Rochester, MN, 1924*	First systematic animal studies demonstrating classic histologic changes in the lungs after RT
Newton (1960) *London, UK, 1960*	Fatal radiation pneumonitis described after whole lung irradiation
Choi and Kanarek (1994), Choi et al. (1990) *Boston, MA, 1977*	Early prospective studies of radiation pneumonitis and changes in PFTs after RT
Mah et al. (1987) *Toronto, Canada, 1987*	Early prospective studies of dose-dependent radiographic changes after RT

PFTs pulmonary function tests

Organ interactions

Some pre-clinical data suggest that there may be interactions between the lung and heart in the development of RT-associated dyspnea. In rats, the respiratory rate after thoracic RT was related to the volume of lung and heart irradiated (Barcellos-Hoff and Dix 1996; Ewan et al. 2002; Yi et al. 1996).

Impact of an in situ *lung cancer on the risk of radiation-induced lung injury*

The data for whole lung radiation are derived essentially from patients without primary lung cancers (e.g., elective lung RT for sarcoma), versus fractionated partial lung radiation, often derived from patients with gross lung cancers. The confounding effect of tumor in the lung makes the study of RT-induced lung injury extremely challenging. Indeed, in several studies, the ability to predict for RT-induced lung injury is improved in patients without large central or occluding tumors. Thus, it might be relevant to develop separate predictive models in patients with intact intraparenchymal lung tumors versus those without such a lesion (i.e., postresection RT for lung cancer, or RT for other thoracic tumors).

Radiation response modifiers

Amifostine is a thio-organic prodrug believed to scavenge harmful free radicals mediating RT-induced injury. Several randomized studies in patients receiving RT for lung cancer note a reduction in RP in the amifostine arm (Ehrhart et al. 1997; Rube et al. 2000; Epperly et al. 1999), although the largest study (from RTOG) was negative (Haiping et al. 2006). However, this study has been criticized because the drug was administered once daily (4 days/week), whereas the RT was delivered twice daily (5 days/week), and thus 60% of the RT fractions were delivered without the protector. Such mixed results, combined with the acute toxicities of amifostine (nausea/vomiting, hypotension, infection, and rash), have dissuaded many from using it in routine practice. One small randomized study demonstrated a protective effect of pentoxifylline, but pentoxifylline is not currently used in routine clinical practice (Nishioka et al. 2004).

Biomarkers

Additional work is needed to assess the predictive ability offered by biomarkers (see Bentzen et al. in this issue), such as TGF-β (measured before and/or during RT) (Table 1) (Denham and Hauer-Jensen 2002).

11 History and Literature Landmarks

Almost immediately after Wilhelm Conrad Röentgen discovered "a new kind of ray" in 1895, X-rays were employed to shrink malignant tumors (Pusey 1905) (Table 10). Primitive X-ray machines were limited by their low energy, and were consequently only able to treat superficial tumors effectively (Bernier et al. 2004). Initially, most tumors were managed with only a few relatively large doses of RT. Although reasonable tumor control was achieved, it was noted that fibrosis often developed in surrounding soft tissues (Evans and Leucutia 1925; Tyler and Blackman 1922). Pulmonary and pleural reactions were, as expected, seldom observed (Evans and Leucutia 1925). Technological advances in the early twentieth century allowed deeper-seated tumors to be treated. The effects of RT on normal tissues deep to the skin surface were subsequently noted. In 1921, Groover et al. (1922) reported the following to the Southern Medical Association:

> In a considerable number of cancers of the breast which have been treated…an irritative, unproductive cough has developed….with a certain amount of dyspnea. Shortly afterward certain pulmonary changes have been demonstrable in the roentgenogram in cases which have previously shown no evidence of intra-thoracic pathology…In at least one case the infiltration assume(d) a more fibrotic appearance. The natural assumption would be that these pulmonary phenomena are due to metastasis, but certain clinical observations have led us to

> consider seriously the possibility of their being caused by the treatment instead…It is at once apparent that it is of vital importance to determine the significance of these pulmonary phenomena…and if due to treatment…they become of very great therapeutic significance.

Shortly thereafter, Tyler and Blackman (1922), Hines (1922), and others reported similar findings. Kenneth Davis, a fellow in Roentgenology at the Mayo Clinic, designed the first extensive animal studies that specifically evaluated the effects of RT on the lungs (Davis 1924). His experiments demonstrated thickening of the alveolar septi and obliteration of alveolar sacs, thickening of the arterial tunica media, and extravasation of "coagulum" and desquamated epithelial cells into the alveoli. The study of RT-induced lung injury has expanded dramatically since these initial reports nearly a century ago.

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Heart, Coronary Arteries, Aorta and Great Vessels, Arteries and Veins, Microcirculation

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Abstract

- Radiotherapy can cause injury to any of the substructures of the heart, including the pericardium, valves, myocardium, and arteries.
- Myocardial injury appears to occur secondary to the vascular events.
- Coronary artery disease often occurs years to decades post-radiotherapy, and is associated with an increased risk of MI and cardiac death.
- Subclinical evidence of cardiovascular disease consistent with microvascular injury can be detected within months of completion of radiotherapy, and the clinical significance of this is unclear.
- Valves have been generally considered to be unaffected by radiotherapy, but recent data suggest that valvular injury is relatively common following radiotherapy.
- The risk of pericarditis following radiotherapy has a strong volume dependence.
- A variety of chemotherapy agents (alone and in combination with radiotherapy) are associated with heart disease.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
AV	Atrioventricular
NT-proBNP	Brain natriuretic peptide and N-terminal fragment
CAC	Coronary artery calcification
EBCTCG	Early breast cancer trialists' collaborative group

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EGFR	Epidermal growth factor receptor
HR	Hazard ratios
HER2	Human epidermal growth factor receptor 2
LAD	Left anterior descending artery
LCX	Left circumflex artery
LSS	Life span study
MR	Magnetic resonance
NTCP	Normal tissue complication probability
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
RT	Radiation treatment
RCA	Right coronary artery
RMA	Right marginal artery
SE	Standard error
SIR	Standardized incidence ratios
SEER	Surveillance, epidemiology and end-results cancer registries
VEGF	Vascular endothelial growth factor

1 Introduction

Circulatory diseases are major causes of morbidity and mortality, accounting for 30–50 % of all deaths in most developed countries. Both radiotherapy and chemotherapy used to treat patients with for malignant diseases may cause early and late cardiovascular toxicity. Whereas cardiovascular disease following radiotherapy is usually observed from 5 to 10 years of follow-up onwards, chemotherapy-related toxicity occurs with a more variable timecourse. Because of the improved prognosis of many patients treated for malignancies, cardiovascular disease is becoming an increasingly important late event that must be understood in order to develop effective interventions. The Biocontinuum of adverse and late effects of the heart is shown in Fig. 1.

2 Anatomy and Physiology: The Functional Unit

2.1 Anatomy

The cardiovascular system consists of the heart, arteries, and veins.

The heart is a hollow, muscular organ lying within a two-layered sac, the pericardium. It is a four-chamber pump consisting of two atria and two ventricles. The heart valves maintain the unidirectional flow of blood in the heart by opening and closing depending on the difference in pressure on each side. The valves between the atria and ventricles prevent backflow of blood from the ventricles to the atria during systole. In addition, the semilunar valves between the heart and the aorta and the heart and the pulmonary arteries prevent backflow from the aorta and the pulmonary arteries into the ventricles during diastole. The heart valves do not have a blood supply, but they are covered with a specific type of endothelium.

Although the heart is filled with blood, the heart muscle requires its own blood supply, namely the coronary arteries. There are two main coronary arteries, the left and right. Both of these arteries originate from the root of the aorta, immediately above the aortic valve. The left main coronary artery (or left main trunk) branches into the circumflex artery (LCX) and the left anterior descending artery (LAD), and the right coronary artery (RCA) branches into right marginal artery (RMA) and the posterior descending artery (PDA). The circumflex artery supplies the left atrium, the side, and back of the left ventricle. The left anterior descending artery supplies the front and bottom of the left

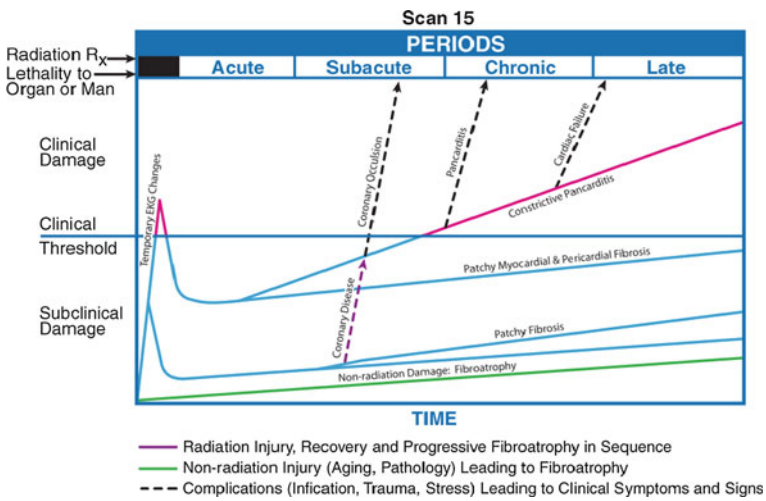

Fig. 1 The biocontinuum of RT-induced heart injury (Published with kind permission of Saunders: Rubin Casarett: Clinical Radiation Pathology, 1968)

ventricle and the front of the septum. The right coronary artery supplies the right atrium, the right ventricle and the bottom portion of both ventricles and the back of the septum (see Fig. 2).

2.2 Histology and Functional Subunit

The major part of the heart, the myocardium, is constituted of cardiac muscle. The inner surface of the myocardium is lined with endocardium, and the outer surface with epicardium. The epicardium is the inner visceral layer of the pericardium. The outer part of the epicardium is lined with mesothelium. Large blood vessels and nerves are found in the epicardium.

All arteries possess three coats: a tunica intima, a tunica media, and a tunica adventitia. The tunica intima is composed of a smooth layer of thin endothelial cells based upon a delicate basement membrane that penetrates between the subendothelial connective tissue and the underlying smooth muscle cells. The tunica media consists of smooth muscle cells and an elastic network. The tunica adventitia is a poorly defined layer of connective tissue in which elastic and nerve fibers and in case of large arteries, small, thin-walled nutrient vessels, and the vasa vasorum, are dispersed.

The three separate layers generally seen in arteries are not well defined in veins. Veins are in general thin-walled with relatively large lumina.

The essential function of the heart is to pump blood to various parts of the body. De-oxygenated blood from the body enters the right atrium, passes into the right ventricle and is pumped by the right ventricle to the pulmonary artery into the lungs. Oxygenated blood returns from the lungs to the heart into the left atrium, passes into the left ventricle and is pumped into the body through the aorta. Throughout the body, blood delivers oxygen and nutrients, picks up waste materials, and flows back to the heart again. The muscle wall from the ventricles is thicker and stronger than the muscle wall from the atria.

Cardiac contraction is generated by the myocytes. Myocytes are highly differentiated cells rich in mitochondria. Adjacent myocytes are separated by intercalated disks and they form a network of branching fibers with the ability to carry forward an action potential. Myocytes contract spontaneously and continuously, under regulation of electrical impulses. The electrical impulse initiates in the sinoatrial node (pacemaker), at the junction between right atrium and superior vena cava, and is propagated to the atrioventricular (AV) node, located between the atria and the ventricles. The distal part of the AV node, the bundle of His, splits into two branches to activate the left and right ventricle, respectively. Norepinephrine and its receptors regulate heart rate and the force of contraction.

3 Pathophysiology

3.1 Pathophysiology of Radiation-Related Toxicity

All structures of the heart and major arteries can be damaged by ionizing radiation. See for summary on risk factors Table 1.

3.1.1 Heart Muscle

The normal adult heart is a slow turnover organ, with low proliferative activity. Previously, it was thought that cardiomyocytes were terminally differentiated, without the capacity for cell division. In order for the myocardium to maintain its vital role, it was assumed that loss of myocytes as a result of injury or aging was compensated by hypertrophy of remaining myocytes or by fibrosis. Recent studies have shown that the mammalian heart has the inherent ability to replace its cardiomyocytes through the activation of a pool of resident primitive cells or the recruitment of hematopoietic stem cells (Anversa et al. 2007).

In addition, there is new evidence that circulating mononuclear cells, including progenitor endothelial cells, can home to sites of ischemic damage in the heart and contribute to new vessel formation by transdifferentiation into endothelial cells and secretion of angiogenic cytokines (Caplice and Doyle 2005).

3.1.2 Arteries

Radiation may damage the endothelium of blood vessels. In large arteries this damage may lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism (Stewart et al. 1995; Veinot and Edwards 1996; Adams and Lipshultz 2005). Experimental data showed that early inflammatory changes in the endothelial cells of irradiated large vessels may lead to monocyte adhesion and trans-migration into the subendothelial space. In the presence of elevated cholesterol levels, these invading monocytes transform into activated macrophages, which ingest lipids and form fatty streaks in the intima, thereby initiating and accelerating the process of atherosclerosis. Proliferation of myofibroblasts is then stimulated by the production of inflammatory cytokines, resulting in a reduction of the arterial lumen (Vos et al. 1983; Tribble et al. 1999; Stewart et al. 2006). Animal studies have shown that radiation predisposes to the formation of macrophage rich, unstable plaque, rather than stable collagenous plaque (Stewart et al. 2006; Pakala et al. 2003). Such lesions are more likely to rupture and cause a fatal heart attack or stroke (Stewart et al. 2010) (see Fig. 3 for histopathology, and Fig. 4 for pathogenesis of vessel injury).

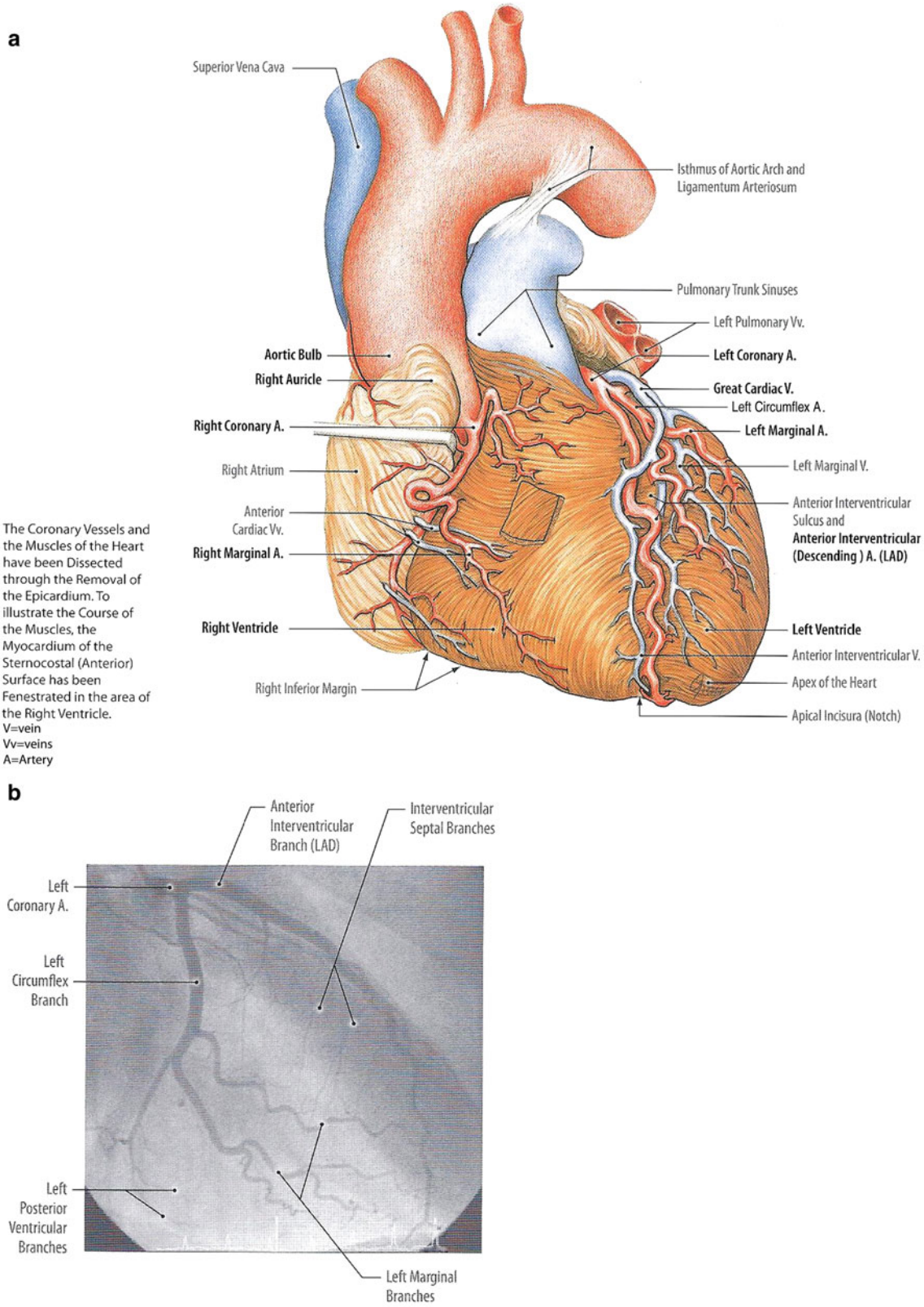

Fig. 2 **a** Gross anatomy of the heart with an emphasis on depiction of coronary arteries. **b** Selective coronary angiogram using an anteroposterior projection demonstrating the left coronary arteries and interventricular branches (with permission from Tillman 2007)

Table 1 Risk factors for the different manifestations of radiation-associated heart disease

Risk factor	Pericarditis	Cardiomyopathy	Coronary artery disease	Arrhythmia	Valvular disease	All causes cardiac death	References
Total dose; (>30–35 Gy)	X	X	X	X	X	X	Schultz-Hector and Trott (2007), Heidenreich et al. (2003), Moser et al. (2006)
Dose per fraction (≥2.0 Gy/day)	X	X	X	Likely	Likely	X	Cosset et al. (1988)
Volume of heart exposed	X	X	X	Likely	Likely	X	Schultz-Hector and Trott (2007), Hancock et al. (1993a)
Younger age at exposure Increased	–	X	X	Likely	Likely	X	Aleman et al. (2007)
Increased time since exposure	–	X	X	X	X	X	Aleman et al. (2007)
Use of adjuvant cardiotoxic chemotherapy	–	X	–	X	X	X	Aleman et al. (2007), Myrehaug et al. (2008), Moser et al. (2006)
The presence of other known risk factors in each individual such as current age, weight, lipid profile, and habits such as smoking	–	–	X	–	–	X	Aleman et al. (2007), Glanzmann et al. (1998)

Modified with permission from Table 10.5 from "BioPediatric Complexities of Growth and Development" Cardiovascular Effects of Cancer Therapy by Adams, Constine, Duffy and Lipshultz (and from Simbre et al. Curr Treat Options Cardiovasc Med 2001) in Survivors of Childhood and Adolescent Cancer (second edition) published by Springer

The anterior location of the heart in the chest, and the relative anterior location of the coronary arteries (in particular the LAD) within the heart, has been suggested to explain the increased risk of radiation-associated heart disease that is observed when thoracic radiation treatment is "weighted" to be preferentially delivered from the anterior direction (Stewart et al. 1995; Byhardt et al. 1975; Morton et al. 1973).

3.1.3 Valves

Since valves do not have blood vessels, radiation-related valvular disease cannot be explained by (micro) vascular damage. However, possibly this damage is consequential to late injury of the surrounding myocardial endothelium leading to fibrosis (Veinot and Edwards 1996).

Valvular leakage could also be secondary to dilated cardiomyopathy. Cardiomyopathy is usually caused by chemotherapy (especially anthracyclines) but may also be seen after radiotherapy probably secondary to vascular damage.

3.1.4 Pericardium

In experimental studies in dogs, rabbits, or rats a single dose of greater than or equal to 15 Gy has been shown to lead to a reversible exudative pericarditis, occurring at around 100 days (Schultz-Hector 1992). Edematous swelling, fibrotic thickening, and adhesions of epicardium and pericardium may develop (Schultz-Hector and Trott 2007; Lauk et al. 1985).

In mammals, the encasement of the heart by a rigid nonpliable pericardium results in characteristic pathophysiologic effects, including impaired diastolic filling of the ventricles, exaggerated ventricular interdependence, and dissociation of intracardiac and intrathoracic pressures during respiration.

In humans, acute pericarditis/pericardial effusion may be observed following irradiation including a considerable part of the heart (Carmel and Kaplan 1976; Cosset et al. 1988). Pericardial effusions may resolve spontaneously. However, constrictive pericarditis does develop in a minority of patients and surgery may be needed (see below).

3.2 Pathophysiology of Chemotherapy-Induced Cardiotoxicity

The mechanisms of cardiotoxicity vary widely among different chemotherapeutics (Kang 2001). The cardiovascular

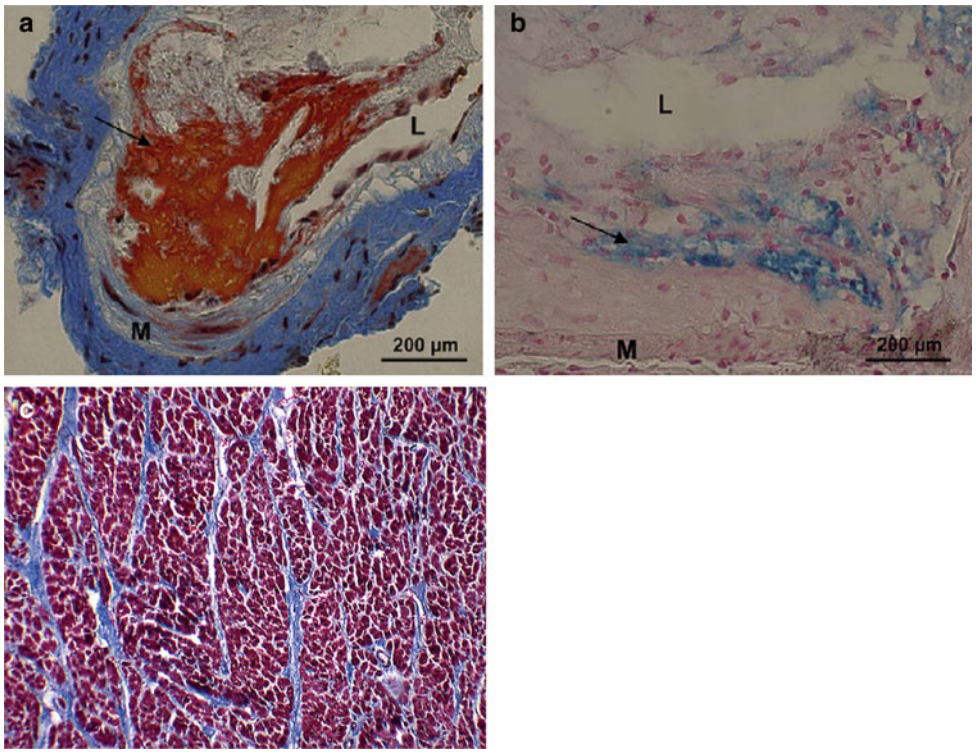

Fig. 3 Pathology. Examples of thrombotic phenotypes of carotid lesions in irradiated ApoE -/- mice. **a** Martius-scarlet-blue staining of lesions 30 weeks after 14 Gy, in which fibrin deposits are stained red (arrow). **b** Perl staining in which iron is stained blue (arrow) in lesions 34 weeks after 20 Gy × 2.0 Gy. L = lumen; M = media. (From Hoving et al. 2008). **c** Example of myocardial fibrosis (fatal) in a patient many years after irradiation for Hodgkin Lymphoma. Whereas normally there should be very little collagen among the dark red myocytes, this heart muscle is criss-crossed by multiple bands of blue collagen. Gomori trichrome stain (with permission from Darby et al. 2010)

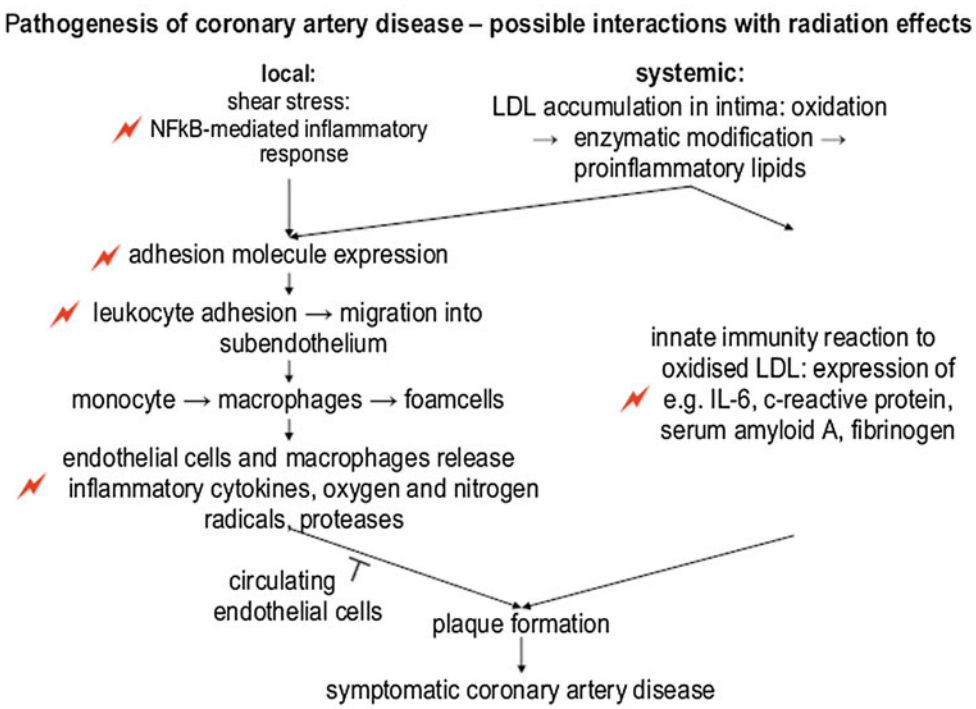

Fig. 4 Schematic representation of the most important steps of pathogenesis of coronary artery disease. Events that have also been observed after radiation are indicated by flashes (with permission from Schultz-Hector and Trott 2007)

Table 2 Potential mechanisms of cardiovascular damage induced by anticancer treatments. A summary of probable mechanisms of cardiotoxicity induced by a range of chemotherapeutic and chemoprevention agents[a] from Albini et al. JNCI 2010 (Albini et al. 2010)

		Effects						
		Systemic-macroenvironment						
		Mitochondrial				Local-microenvironment		
Examples of chemotherapeutics	Possible cardiovascular damage	DNA damage	ATP block	Apoptotic protein release	ROS generation	Endothelial cell damage/ spasms	Cell signaling/ survival block	ADCC
Anthracyclines and anthraquinolones	CHF, LVD, acute myocarditis, and arrhythmia	+	+	+	+	−	−	−
Capecitabine, 5-fluorouracil, cytarabine	Ischemia, pericarditis, CHF, and cardiogenic shock	+	+	+	+	+	−	−
Paclitaxel, vinca alkaloids	Sinus bradicardia, ventricular tachycardia, atrioventricular block, hypotension, CHF, and ischemia	+	?	?	?	?	−	−
Cyclophosphamide	Neurohumoral activation, mitral regurgitation	+	?	?	?	+	−	−
Imatinib	Arrythmias, CHF, angioedema, and LVD	−	+	+	−	<>	<>	−
Sorafenib	Hypertension, arrhythmias	−	?	?	−	<>	<>	−
Sunitinib	Hypertension, arrhythmias	−	+	?	−	<>	<>	−
SERMs	LDL/HDL modulation, thromboembolism	−	−	−	−	−	−	−
Trastuzumab	Arrhythmias, CHF, angioedema, and LVD	−	−	−	−	<>	<>	+
Bevacizumab	Hypertension, thromboembolism, and GI tract bleeding	−	−	−	−	<>	<>	−
COX-2–specific inhibitors	Thromboembolism	−	−	−	−	<>	−	−
Thorax irradiation	Myocardial fibrosis, valvular heart disease, and LVD	+	−	<>	+	+	−	−

[a] + = likely; − = unlikely; ? = unknown; <> = probable. *ADCC* antibody-dependent cellular cytotoxicity; *CHF* congestive heart failure; *COX-2* cyclooxygenase 2; *GI* gastrointestinal tract; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *LVD* left ventricular dysfunction; *ROS* reactive oxygen species; *SERMs* selective estrogen receptor modulators. For references, see text

system has numerous different targets that can be subject to damage (Albini et al. 2010). Some drugs directly damage cardiomyocytes or cause inflammation of the pericardium. Some drugs damage the intima of blood vessels and thereby engage the coagulation system, promoting blood clotting in the vessels predisposing to thromboembolic events and consequent cardiovascular and cerebrovascular ischemia. Some drugs cause hypertension with acute and long-term effects on cardiac hypertrophy and insufficiency. See for summary on potential mechanisms and risk factors Tables 2 and 3.

3.2.1 Anthracyclines

Anthracycline-induced cardiotoxicity has been divided into acute, occurring immediately after infusion of the drug, early onset chronic progressive, occurring during or within a year after treatment, and late-onset chronic progressive, occurring more than a year after treatment with anthracycline.

Several different biochemical changes are seen in cellular and animal studies after exposure, and the cardiotoxicity after exposure is likely to be the result of several biochemical insults (Barry et al. 2007; Giantris et al. 1998; Herman et al. 1999; Wouters et al. 2005). Iron-mediated free radical formation leading to apoptosis seems to be important for acute cardiotoxicity (Minotti et al. 2004). However, chronic cardiomyopathy seems to develop due to a combination of diverse processes as follows: increased membrane lipid peroxidation; inhibition of nucleic acid and protein synthesis; release of vasoactive amines; changes in

Table 3 Risk factors for Anthracycline-induced cardiotoxicity in decreasing order of importance

Risk factor	Features
Total cumulative dose	Most significant predictor of abnormal cardiac function
Age	For comparable cumulative doses, younger age predisposes to greater cardiotoxicity
Length of follow-up	Longer follow-up results in higher prevalence of myocardial impairment
Gender	Females more vulnerable than males for comparable doses
Concomitant mediastinal irradiation	Enhanced toxicity; not clear whether additive or synergistic

Modified with permission from Table 10.4 from "BioPediatric Complexities of Growth and Development" Cardiovascular Effects of Cancer Therapy by Adams, Constine, Duffy and Lipshultz (and from Simbre et al. Curr Treat Options Cardiovasc Med 2001) in Survivors of Childhood and Adolescent Cancer (second edition) published by Springer

adrenergic function and adenylate cyclase; abnormalities in the handling of Ca^{2+}; reduced expression of specific genes possibly caused by altered expression and function of anthracycline sensitive transcriptional regulatory proteins; impairment of membrane binding, assembly, and enzymatic activity of mitochondrial creatine kinase; induction of nitric oxide synthase, leading to nitric oxide and peroxinitrite formation and to inactivation of myofibrillar creatine kinase or activation of metalloproteinases (Wouters et al. 2005; Minotti et al. 2004). Whether and how these processes contribute to the development of chronic cardiotoxicity is still not clear. Moreover, it is not clear how iron and reactive oxygen species interact with these processes.

Compared with the cells of other organs, cardiac cells are more susceptible to free radical damage because of the highly oxidative metabolism and relatively poor antioxidant defenses (Doroshow et al. 1980). Additionally, anthracyclines have a high affinity for cardiolipin present in the inner mitochondrial membrane leading to accumulation of anthracyclines in cardiomyocytes (Goormaghtigh et al. 1990).

The anthracycline damage to cardiomyocytes causes apoptosis, thereby decreasing the number of myocardial cells (Arola et al. 2000). The wall of the left ventricle becomes thinner, and the contractility of the myocardium decreases, leading to depressed overall function of the left ventricle (Lipshultz et al. 1991; Giantris et al. 1998; Sorensen et al. 1995).

Recent research indicates that anthracyclines cause damage to the cardiac progenitor cells in particular, causing massive apoptotic death, thus reducing the reserve of functionally competent cardiac progenitor cells. This process may contribute to the development of anthracycline-mediated cardiomyopathy in children. In adults, decrease in cardiac stem cells may impair cardiac response to injury. The cumulative effects of anthracyclines on various types of cardiac tissue are summarized in Fig. 5 (Chen et al. 2011). In the future, cardiac progenitor cells may have a potential role in ameliorating cardiotoxicity of cancer therapy. A recent study in rats suggested that it might be possible to prevent cardiomyopathy caused by chemotherapy by obtaining cardiac progenitor cells before initiating cardiotoxic treatment and using them for prevention or management of heart failure (De Angelis et al. 2010).

A number of different drugs have cardioprotective properties against anthracycline cardiotoxicity (Wouters et al. 2005). However, due to the risk that these drugs may also reduce the anti-tumor activity of the anthracyclines, they have not gained acceptance except for very special clinical situations.

3.2.2 Alkylating Agents

Cyclophosphamide cardiotoxicity is characterized by hemorrhagic myocarditis in the acute phase. The precise mechanism is unknown, but it is hypothesized that cyclophosphamide causes direct endothelial injury leading to extravasation of toxic metabolites resulting in damage to cardiomyocytes, interstitial hemorrhage, and edema (Goldberg et al. 1986; Gottdiener et al. 1981; Morandi et al. 2005; Pai and Nahata 2000). Microemboli in cardiac capillaries may develop, giving rise to ischemic myocardial damage (Gottdiener et al. 1981; Morandi et al. 2005). Coronary vasospasm is another possible mechanism (Pai and Nahata 2000).

Ifosfamide cardiotoxicity may possibly cause myocardial damage by the same mechanisms as cyclophosphamide, but hemorrhagic myocarditis has not been described, so other unknown mechanisms may be at play (Quezado et al. 1993).

3.2.3 Antimetabolites

Fluorouracil and its prodrug capecitabine may cause cardiotoxicity by mechanisms which are as yet not fully elucidated. Coronary vasospasms have been proposed (Akhtar et al. 1993; de Forni et al. 1992; Kosmas et al. 2008; Luwaert et al. 1991; Shoemaker and Arora 2004; Sudhoff et al. 2004; Wacker et al. 2003). However, there is also evidence for a direct effect on the metabolism of the cardiomyocytes (de Forni et al. 1992; Kohne et al. 1998; Sasson et al. 1994). Symptoms usually start several hours after repeated administrations of the drug. In view of the short half-life of fluorouracil, it seems likely that cardiotoxicity is caused by metabolites which accumulate. Evidence points to metabolites formed by dihydro-pyrimidine

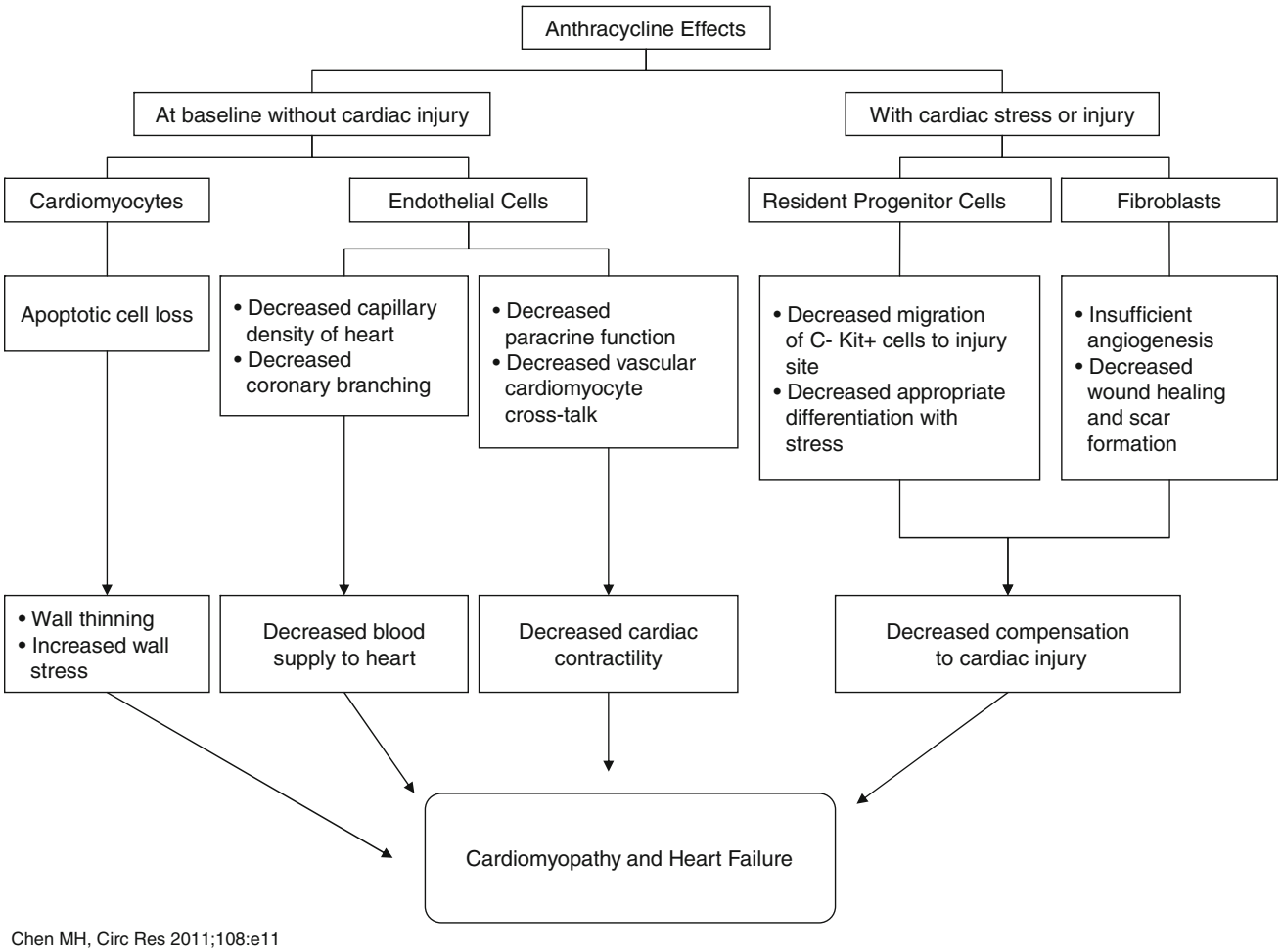

Fig. 5 Anthracycline effects on different cardiac tissues (including myocytes and stems cells) and how it results in heart failure (with permission Chen et al. 2011)

dehydrogenase degradation of fluorouracil (Di Paolo et al. 2001; Van Kuilenburg et al. 2002).

3.2.4 Antimicrotubule Agents

Myocardial ischemia and infarction have been associated with paclitaxel and docetaxel administration. The etiology is thought to be multifactorial, including histamine release by the cremophor of the paclitaxel formulation (Rowinsky et al. 1991). Paclitaxel may also cause arrhythmias, possibly via direct effects on the Purkinje system or extracardiac autonomic control (McGuire et al. 1989), but also via histamine release by the cremophor (Rowinsky et al. 1991; Arbuck et al. 1993).

Vinca alkaloids can also cause arrhythmias, ischemia, and congestive heart failure (Yeh et al. 2004).

3.2.5 Monoclonal Antibodies

Monoclonal antibodies used in cancer therapy typically target growth factors or their receptors thereby inhibiting the tyrosine kinases normally activated through interaction between the growth factor and the corresponding receptor.

3.2.5.1 Bevacizumab

Arterial thrombotic events, including myocardial infarction, are associated with treatment with bevacizumab. The mechanism is unclear, but it is thought that anti-vascular endothelial growth factor (VEGF) therapy may decrease the capability of endothelial cells to regenerate in response to trauma, leading to defects in the interior vascular lining with exposure of subendothelial collagen, increasing the risk of thrombotic events (Kamba and McDonald 2007; Kilickap et al. 2003).

Furthermore, antiangiogenic therapy is known to cause hypertension by mechanisms which are not fully understood. It is possibly related to VEGF inhibition, which decreases nitric oxide production in the arterioles (Kamba and McDonald 2007). Nitric oxide is a natural vasodilator,

and blocking its production leads to increased peripheral vascular resistance and blood pressure. Angiogenesis is an important component of the normal adaptive response to pressure load, and inhibition of VEGF signaling may be even more serious in hypertensive patients (Izumiya et al. 2006; Shiojima et al. 2005).

3.2.5.2 Trastuzumab

Human epidermal growth factor receptor 2 (HER2) has an essential role in the development of the embryonic heart (Erickson et al. 1997; Lee et al. 1995a), and HER2 is expressed on adult myocardiocytes (Strasser et al. 2001; Zhao et al. 1998). Preclinical experiments have shown that activation of the HER2 receptor induced by its ligand neuregulin promotes cardiomyocyte survival (Zhao et al. 1998). Cardiotoxicity of trastuzumab is most likely secondary to inhibition of HER2 receptor on cardiomyocytes, thereby interfering with their normal growth and repair, whereas there is little evidence of cell death in the adult myocardium due to HER2 inhibition, which may explain the reversibility of trastuzumab cardiotoxicity (Crone et al. 2002; Ewer and O'Shaughnessy 2007; Ozcelik et al. 2002; Suter et al. 2007). However, other mechanisms not involving HER2 signaling may also be operating (Guglin et al. 2008).

3.2.5.3 Cetuximab and Panitumumab

These antibodies target the epidermal growth factor receptor (EGFR), and no cardiotoxicity has been reported with these two drugs.

3.2.6 Small Molecule Tyrosine Kinase Inhibitors

Cardiotoxicity of tyrosine kinase inhibitors falls into two categories (Chen et al. 2008). The first relates to the tyrosine kinase target for cancer therapy having an important role in normal cardiomyocyte survival. Inhibition therefore causes myocardial dysfunction. The second is characterized by inhibition of a kinase which is not the intended target of the drug but which is important in normal cardiomyocytes. This situation is more likely the broader the range of targets for the tyrosine kinase inhibitor in question.

With the growing number of tyrosine kinase inhibitors being developed and approved, the likelihood will increase that some of them inhibit novel kinase targets for which little clinical data exist on associations with cardiotoxicity (Chen et al. 2008; Chen 2009; Cheng and Force 2010).

3.2.6.1 Lapatinib

Lapatinib cardiotoxicity is likely related to HER2 inhibition, as mentioned previously for trastuzumab. However, the risk associated with lapatinib is smaller. The difference may be due to the fact that monoclonal antibodies cause antibody dependent cellular and complement-dependent cytoxicity which could augment cardiotoxicity (Imai and Takaoka 2006). Moreover, differential inhibition and/or activation by lapatinib compared to trastuzumab of downstream signaling pathways may also be responsible (Spector et al. 2007).

3.2.6.2 Imatinib

Animal studies have shown cardiotoxicity in cardiomyocytes. Cardiotoxicity is most likely due to Abl inhibition in cardiomyocytes (Force et al. 2007; Kerkela et al. 2006). This seems to lead to induction of endoplasmic reticulum stress response, although the mechanisms are not clear. The endoplasmic reticulum stress response leads to cellular apoptosis. Imatinib-induced cardiotoxicity in patients is still an issue of debate (Breccia 2011).

3.2.6.3 Dasatinib

Like imatinib, dasatinib inhibits Abl, and the mechanism of cardiotoxicity may be similar. However, dasatinib inhibits a number of other kinases, which may be involved in the cardiotoxicity (Chen et al. 2008).

3.2.6.4 Nilotinib

Nilotinib, like imatinib and dasatinib, inhibits Abl. However, it seems to have a favorable toxicity profile, and the only cardiotoxicity reported is QT prolongation.

3.2.6.5 Sunitinib

Sunitinib is a multi-target tyrosine kinase inhibitor. It has been shown in human and animal studies to cause mitochondrial damage in cardiomyocytes (Chu et al. 2007) (see Fig. 6), with ensuing heart failure and cardiomyopathy in a minority of patients. These symptoms improve with discontinuation of the agent and are responsive to heart failure therapy. Animal studies suggest that sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase (Kerkela et al. 2009). Further work has also suggested that sunitinib cardiotoxicity is caused by inhibition of ribosomal kinase leading to activation of the intrinsic apoptotic pathway (Force et al. 2007). Hypertension may also play a role (Chu et al. 2007; Khakoo et al. 2008).

3.2.6.6 Sorafenib

Sorafenib is also a multi-target tyrosine kinase inhibitor, and it may cause cardiac damage by the same mechanisms as sunitinib. However, sorafenib also causes inhibition of the Raf kinases which may lead to enhanced cardiomyocyte apoptosis and fibrosis of the heart (Yamaguchi et al. 2004).

3.2.6.7 Gefitinib and erlotinib

These drugs target the EGFR tyrosine kinase, and no cardiotoxicity has been reported with these two drugs.

Endomyocardial Biopsy from Patients who Developed Sunitinib-induced Heart Failure

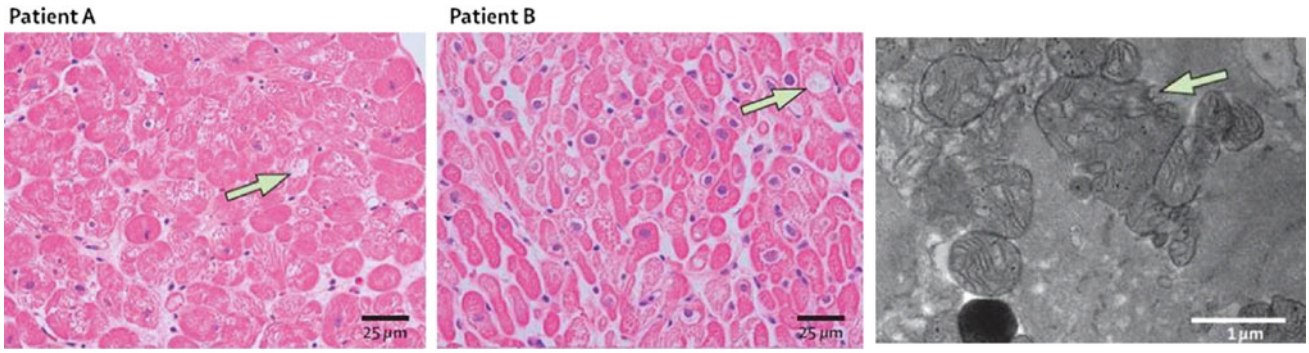

Fig. 6 Endomyocardial biopsy from patients who developed sunitinib-induced heart failure. Representative light photomicrographs from patients A and B (*left+middle panels*) showed cardiomyocyte hypertrophy with mild degenerative changes and diffuse, and moderate myocyte vacuolization (*arrows*). There was no edema, interstitial or replacement fibrosis, regional infarct or focal cell necrosis, myocarditis, or inflammation. Transmission election micrograph from patient A (*right*) showed swollen, abnormal mitochondrial configurations (*arrow*) with effaced cristae (with permission from Chu et al. 2007)

3.2.7 Proteasome Inhibitors

Bortezomib is associated with the development of heart failure, but the mechanism is unknown. It has been proposed that the inhibition of proteasomes in the myocytes is the direct cause of cardiotoxicity (Voortman and Giaccone 2006). In patients with chronic (even subclinical) cardiomyopathy, the ubiquitin–proteasome system is activated, which may be an adaptive mechanism for maintaining a normal stroke volume. In this situation, proteasome inhibition may cause manifest heart failure.

3.2.8 Angiogenesis Inhibitors

With regard to monoclonal antibodies and tyrosine kinase inhibitors acting via the VEGF pathway (bevacizumab, sunitinib), see above.

3.2.8.1 Thalidomide

Thalidomide is associated with the development of bradycardia. The mechanism remains unclear. It has been suggested to be due to the central sedative effects of the drug or to vasovagal activation. Thalidomide reduces the level of TNF-alpha which causes inhibition of the dorsal motor neurons including the nucleus of the vagus nerve. This could conceivably lead to over-reactivity of the parasympathetic nervous system leading to bradycardia. In some patients, thalidomide may cause hypothyroidism which may also lead to bradycardia (Fahdi et al. 2004; Kaur et al. 2003).

3.2.9 Histone Deacetylase Inhibitors

Vorinostat has been associated with QT prolongation. The mechanism is unknown.

3.2.10 Arsenic Trioxide

Arsenic trioxide has been associated with QT prolongation, and the mechanism is unknown.

4 Clinical Syndromes: Radiation Versus Chemotherapy and Interactions

The heart is a complex organ composed of distinct anatomic components that work in synchrony for effective global function. Injury to any one component of the organ can compromise function or render the entire organ dysfunctional. Conversely, the heart also has tremendous reserve, and can sustain a moderate degree of injury that remains subclinical. We will discuss the effects of radiotherapy and systemic therapy on several anatomical parts of the cardiovascular system.

4.1 The Heart

4.1.1 Effects of Radiation on the Heart

4.1.1.1 Radiation-Associated Heart Disease: Epidemiological Data

Radiation-associated heart disease includes a wide spectrum of cardiac disease, and combined disease of the coronary arteries, the heart valves, the myocardium, and the conductive system may occur (Adams et al. 2003; Aleman et al. 2007). These conditions usually only become symptomatic 10–15 years after exposure of the heart to irradiation, leading to an increased risk of (fatal) cardiovascular events

Table 4 Endpoints related to radiation-induced heart disease

	Focal	Global
Subclinical (usually objective)	Abnormalities in regional perfusion or wall motion via SPECT/MRI Valvular abnormalities via ECHO Asymptomatic coronary lesions Pericardial thickening on imaging or a pericardial rub heard on exam EKG abnormalities	Global imaging abnormality (e.g. diffuse hypocontractility) Asymptomatic reduced EF
Clinical (usually subjective)	Coronary artery disease Myocardial infarction Valvular disease	Congestive heart failure Pericarditis/pericardial effusion Arrhythmia Autonomic dysfunction

after for instance mediastinal irradiation for Hodgkin lymphoma and after irradiation for left-sided breast cancer; symptomatic abnormalities may develop much earlier. (Hancock et al. 1993a; Stewart et al. 1995; Adams et al. 2004; Boivin et al. 1992; Carlson et al. 1991; Clarke et al. 2005; Darby et al. 2003, 2005; Giordano et al. 2005; Glanzmann et al. 1998; Gustavsson et al. 1990; Hojris et al. 1999; Lee et al. 2000; Lipshultz and Sallan 1993; Lund et al. 1996; Paszat et al. 1998; Piovaccari et al. 1995; Rutqvist and Johansson 1990; Swerdlow et al. 2007; Taylor et al. 2006). The reported incidence of injury is thus clearly related to the endpoints being considered. It is often useful to stratify the various endpoints (albeit somewhat imperfectly) into categories as shown in Table 4.

The long delay before expression of serious damage probably explains why the radiation sensitivity of the heart has previously been underestimated.

Information on mortality from cardiovascular diseases (CVDs) has been available in many countries for quite some time, whereas the information of incidence rates of CVD has been scarce. Gradually, incidence rates of several CVDs have become available. In addition, incidence rates of hospitalization for ischemic heart disease (Reinders et al. 1999) and of utilization of valve surgery, percutaneous interventions, and coronary bypass graft surgery among patients with HL (Hull et al. 2003) compared with general population rates, have been used as surrogate markers for CVD incidence.

Epidemiological studies on survivors of Hodgkin lymphoma show relative risk estimates for cardiac deaths in the range of 2–7, depending on the age of the patients (increased risks for irradiation at young age), the radiation therapy methods used, and the follow-up time (Hancock et al. 1993a; Adams et al. 2003; Boivin et al. 1992; Swerdlow et al. 2007; Aleman et al. 2003). In a Dutch study 3- to 5-fold increased standardized incidence ratios (SIR) of various heart diseases were observed in patients treated for Hodgkin lymphoma before the age of 41 years relative to the general population, even after a follow-up of more than 20 years (Aleman et al. 2007). The 25-year cumulative incidence of heart failure or cardiomyopathy with death from any cause as competing risk following mediastinal radiotherapy only was 6.8 %. The persistence of increased risk over prolonged follow-up time is of concern because this implies increasing absolute excess risks over time, due to the rising incidence of cardiovascular diseases with age.

Increased morbidity from cardiac diseases has been widely reported after treatment for breast cancer, especially using older radiotherapy techniques (Adams et al. 2003; Verheij et al. 1994; Gaya and Ashford 2005; Senkus-Konefka and Jassem 2007). The early breast cancer trialists'collaborative group (EBCTCG) evaluated the effects of local treatment on death from breast cancer and other causes in a collaborative meta analysis evaluating 42,000 women. This study showed a clear benefit of radiotherapy for local control and risk of death from breast cancer. However, there was, at least with some of the older radiotherapy regimens, a significant excess of nonbreast-cancer mortality in irradiated women [rate ratio 1.12; standard error (SE) 0.04] mainly from heart disease (rate ratio 1.27; SE 0.07) (Clarke et al. 2005).

The SEER database (surveillance, epidemiology, and end-results cancer registries) analysis also provides evidence of increased risk of myocardial infarction due to radiotherapy (Darby et al. 2005; Paszat et al. 1998). In a cohort of 308,861 women treated for early breast cancer, tumor laterality had no influence on subsequent mortality for women who did not receive radiotherapy. However, for women irradiated in the period of 1973–1982, there was a significant increase in cardiac mortality for left versus right-sided tumor (1.2 at <10 years, 1.42 at 10–14 years and 1.58 at >15 years). For women irradiated between 1983 and 1992, these risks had decreased to 1.04 at <10 years and 1.27 at >10 years.

Another large study ($n > 4{,}000$) investigated treatment-specific incidence of cardiovascular diseases in 10-year survivors of breast cancer treated from 1970 to 1986 in the Netherlands (Hooning et al. 2007). When comparing breast cancer patients who did or did not receive radiotherapy, radiation to the internal mammary chain was associated with significantly increased risk of cardiovascular disease (estimated mean, fractionated dose to the heart 6–15 Gy), while for breast irradiation alone no increased risk was

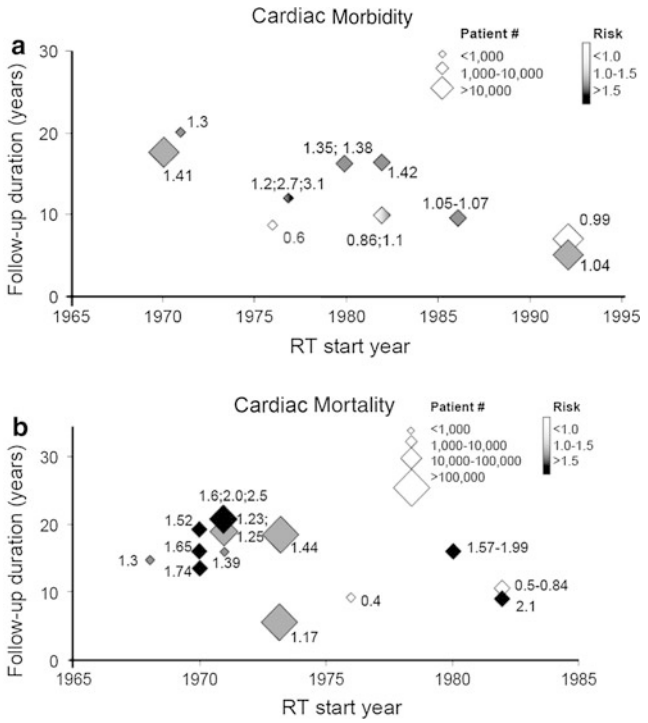

Fig. 7 The interaction of treatment era (based on patient accrual start-year) *and* follow-up duration on cardiac morbidity (panel **a**) and mortality (panel **b**) risk. The number (s) beside each point is the reported 'risk (s)' of cardiac morbidity/mortality in the published trial. The size of the diamonds represents trial sample size, and the shading represents the risk of cardiac morbidity (*black*: >1.5, *gray*: 1–1.5, and *white* as ≤1) From Demirci IJROBP 2009

observed (estimated mean, fractionated dose to the heart <7 Gy). For patients treated before 1979, radiation was associated with hazard ratios (HR) of 2.6 and 1.7 for myocardial infarct and congestive heart failure, respectively. For patients irradiated after 1979, the risk of myocardial infarct declined toward unity but the risks for congestive heart failure and valvular dysfunction remained significantly increased (HR 2.7 and 3.2, respectively). Smoking and radiotherapy together were associated with a more than additive effect on risk of myocardial infarction (HR = 3.04).

In concert, these studies suggest that radiotherapy for left-sided breast cancer has the potential to increase the risk of cardiac morbidity and mortality, but that these risks are markedly reduced with newer radiation therapy techniques. However, since radiotherapy-induced heart disease is generally believed to not be clinically manifest until >10–15 years post radiotherapy, and since the follow-up duration is shorter in the studies using more modern techniques (vs. the older techniques), additional follow-up is needed to be confident that the more modern techniques are indeed "safe". The interaction between the duration of follow-up, the 'era of the radiotherapy' (taken as a surrogate for the 'modern-ness' of the radiotherapy techniques), and the RR of a cardiac event associated with radiotherapy, is shown in Fig. 7. Nevertheless, we are reassured that the more modern approaches markedly reduce the volume of heart exposed to radiotherapy, and that the available data suggest modern radiotherapy for breast cancer is not associated with a marked increase in cardiac events (albeit with modest follow-up time).

Many factors appear to influence the risk of CVDs. Table 1 summarizes the association between various risk factors and the different cardiac events. The highest relative risks are reported for those treated at young age (Aleman et al. 2007; Mulrooney et al. 2009; Hooning et al. 2007; Chen et al. 2008; Swerdlow et al. 2007; Myrehaug et al. 2008) and only slightly increased risks or no increased risks are reported in patients treated at 65 years or older (Swerdlow et al. 2007).

4.1.1.2 Radiation-Associated Heart Disease: Damage to Coronary Arteries

Although radiation damage to the coronary arteries may be immediate, clinical manifestation of damage does not usually appear until 10 or more years after radiation exposure.

Radiation may cause damage to the vascular endothelium of large arteries and therefore lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism.

Because of reduction of the arterial lumen to variable degrees, a spectrum of clinical manifestations of ischemic heart disease may be observed such as stable angina pectoris, unstable angina, myocardial infarction, and chronic ischemic heart disease.

An American study including 961 stage I-II breast cancer patients treated from 1977 to 1995 treated with conventional tangential beam radiation treatment (RT) showed that a statistically significant higher prevalence of stress test abnormalities was found among left (27 of 46; 59 %) versus right-side irradiated patients (3 of 36; 8 %; $P < 0.001$) at a median follow-up of 12 years. Furthermore, 19 of 27 of left-sided abnormalities were in the left anterior descending artery territory. Thirteen left-side irradiated patients also underwent cardiac catheterization revealing 12 of 13 with coronary stenoses (92 %) and 8 of 13 with coronary stenoses (62 %) solely in the left anterior descending artery (Correa et al. 2007; Tsibiribi et al. 2006a, b; Shapiro et al. 1998).

Furthermore, an increased risk of restenosis after coronary artery stenting has been reported in patients treated with thoracic radiation for lymphoma (Schomig et al. 2007; Manojlovic et al. 2008; Halyard et al. 2009).

4.1.1.3 Radiation-Associated Heart Disease: Damage to the Valves

Increased risks of valvular problems (valvular regurgitation in the aortic or mitral valve, and sometimes aortic stenosis) with or without clinical symptoms have been reported following radiotherapy for Hodgkin lymphoma (Aleman et al. 2007; Chen et al. 2011; Adams et al. 2004; Glanzmann et al. 1998; Lund et al. 1996; Heidenreich et al. 2003; Jones et al. 2007).

There are conflicting data following treatment for breast cancer (Hooning et al. 2007; Harris et al. 2006). Progressive valvular dysfunction has also been shown during long-term follow-up after treatment for Hodgkin lymphoma with mediastinal radiotherapy and/or anthracyclines (Wethal et al. 2009). Hodgkin lymphoma patients also have a significantly higher risk (SIR 8.4) of requiring valve surgery 15–20 years after radiotherapy (Hull et al. 2003).

4.1.1.4 Radiation-Associated Heart Disease: Damage to the Pericardium

Acute pericarditis is nowadays uncommon because of improved radiation techniques and lower radiation doses to smaller cardiac volumes. Patients may present with pleuritic chest pain, fever, tachycardia, a pericardial rub, and characteristic electrocardiographic abnormalities. These symptoms and pericardial effusions may resolve spontaneously. Symptomatic treatment analgesic and anti-inflammatory drugs are usually applied to relieve the pain. Constrictive pericarditis does however develop in a minority of patients. Medical treatment may temporarily alleviate symptoms of heart failure, but patients may need a pericardiectomy (Cosset et al. 1991; Bertog et al. 2004; Galper et al. 2010).

In the past, when generally larger radiation fields were used, for instance, in Hodgkin lymphoma treatment pericarditis was seen relatively frequently. In the early Stanford study, the risk of (a) symptomatic pericarditis was 20 % following whole-heart irradiation to 30 Gy, versus 7 % with the placement of a left-ventricular block at 15 Gy, and 2.5 % with a subcarinal block at 25–35 Gy (Carmel and Kaplan 1976).

Another European study including patients treated several decades ago has estimated that 4.8 % of Hodgkin lymphoma patients treated enveloped pericarditis approximately 18 years post-radiation therapy; the cumulative incidence for pericardial disease requiring surgery in these patients rose from only 0.1 % at 5 years post- radiation therapy to 1.3 % at 25 years from treatment (Galper et al. 2010).

More recently, a variety of dose-volume-histogram-based parameters were reported to be related to pericardial effusion for patients treated for esophageal cancer (Wei et al. 2008; Martel et al. 1998). Martel et al. (1998) implicated fraction size, mean, and maximum dose as a predictors for pericarditis. Wei et al. (2008) reported that a variety of DVH-based parameters (e.g., V3 to V50 and mean dose) predicted for pericardial effusions. The dosimetric parameters were highly correlated with each other, making comparisons of their predictive abilities difficult. See for detailed information Table 5.

4.1.2 Effects of chemotherapy on the heart

Several systemic cancer therapies have been associated with the development of left ventricular dysfunction and heart failure.

4.1.2.1 Anthracyclines

Anthracyclines are used to treat a wide range of cancers including breast, uterine, ovarian and lung cancers, leukemias, and lymphomas. The incidence of anthracycline cardiotoxicity depends on the medication and the cumulative dose. For doxorubicin the reported incidence of heart failure is 3–5 % with doses of 400 mg/m^2, 7–26 % with doses of 550 mg/m^2, and 18–48 % with doses of 700 mg/m^2 (Wouters et al. 2005; Swain et al. 1997; Von Hoff et al. 1979). A 5 % risk of cardiomyopathy is seen with a cumulative dose of doxorubicin of 450 mg/m^2, of daunorubicin of 900 mg/m^2, of epirubicin of 935 mg/m^2, and of idarubicin of 223 mg/m^2 (Wouters et al. 2005; Keefe 2001), and these doses are generally regarded as the maximum lifetime cumulative dose allowed. However, no threshold dose exists below which no left ventricular dysfunction is seen. Liposomal doxorubicin, epirubicin, and idarubicin seem to have a lower incidence of heart failure. However, the longer the follow-up, the higher the incidence of cardiac dysfunction is reported to be. A higher risk is reported with intravenous high single doses, drug infusion lasting <30 min, prior radiotherapy involving the heart, use of other concomitant agents such as cyclophosphamide, trastuzumab or paclitaxel, female gender, young and old age, and underlying cardiovascular disease (Aleman et al. 2007; Myrehaug et al. 2008; Leonard et al. 2009; Lipshultz et al. 1995, 2008; Moser et al. 2006; Stickeler et al. 2009; Trudeau et al. 2009).

Acute anthracycline cardiotoxicity occurs in <1 % of patients, and manifests immediately after infusion as a reversible depression of myocardial function (Giantris et al. 1998; Wouters et al. 2005). Discontinuation of the anthracycline often leads to improvement in the cardiac function.

Early onset chronic progressive anthracycline cardiotoxicity, usually presenting within 1 year of anthracycline treatment, occurs in 1–3 % of patients. Late onset chronic anthracycline cardiotoxicity occurs at least 1 year after anthracycline treatment in 1.6–5 %, and even higher incidence figures are reported for children, depending on what severity of symptoms are required for the diagnosis. However, it may not become clinically evident until 10–20 or

Table 5 Pericarditis/pericardial effusion: Dose-volume predictors and NTCP parameters

Authors, year, reference	Diagnosis, No. of patients, years of treatment	OAR	Fractionation schedule, dose data	Predictive parameters	NTCP parameters
Carmel and Kaplan[a] (1976)	Hodgkin lymphoma 377 Patients 1964–1972	Pericardium		At $D_{pericardium}$ >30 Gy: 50 % rate of pericarditis, 36 % requiring treatment	
Cosset et al. (1991)	Hodgkin lymphoma 499 Patients 1971–1984		35–43 Gy/ 2.5–3.3 Gy/ fraction pre-3D dose data	$D_{Mediastinum}$ ≥41 Gy, d/fraction ≥ 3 Gy (marginal significance)	
Burman et al. (1991)	Historical data				LKB[b] *TD50* = 48 Gy, *m* = 0.10 *n* = 0.35
Martel et al. (1998)	Esophagus 57 Patients 1985–1991	Pericardium	37.5–49 Gy/ 1.5–3.5 Gy/ fraction 3D data	D_{mean} > 27.1 Gy[c], D_{max} > 47 Gy[c], d/fraction 3.5 Gy	LKB (95 % CI) *TD50* = 50.6 Gy (−9; 23.1), *m* = 0.13 (−0.07; 0.13), *n* = 0.64 (−0.58; 3)
Wei et al. (2008)	Esophagus 101 Patients 2000–2003	Pericardium	45–50.4 Gy/ 1.8–2.0 Gy/ fraction 3D data	D_{mean} pericardium > 26.1 Gy, V_{30} < 46 %[d]	

CI confidence interval; *LKB* Lyman–Kutcher–Burman (model); *OAR* organs at risk; *NTCP* normal tissue complication probabilities

[a] Patients were grouped according to the estimated pericardium doses. Incidence of pericarditis was distributed as follows: 14/198 (7 %): ≤ 6 Gy; 5/42 (12 %): 6–15 Gy; 23/123 (19 %): 15–30 Gy; 7/14 (50 %): >30 Gy. For pericarditis requiring treatment the corresponding distribution was: 3/198 (1.5 %), 4/42 (9.5 %), 8/123 (6.5 %), and 5/14 (36 %)

[b] In the LKB model (Kutcher and Burman 1989; Lyman 1985) the parameters meaning is *TD50:* dose to the whole organ which will lead to complication in 50 % of the population; *m* is related to the steepness of the dose–response curve, *n* represents the volume effect (large volume effect for *n* close to unity; small volume effect for *n* close to zero)

[c] Corrected to 2 Gy per fraction, $\alpha/\beta = 2.5$ Gy

[d] Wei et al.: the risk of effusion was 13 % with a V30 < 46 Gy (or mean pericardial dose <26 Gy) versus 73 % in patients with a V30 > 46 Gy (or mean dose >26 Gy)

even 30 years after treatment. Chronic progressive cardiotoxicity typically presents as dilated cardiomyopathy (Lipshultz et al. 2008).

4.1.2.2 Alkylating Agents

Cyclophosphamide is an alkylating agent commonly used in the treatment for a variety of nonmalignant and malignant conditions including breast cancer, leukemia, lymphoma, multiple myeloma, mycosis fungoides, neuroblastoma, ovarian cancer, and retinoblastoma (Floyd et al. 2005). Cyclophosphamide has been associated with heart failure in 7–28 % of patients (Goldberg et al. 1986; Gottdiener et al. 1981; Pai and Nahata 2000; Braverman et al. 1991). The risk is dose related, occurring mainly in patients receiving >150 mg/kg and >1.5 g/m^2/day. It occurs within 1–10 days after the administration (Pai and Nahata 2000), and the clinical manifestations range from asymptomatic pericardial effusions to overt heart failure and myopericarditis (Gottdiener et al. 1981; Braverman et al. 1991). Cardiac failure following cyclophosphamide usually resolves over 3–4 weeks and is treated with supportive care (Floyd et al. 2005). Risk factors include previous anthracycline treatment and mediastinal radiotherapy (Goldberg et al. 1986; Pai and Nahata 2000).

Ifosfamide has been associated with cardiotoxicity in 17 % of patients (Pai and Nahata 2000; Quezado et al. 1993), occurring mainly in patients receiving doses >12.5 g/m^2 (Pai and Nahata 2000). Heart failure occurred within 6–23 days after treatment.

4.1.2.3 Antimetabolites

Fluorouracil is mainly used in the treatment for patients with cancer of the digestive tract especially colorectal cancer and head and neck cancer. Fluorouracil has been associated with symptoms of cardiotoxicity in 1–18 % of patients, most commonly as angina-like chest pain, but ischemic ECG changes may be seen in up to 68 % (Yeh and Bickford 2009; de Forni et al. 1992; Wacker et al. 2003; Jensen and Sorensen 2006; Keefe et al. 1993; Labianca et al. 1982; Tsavaris et al. 2002). In rare cases myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and sudden death have been reported (Meyer et al. 1997; Van Cutsem et al. 2002). The overall mortality of symptomatic fluorouracil cardiotoxicity has been estimated at 2.2–13 %

(de Forni et al. 1992; Wacker et al. 2003; Keefe et al. 1993; Labianca et al. 1982; Tsavaris et al. 2002; Robben et al. 1993). Cardiac events generally occur within 5 days after administration. The risk of cardiotoxicity is associated with high doses (>800 mg/m^2), continuous infusion, prior cardiovascular disease or mediastinal radiotherapy, and concurrent chemotherapy (de Forni et al. 1992; Kosmas et al. 2008; Jensen and Sorensen 2006; Labianca et al. 1982; Tsavaris et al. 2002; Meyer et al. 1997; Van Cutsem et al. 2002; Cardinale et al. 2006a, b; Rezkalla et al. 1989).

Capecitabine, an oral prodrug of fluorouracil, has been associated with cardiotoxicity with an incidence of 3–9 % (Kosmas et al. 2008; Van Cutsem et al. 2002; Ng et al. 2005; Saif et al. 2008; Walko and Lindley 2005). Typically, angina symptoms occurred 4–5 days after therapy (Jensen and Sorensen 2006) with ischemic ECG changes present in many cases (Cardinale et al. 2006a; Frickhofen et al. 2002; Schnetzler et al. 2001), but without echocardiography or coronary angiogram abnormalities (Yeh and Bickford 2009; Cardinale et al. 2006a; Schnetzler et al. 2001). Prior fluorouracil cardiotoxicity and possibly prior symptoms of coronary artery disease were risk factors (Labianca et al. 1982; Saif et al. 2008; Frickhofen et al. 2002; Schober et al. 1993).

4.1.2.4 Antimicrotubule Agents

Docetaxel is employed in the treatment of breast cancer and prostate cancer. It has been reported to be associated with heart failure in 2.3–8 % of patients (Martin et al. 2005; Marty et al. 2005). Myocardial ischemia has been reported to occur in 1.7 % of patients (Yeh and Bickford 2009; Vermorken et al. 2007).

Paclitaxel is used in patients with lung cancer, ovarian cancer, and breast cancer. It has been reported to be associated with ischemia in 5 % of patients (Rowinsky et al. 1991) and with myocardial infarction in 0.5 % (Arbuck et al. 1993). The cardiac events occurred up to 14 days after paclitaxel administration (Arbuck et al. 1993), and risk factors were previous cardiac disease including hypertension and coronary artery disease. Paclitaxel has also been associated with bradycardia, which is usually without clinical significance, but may in rare cases have clinically significant hemodynamic effects. Hypersensitivity reactions with histamine release have been implicated, and premedication to prevent hypersensitivity reactions may prevent bradycardia as well.

Vinca alkaloids, used in the treatment of lymphomas, nonsmall cell lung cancer, breast cancer, and testicular cancer, have also been incriminated. Significantly (2 fold or more) increased risks of death from myocardial infarction (Swerdlow et al. 2007) or more general cardiovascular diseases (Tukenova et al. 2010) have been reported.

4.1.2.5 Monoclonal Antibodies

Bevacizumab is a monoclonal antibody that inhibits the activity of human VEGF. It is approved for use in the setting of first-line metastatic colon cancer in combination with intravenous FU-based chemotherapy. It is also used in the treatment of nonsmall cell lung cancer and brain tumors. Bevacizumab has been associated with heart failure in 1.7–3 % of patients (Miller et al. 2005, 2007). Moreover, arterial thrombotic events have been reported in 3.8 % of patients with myocardial infarctions in 0.6 % (Scappaticci et al. 2007). Arterial thrombotic events could occur at any time during therapy, and they did not seem to be related to dose or cumulative exposure. Risk factors were older age and prior arterial thrombotic events (Scappaticci et al. 2007). The most common cardiotoxicity with bevacizumab treatment is, however, hypertension, which is reported to occur in 4–35 % of patients (Miller et al. 2005, 2007; Cobleigh et al. 2003; Hurwitz et al. 2004; Johnson et al. 2004; Kabbinavar et al. 2005; Pande et al. 2007; Yang et al. 2003). Hypertension might develop at any time during therapy, and higher dose has been suggested as a risk factor (Kabbinavar et al. 2005). Most patients can continue bevacizumab in combination with antihypertensive drugs.

Trastuzumab, used in patients with breast cancer, is associated with cardiomyopathy in 2–7 % of patients when the drug is used alone. However, when trastuzumab is used with paclitaxel the incidence is 2–13 %, and when used with an anthracycline it is up to 27 % (Ewer and O'Shaughnessy 2007; Suter et al. 2007; Gianni et al. 2007; Guarneri et al. 2006; Perez et al. 2008a; Romond et al. 2005; Seidman et al. 2002; Slamon et al. 2001; Tripathy et al. 2004; Vogel et al. 2002). Risk factors are age >50, pretreatment borderline left ventricular ejection fraction, prior cardiovascular disease, and prior treatment with anthracyclines to higher cumulative doses (287 mg/m^2 vs. 257 mg/m^2 for doxorubicin, 480 mg/m^2 vs. 422 mg/m^2 for epirubicin) (Suter et al. 2007; Guglin et al. 2008; Gianni et al. 2007; Guarneri et al. 2006; Perez et al. 2008a, b; Seidman et al. 2002; Tan-Chiu et al. 2005). Hence, increased cardiac stress seems to increase the risk of trastuzumab associated cardiac side effects, which may explain why it appears to be more frequent in clinical practice than in controlled trials (McArthur and Chia 2007). Trastuzumab cardiotoxicity is not dose related, and it is frequently reversible. However, if combined with anthracyclines, the frequency and risk of anthracycline induced myocyte death might increase (Zuppinger et al. 2007).

4.1.2.6 Small Molecule Tyrosine Kinase Inhibitors

Lapatinib is used in the treatment of disseminated breast cancer. It has been reported to be associated with

symptomatic (grade 3 or 4 heart failure) cardiotoxicity in 0.2 % of patients and with asymptomatic events (>20 % decrease in left ventricular ejection fraction without symptoms) in 1.4 % of patients (Perez et al. 2008b). The risk was increased in patients with prior anthracycline treatment (2.2 %) or prior trastuzumab treatment (1.7 %). The mean time to onset of symptoms was 13 weeks. Lapatinib has also been reported to cause QT prolongation in 16 % of patients treated with varying doses (Yeh and Bickford 2009). Lapatinib thus seems to be less cardiotoxic than trastuzumab. This may partly be due to selection bias in the trials of patients receiving lapatinib, but recent data indicate an underlying molecular mechanism for the apparent difference in cardiotoxicity, as lapatinib, but not trastuzumab protects against TNF-alpha-induced cardiomyocyte death (Spector et al. 2007).

Imatinib, used in the treatment of chronic myeloid leukemia and in gastro-intestinal stromal tumors, has been associated with rare heart failure (Kerkela et al. 2006). The incidence of clinical heart failure in patients treated with imatinib has been reported as 0.5–1.7 % (Atallah et al. 2007; Hatfield et al. 2007). Whether the imatinib-associated cardiotoxicity is reversible or not is still unknown.

Dasatinib, also used in the treatment of chronic myeloid leukemia, has been reported to be associated with heart failure in 2–4 % of patients, and QT prolongation has been reported to occur in 2–3 % of patients treated with dasatinib (Yeh and Bickford 2009).

Sunitinib, simultaneously approved for the treatment of renal cell carcinoma, and gastrointestinal stroma tumor, has been associated with left ventricular dysfunction in 4–11 % of patients, with symptomatic heart failure in 2.7–8 % (Chu et al. 2007; Khakoo et al. 2008). The mean time to the development of heart failure varied between 22 days and 27 weeks, and the only risk factor was prior coronary artery disease. Although heart failure responded to medical therapy, it did not seem to be fully reversible (Khakoo et al. 2008). Moreover, sunitinib has been associated with hypertension in 5 to 47 % (Chu et al. 2007), in different clinical trials, with grade 3 occurring in 2–8 % (Chu et al. 2007; Burstein et al. 2008; Demetri et al. 2006; Motzer et al. 2006a, b, 2007; Azizi et al. 2008).

Sorafenib, approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma, causes hypertension in a significant number of patients. The overall incidence in a recent meta analysis was 23.4 %, with grade 3 and 4 reported in 2.1–30.7 % in different studies (Wu et al. 2008). Sorafenib has also been associated with myocardial ischemia in 3 % of patients in clinical trials, which is significantly higher than in patients treated with placebo (Yeh and Bickford 2009; Escudier et al. 2007).

Kinase Inhibition Determines TKI-induced Toxicity to Normal Tissue:

- Cardiotoxicity is NOT a class effect for TKIs.
- Cardiotoxicity determined by the specific kinases that a TKI inhibits (whether on-target or off-target).
- Small molecule TKIs inherently inhibit many different kinases than monoclonal antibodies.
- Multi-targeted TKIs inhibit more kinases (i.e., sunitinib > imatinib).
- Certain inhibited kinases are essential to tumor cell killing and also turn out to be necessary for cardiomyocyte survival.
- Constant balance between enhanced tumor cell killing versus potential increased risk of cardiotoxicity.

4.1.2.7 Vorinostat

Vorinostat is approved for the treatment of cutaneous T cell lymphomas. Vorinostat had been reported to be associated with QT prolongation in 3.5–6 % of patients (Yeh and Bickford 2009; Olsen et al. 2007). Risk factors are female gender, older age, previous myocardial ischemia, heart failure, electrolyte imbalances, bradycardia, and medication with QT prolonging drugs (Yeh and Bickford 2009; Vorchheimer 2005).

4.1.2.8 Thalidomide

Thalidomide is used in the treatment of multiple myeloma. Bradycardia has been associated with thalidomide treatment in 2–55 % of patients. Most patients are asymptomatic, but some patients may experience fatigue, syncope, or dizziness. Patients developing third-degree atrioventricular block need a permanent pacemaker.

4.1.2.9 Arsenic Trioxide

Arsenic trioxide is used in the treatment of certain leukemias. QT prolongation has been reported in patients treated with arsenic trioxide in 26–93 % of patients (Barbey et al. 2003; Huang et al. 1998; Ohnishi et al. 2002; Shigeno et al. 2005; Singer 2001; Unnikrishnan et al. 2004; Westervelt et al. 2001). The QT interval has been reported to be prolonged from 1 to 5 weeks after treatment and then returned to baseline (Soignet et al. 2001).

4.1.2.10 Toxic Effect of Systemic Therapy on Coronary Arteries

Direct effects of chemotherapy on coronary arteries are rare.

Fluoropyrimidines (i.v. 5 fluoro-uracil (5FU) or oral capecitabine), may cause myocardial ischemia and decreased contractility of the heart (Kosmas et al. 2008; Tsibiribi et al. 2006a, b; Manojlovic et al. 2008). A spasm

of the coronary arteries is often considered to be the most important cause. The underlying mechanism is not fully elucidated yet. Experimental studies in rabbits indicate that a spasm of the coronary arteries is not the only mechanism of 5FU cardiotoxicity, and that apoptosis of myocardial and endothelial cells can result in inflammatory lesions mimicking toxic myocarditis (Tsibiribi et al. 2006a, b).

4.1.3 Effects of Combined Modality Treatment on the Heart

Whether toxicity following chemotherapy and radiotherapy are additive or synergistic is still unclear. Several clinical studies in lymphoma patients showed that anthracycline-containing therapy may further increase the radiation-related risk of congestive heart failure and valvular disorders by 2- to 3-fold compared to radiotherapy alone (Aleman et al. 2007; Moser et al. 2006). A Dutch study including 5-year survivors of Hodgkin lymphoma treated before age 41 showed that the 25-year actuarial risks of heart failure after mediastinal radiotherapy alone versus anthracycline-based chemotherapy in combination with mediastinal radiotherapy were 7.5 versus 10.7 % respectively (Aleman et al. 2007).

Myrehaug et al. 2008 evaluated the risk of hospital admission for cardiac disease in Hodgkin lymphoma patients, adjusting for age, sex, treatment, cardiac risk factors, and competing causes of death. They showed that for females and males treated with doxorubicin plus mediastinal radiotherapy at age 40, the estimated 15-year incidence rate of cardiac hospitalization was 7.3 and 16.5 %, respectively, rates 5–15 % higher than expected. They also showed that the cardiotoxic effects of radiotherapy and chemotherapy may be more than additive.

A prospective study in breast cancer patients compared 10 versus 5 cycles of doxorubicin (A) (45 mg/m2) and cyclophosphamide (C) (500 mg/m^2) chemotherapy. In retrospective subgroup analysis of patients treated with radiotherapy, an increased rate of cardiac events was found among patients receiving 10 cycles of chemotherapy and radiotherapy (Shapiro et al. 1998), with a 6-year median follow-up.

Trastuzumab and other systemic agents (e.g., taxanes and biologicals) will be used more commonly along with thoracic radiotherapy in patients. There is only limited data on possible interactions between these agents and radiation with respect to cardiotoxicity. In a recent multicenter, prospective trial assessing the utility of trastuzumab in breast cancer, the concurrent use of trastuzumab along with left-sided RT appeared to be safe, albeit with a follow-up of only 3.7 years (Halyard et al. 2009) Dose-volume data regarding the degree of heart irradiation were not reported; though purposeful irradiation of the internal mammary nodes was not permitted.

4.2 Toxic Effects on Other Blood Vessels

Arteries may be damaged by radiation. Veins seem to be less vulnerable to radiation effects. The clinically most important arterial radiation-related problems are mentioned below.

4.2.1 Carotid Arteries

Damage to the carotid arteries is of special importance. Significantly, increased risks of stroke have also been described in patients treated with radiotherapy for head-and-neck cancer (60–70 Gy; RR 2.1–9.0, depending on follow-up) (Dorresteijn et al. 2002; Haynes et al. 2002; Scott et al. 2009), Hodgkin lymphoma (median dose approximately 40 Gy; RR 2-to 4-fold increased) (Bowers et al. 2005; De Bruin and Dorresteijn 2009) and in long-term survivors of childhood leukemia and brain tumors treated with >30 Gy cranial radiotherapy (RR 5.9 and 38, respectively) (Bowers et al. 2006). The latter study also demonstrated a relationship between radiation dose and RR stroke, with significantly higher risks for cranial doses of >50 Gy compared with 30–50 Gy.

In a Dutch retrospective cohort study of 2,201 5-year survivors of Hodgkin lymphoma treated before age 51 between 1965 and 1995, there was a substantially increased risk of stroke and TIA, associated with radiation to the neck and mediastinum (De Bruin and Dorresteijn 2009). Most ischemic events were from large artery atherosclerosis (36 %) or cardioembolisms (24 %). The standardized incidence ratio for stroke was 2.2 (95 % confidence interval [CI] = 1.7–2.8), and for TIA, it was 3.1 (95 % CI = 2.2–4.2). The risks remained elevated, compared with those in the general population, after prolonged follow-up. Treatment with chemotherapy was not associated with an increased risk. Hypertension, diabetes mellitus, and hypercholesterolemia were associated with the occurrence of ischemic cerebrovascular disease, whereas smoking and overweight were not.

4.2.2 Aorta

Increased risks of atherosclerosis following radiation exposure of other arteries have been reported, leading to stenosis of the subclavian artery, (Hull et al. 2003) of the aorta (Piedbois et al. 1990), and of arteries supplying the small bowel (Patel et al. 2006). Described numbers of patients are however small.

In a recent small case–control study, treatment with anthracyclines has been shown to increase aortic stiffness significantly within 4 months of treatment compared with controls (Chaosuwannakit et al. 2010). Stiffening of the aorta increases left ventricular afterload, and it is an independent predictor of adverse cardiovascular events. Stiffening of the aorta was correlated with the cumulative anthracycline dose. The addition of trastuzumab or cyclophosphamide did not increase the risk of stiffening.

4.2.3 Microcirculation

Damage to the peripheral circulation can impair circulation and predispose to thrombosis. The impact of antineoplastic therapies on the peripheral circulation can be ascribed to damage to the intima of vessels. Damage to the vessel can involve injury to the intimal layer or disruption of endothelial cell-to-cell communication. In either case, the loss of integrity of the vessel lining activates the coagulation cascade. Hemorrhage and arterial thromboembolism have been observed in patients treated with angiogenesis inhibitors such as thalidomide and lenalidomide (van Heeckeren et al. 2007). Venous thromboembolism has been associated with different chemotherapeutic agents such as alkylating agents (in particular cisplatin), angiogenesis inhibitors, histone deacetylase inhibitors, and tyrosine kinase inhibitors (Czaykowski et al. 1998; Rodeghiero and Elice 2003; Zangari et al. 2007).

Drugs that modify the expression pattern of adhesion molecules such as integrins and cadherins on endothelial cells alter cell to cell and cell to matrix connections and interrupt endothelium integrity. This leads to an increased risk of hemorrhage and thromboembolism. This is the case for some drugs such as doxycycline and lenalidomide (Fainaru et al. 2008; Lu et al. 2009; Matsumura et al. 1997).

4.2.4 Possible Interaction Between Macrovascular and Microvascular Injury for the Myocardium

Radiation appears to cause both microvascular injury to the myocardium as well as macrovascular injury to the coronary arteries. How these two types of injury interact to cause clinical dysfunction is uncertain. A reasonable hypothesis is as follows. Radiotherapy causes microvascular injury in the relatively short-term interval post radiotherapy (months to years). This usually remains asymptomatic perhaps since the myocardium has an extensive network of collateral flow. In addition, radiotherapy also causes damage to the coronary arteries, but typically on a longer time scale (years to decades). When an obstructive coronary lesion develops, it might be more likely to cause a clinical event due to the relative loss of collateral flow (from the microvascular injury) (see Fig. 8; from Darby et al. 2010).

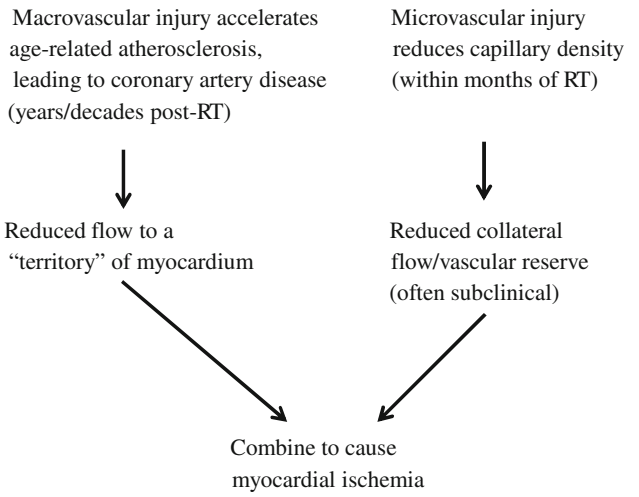

Fig. 8 Schematic illustration of how microvascular and macrovascular radiation-related cardiac injury could theoretically combine to cause myocardial ischemia after RT (From Darby IJROBP 2010)

5 Radiation Tolerance

5.1 Radiation dose- volume effects of the heart

Data on relationships between cardiovascular toxicity in relation to radiation dose, radiation volume, and irradiated structure are still scarce, and thus much uncertainty remains.

Mortality data from the life span study (LSS) of the Japanese atomic bomb survivors and from occupational and environmental studies provide some evidence of a dose response for mortality from heart diseases and stroke (Shimizu et al. 1999; Preston et al. 2003; Little 2009, 2010) (Fig. 9).

A recent report (AGIR 2010), calculating aggregate risks from many studies, estimated an excess relative risk per Gy (ERR/Gy) of 0.10 (95 % CI 0.07, 0.13) for morbidity and 0.08 (95 % CI 0.04, 0.12) for mortality from circulatory disease taken as a whole (Subgroup on Circulatory Disease Risk of the Advisory Group on Ionizing Radiation 2010; ICRP Report 2012).

There are indications that cardiotoxicity from therapeutic radiation is related to total radiation dose and dose per fraction to the heart (Hancock et al. 1993a; Heidenreich et al. 2007; Darby et al. 2010; Gagliardi et al. 2010). Large doses per fraction are expected to be relatively more damaging to the heart than low doses per fraction, and indeed increased complication rates were reported for Hodgkin lymphoma patients treated with 3×3.3 Gy per week, compared with patients treated with 4×2.5 Gy per week to the same total dose (Cosset et al. 1988).

Furthermore, the volume of the heart included in the irradiation field influences the risk of cardiotoxicity (Schultz-Hector and Trott 2007; Moser et al. 2006; Tukenova et al. 2010). For pericarditis, TD 5/5 values (total dose for 5 % incidence at 5 years) of 60, 45, and 40 Gy have been estimated when 1/3, 2/3, and the whole heart is irradiated using 2 Gy per fraction (Emami et al. 1991). A reduction in the increased risk of death from cardiovascular diseases other than myocardial infarction has been reported in Hodgkin lymphoma patients treated after partial

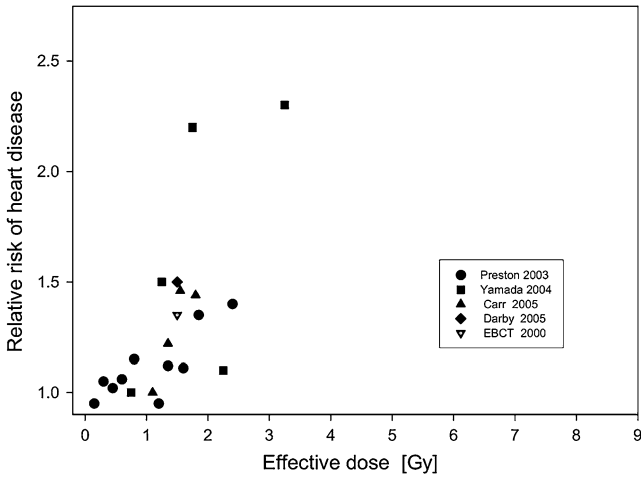

Fig. 9 Relative risk of death from heart disease increases with radiation dose: Preston et al. (Preston 2003) and Yamada et al (Yamada 2005) reported on cardiac mortality in atomic bomb survivors (life span study [LSS]); Carr et al. (Carr 2005) reported on mortality from coronary heart disease at >10 years after radiation therapy of peptic ulcers; Darby et al. (Darby 2005) and the Early Breast Cancer Trialists group (EBCTCG 2000) analyzed mortality from heart disease after radiotherapy for breast cancer. Figure adapted from Schultz-Hector and Trott (Schultz-Hector 2007)

shielding of the heart and restriction of the total, fractionated, mediastinal dose to <30 Gy (Hancock et al. 1993, b). Radiotherapy techniques have greatly improved over the past 20 years, leading to more homogeneous dose distributions and reduced risks of toxicity (Lee et al. 1995, b). In two more recent reports on cardiotoxicity in childhood cancer survivors dose- and volume effects have been studied in detail. Tukenova et al. (Tukenova et al. 2010) report a linear relationship between the average radiation dose to the heart and the risk of cardiac mortality (with an estimated relative risk at 1 Gy of 1.6; i.e., a 60 % increase). Mulrooney et al. 2009 also find indications for a relationship between the risk of cardiovascular disease and mean radiation dose to the heart (Mulrooney et al. 2009) (see Fig. 10). Compared with siblings, survivors of childhood cancer were significantly more likely to report CHF (hazard ratio [HR] = 5.9), MI (HR = 5.0), pericardial disease (HR = 6.3), or valvular abnormalities (HR = 4.8). Cardiac radiation exposure of 15 Gy or more increased the risk of CHF, MI, pericardial disease, and valvular abnormalities by 2- to 6-fold compared with nonirradiated survivors. There was no evidence for increased risk following doses less than 5 Gy, and slight elevations in risk were not statistically

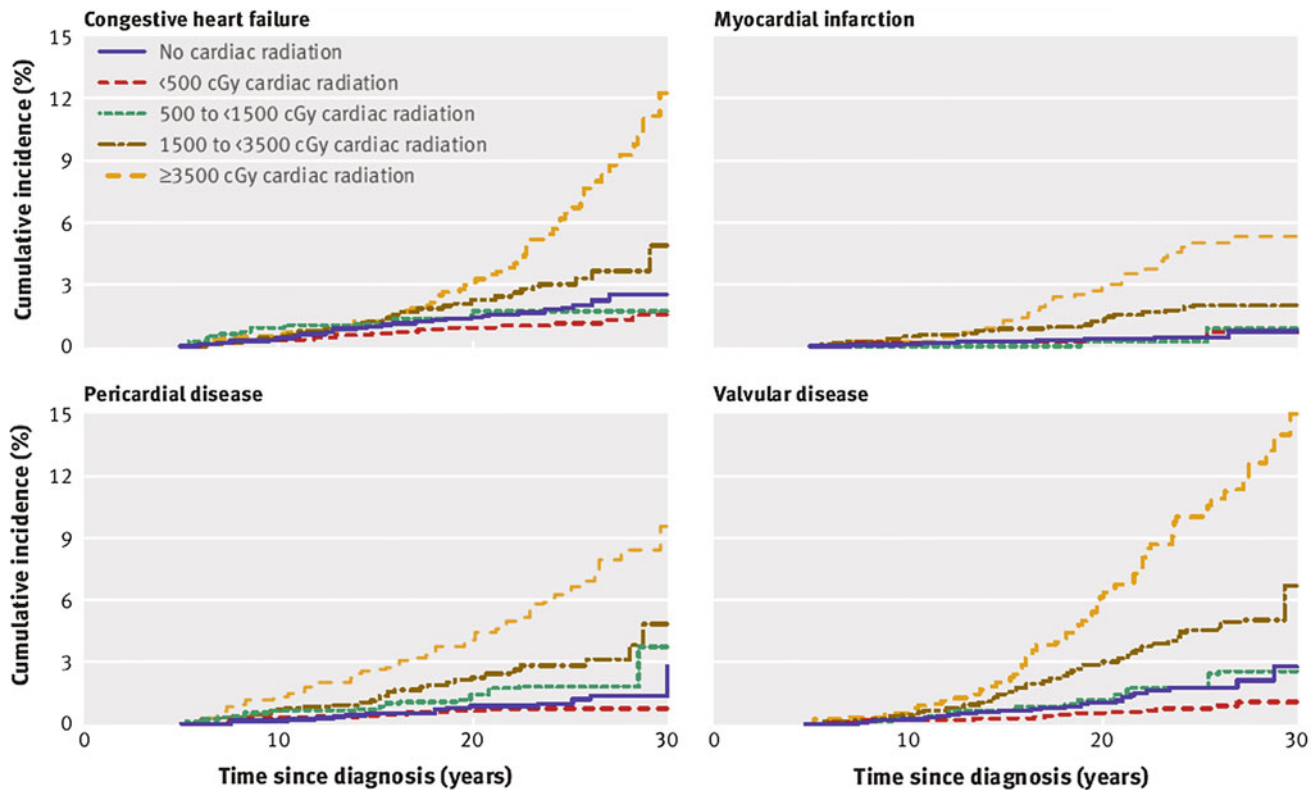

Fig. 10 Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose from Mulrooney (Mulrooney 2009)

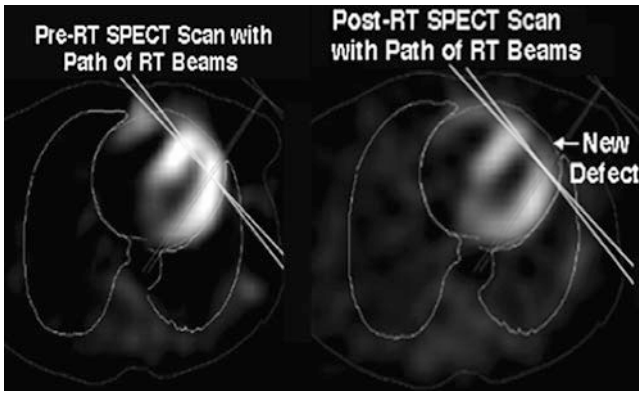

Fig. 11 Representative axial images pre-RT (*left panel*) and post-RT (*right panel*) cardiac SPECT perfusion scans. The deep borders of the tangential RT beams are shown as *solid lines*. A new perfusion defect in the anterior left ventricle after radiation is seen (From Darby IJROBP 2010)

significant following doses between 5 to 15 Gy. Exposure to 250 mg/m^2 or more of anthracyclines also increased the risk of CHF, pericardial disease, and valvular abnormalities by 2 to 5 times compared with survivors who had not been exposed to anthracyclines.

Clinically, significant cardiovascular abnormalities, like reduced left ventricular dimensions, valvular, and conduction defects, are very common, even in asymptomatic cancer survivors (Adams et al. 2004; Heidenreich et al. 2003).

Several studies have considered subclinical endpoints to assess radiotherapy-induced injury (Girinsky et al. 2000; Marks et al. 2005). For example, in a prospective study of 114 women with breast cancer, left-sided tangential photon fields appear to cause reductions in regional myocardial perfusion at relatively short times post-radiotherapy (e.g. 0.5–2 years) (Marks et al. 2005) (Fig. 11). The perfusion defects are associated with the irradiated area, and not with the territory of a coronary artery (Lind et al. 2003), thus suggesting that the radiation-induced injury is at the microvascular level. These perfusion abnormalities are associated with corresponding abnormalities in wall motion, but not reductions in ejection fraction (Marks et al. 2005) and are largely persistent up to 6 years post-radiotherapy. Such perfusion abnormalities are seen in $\approx$20, $\approx$30 and >50 % of patients with <1, 1–5, and >5–10 % of their left ventricle within the planned tangential fields (suggesting a strong volume dependence) (Evans et al. 2006). The clinical relevance of these perfusion abnormalities is unknown. These results are largely consistent with the findings from several other studies. Several studies have assessed for perfusion abnormalities post-radiotherapy for breast cancer (See Table 6). Most detect perfusion abnormalities, and these defects can be associated with wall motion abnormalities (Seddon et al. 2002). Similarly, in patients irradiated for Hodgkin lymphoma or other intrathoracic tumors, perfusion defects are also often seen (See Table 6), but these are usually not associated with any clinical events. The follow-up in these studies, however, may be too short to detect clinically meaningful events.

Recently, pre-existing heart disease was shown to be associated with an increased risk of cardiac hospitalization following treatment for Hodgkin lymphoma, particularly mediastinal radiotherapy with or without anthracyclin-containing chemotherapy (Myrehaug et al. 2010).

5.2 Summary and Recommendations Concerning Radiation Tolerance of the Heart

Overall, these observations demonstrate that incidental irradiation of the heart can cause dose- and volume-dependent cardiotoxicity. For example, there is a clear risk of Coronary Artery Disease (CAD) after radiotherapy, typically manifest >10–15 years post-RT, as well as pericardial injury occurring sooner post-RT. More sensitive tests (e.g., imaging) can detect more subtle changes (often relatively soon post-RT), but the clinical relevance of these findings is unclear. Given the paucity of good dose-volume-outcome data (especially for the more meaningful long-term risks), it is challenging to formulate strict dose-volume guidelines. One is left perhaps to conclude that there are no particular 'safe' doses/volumes, and that one should minimize all exposures to the degree possible. Indeed, the recent Quantec review (Gagliardi et al. 2010) similarly was unable to recommend strict guidelines. They concluded saying, "Radiation-induced cardiac complications have different significance and implications depending on the clinical scenario". As such, constraints/NTCP values can be used only for guidance; they must always be considered in relation to probability of tumor control and the specific patient. Nevertheless, the following broad dose-volume guidelines are suggested. In patients with breast cancer, it is recommended that the irradiated heart volume be minimized to the greatest possible degree without compromising the target coverage. In many cases, conformal blocking and breath-hold techniques can essentially eliminate the heart from the primary beams. If NTCP models for cardiac mortality are used, it should be considered that an NTCP value 5 % could jeopardize the beneficial effect on survival of radiotherapy. So as not to underestimate this risk, the most conservative approach is provided by the use of the [steepest available] dose–response curve, that is, the one from the breast data (Gagliardi et al. 1996).

Although currently, there is no direct evidence that successful treatment of traditional cardiac risk factors will alter the natural history of radiation-associated cardiac disease, it is prudent to optimize patient cardiovascular risk

Table 6 Studies assessing for perfusion defects following radiotherapy for breast cancer. Adapted from Prosnitz RG, Marks LB: Radiation-induced heart disease: vigilance is still required. J Clin Oncol 23:7391–4, 2005

Author	Years post-RT	Patient subset	Rate of perfusion defects
Gyenes (Gyenes 1994)	≈18	Left-sided, photon/electron-treated	5/20
	19	Right-sided,photon/electron-treated	0/17
Hojris (Hojris 2000)	8	Left-sided, electrons	4/9
		No RT	4/7
Cowen (Cowen 1998)	≈8	Left-sided, photons	0/17
Seddon (Seddon 2002)	≈7	Left-sided, photons	7/24
		Right-sided, photons	2/12
Gyenes (Gyenes 1996)	≈1	Left-sided, photons	4/4
		Left-sided, electrons	2/8
Marks (Marks 2005)	0.5–2	Left-sided, photons: % of Left ventricle estimated to be in the tangents:	
		<1	≈20 %
		1–5	≈30 %
		>5 %	≈ >50 %

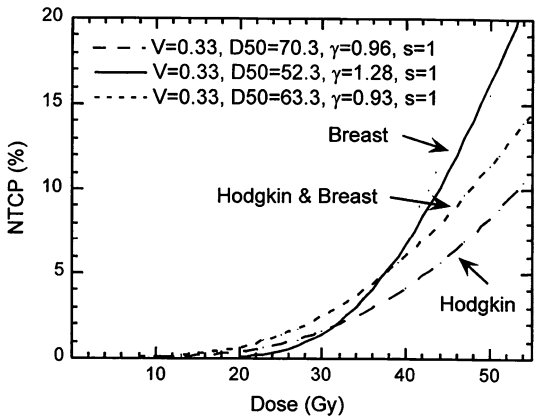

Fig. 12 Dose–response curves for long-term cardiac mortality based on Hodgkin's disease and breast cancer datasets (from Eriksson 2000)

profiles (Executive Summary of the Third Report of the National cholesterol Education Program (NCEP) 2001; Mosca et al. 2007; Jones et al. 2007) (Fig. 12).

6 Prevention and Management

6.1 Prevention

6.1.1 Prevention radiation-related cardiovascular toxicity

With respect to radiation, it is important to use conventionally fractionated radiation, and to limit both radiation dose and volume as is clinically possible/practical. Modern radiation techniques such as intensity modified radiotherapy may facilitate a reduction in heart exposure without compromising the radiation dose in the target volume. Inspiratory breathholding techniques during delivery of radiation therapy for left-sided breast cancer can reduce incidental cardiac exposure, while maintaining radiation dose to the target (Chen et al. 1997, 2002; Lu et al. 2000). The diaphragm is pulled downwards, displacing the heart caudally and often medially. Inspiration increases the anterior–posterior diameter of the chest and displaces the left breast away from the heart. These anatomic changes result in decreased cardiac irradiation, with complete displacement of the heart outside the field in 21 % of patients (Crone et al. 2002; Chen et al. 1997). Clinical introduction of these and other novel simulation techniques has shown initial promise (Korreman et al. 2006). Ongoing research is expected to give more information concerning which cardiac structures are most critical and whether it is less harmful to include a slightly larger volume to a low dose or a smaller volume to a slightly higher dose.

Optimization of treatment choice is still an important subject of study. In the future, we hope to be able to identify survivor groups at high risk of late adverse effects (based on treatment and/or genotype) for which screening should be recommended and/or intervention trials could be designed.

Although the design of mediastinal fields for some cancers may not allow for the effective use of respiratory maneuvers, it is worth exploring every possible means to decrease cardiac and valvular exposure when designing radiation portals.

6.1.2 Prevention chemotherapy-related cardiovascular toxicity

The evidence about the effectiveness of technologies to reduce or prevent cardiotoxicity from anthracyclines is limited in quantity and quality (van Dalen et al. 2008; 2009). The available evidence mainly comes from treatment of children. Optimization of chemotherapy dosage schedules, for instance anthracycline dosage schedules (i.e., avoiding peak doses), has been studied. However, so far results have been disappointing (van Dalen et al. 2009).

Anthracyclines release free radicals that damage the cardiac myocytes, which are especially susceptible to free radical damage because of their highly oxidative metabolism and poor antioxidant defenses. The free-radical scavenging cardioprotectant, dexrazoxane has been shown to reduce anthracycline-associated myocardial injury in rats (Herman et al. 2001) and in selected studies in humans (Swain et al. 1997). Lipshultz demonstrated that in children with acute lymphoblastic leukemia treated with anthracycline, the concomitant use of dexrazoxane resulted in less troponin T release during therapy (Lipshultz and Adams 2010). Eight years later, these patients also had higher LVEFs as compared to the control group that received no dexrazoxane (Chen et al. 2011; Lipshultz et al. 2004). Greater use of this compound has been limited by concern about its possible interference with anthracycline's anticancer activity (Yeh and Bickford 2009). This delicate balance between cancer cure and cardioprotection is an ongoing area of investigation and research.

Furthermore, there are some indications of a possible beneficial effect of angiotensin-converting enzyme inhibitors (ACEI) and of beta blockers (Noori et al. 2000) after cardiotoxic chemotherapy (Cardinale et al. 2006b), especially with initiation within 6 months of diagnosis of cardiotoxicity (Cardinale et al. 2010) Cardinale has shown that early initiation of ACEI and beta blockers is cardioprotective (Cardinale et al. 2010). These treatments not only help prevent late cardiac events; they also improve LVEF in those who show an early decrease in LVEF during anthracycline therapy (Cardinale et al. 2010). These results are pertinent because another study had initially shown no permanent improvement in LVEF in children with anthracycline-associated cardiomyopathy who were started on ACEI 6–7 years after treatment (Lipshultz et al. 2002). The difference may reflect the differing population of adults and pediatrics and also the different time course in initiation of ACEI.

6.1.3 Prevention of cardiovascular toxicity related to novel targeted therapy

We are just beginning to understand the potential cardiovascular effects of the multitude of new targeted agents that are being approved. However, there is some data already that suggest aggressive management of hypertension both prior to initiation of targeted therapy with VEGF inhibitors and also during therapy, may reduce the risk of heart failure associated with certain agents. Patients in Phase III trials of sunitinib that excluded hypertensive patients had lower incidence of heart failure on sunitinib, a multi-targeted tyrsoine kinase inhibitor that also inhibits VEGFR (Chen et al. 2008; Chu et al. 2007; Maitland et al. 2010). In this age of personalized medicine, anti-cancer regimens would eventually be optimized for each individual with improved understanding of an individual's particular likelihood of response and a risk of cardiotoxicity. Collaboration between oncologists and cardiologists in the management of patients with cancer would optimize the chance for a "cure" while minimizing potential cardiovascular issues in the years to come (Albini et al. 2010; Hampton 2010).

6.2 Management

Diagnosis and management of treatment-related cardiotoxicity in cancer survivors are complex endeavors. One reason why the diagnosis is so difficult is because radiation-associated and chemotherapy-associated effects often emerge decades after exposure. Another difficulty of diagnosis is that as cancer survivors age, like their healthy counterparts, they accrue additional co-morbidities for cardiovascular disease. Thus, it can be difficult to definitively attribute late cardiovascular effects to cancer therapy versus other age-related comorbidities.

Ultimately, the best way to ameliorate late-onset effects is through increased awareness and vigilance. To that end, we discuss five common cardiovascular effects associated with cancer treatment, in order to guide clinicians when referring these patients for further cardiac screening. In addition, we will give an overview of their cardiac work-up and propose some recommendations for how physicians can help these patients manage and minimize cardiovascular risks and events.

6.2.1 Heart Failure

Heart failure is one of the most serious complications of anti-cancer therapy. It is the end stage of several types of cardiovascular disease that impairs either ventricular filling or ventricular ejection. Heart failure ensues when the compensatory mechanisms of the heart are overwhelmed, and cardiac output falls with resulting fluid overload. However, no single test is diagnostic for heart failure; therefore the diagnosis of heart failure is complex, and can be made only after detailed evaluation and assessment. The patient's history, physical examination, noninvasive testing and imaging, and serum biomarkers must all be integrated

to determine the diagnosis of heart failure, along with its etiology and severity (Hunt et al. 2009).

Heart failure symptoms include dyspnea, fatigue, and exercise intolerance. The nonspecific nature of these symptoms means that diagnoses other than heart failure also must be considered. For example, dyspnea may result from pulmonary disease or as an equivalent for angina in patients with occult coronary artery disease. In addition to heart failure, fatigue in cancer survivors may result from depression and/or medical deconditioning.

On physical examination, signs of volume overload include jugular venous distention, ascites, and peripheral edema. Symptoms of heart failure in conjunction with signs of edema on physical examination strengthen the likelihood of heart failure. However, peripheral edema can be caused by noncardiac diseases, e.g., liver failure and renal dysfunction, both of which may also be a result of anti-cancer therapy.

EKG can aid in establishing whether coronary disease or arrhythmias are likely causes of heart failure. Chest X-ray may be useful, if there is demonstration of cephalization of pulmonary vasculature, peribronchial cuffing, or edema. Echocardiography also should be considered as a diagnostic tool in patients with suspected heart failure, since echocardiography can potentially elucidate differentials such as dilated cardiomyopathy, diastolic dysfunction, coronary artery disease, valvular heart disease, and/or pericardial disease. Furthermore, pulse and tissue doppler imaging performed during echocardiography allows assessment of cardiac hemodynamics that may suggest low output states or elevations in atrial or ventricular chamber pressures.

In addition to traditional imaging methods, serum biomarkers can also be useful in helping diagnose heart failure in patients whose diagnosis is unclear. The serum biomarkers brain natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP) are most commonly used. BNP is a natriuretic hormone, produced predominantly by the heart, and released into the circulation after it is cleaved from the C-terminal of its pro-hormone pro-BNP. The N-terminal fragment (NT-proBNP) that also results from the cleavage of pro-BNP, is released into the blood circulation along with BNP. In heart failure patients, elevations of both BNP and NT-proBNP levels are seen (Palazzuoli et al. 2010). However, there are limitations to BNP or NT-proBNP measurements, since other diseases such as sepsis may also cause abnormal BNP levels. Furthermore, some heart failure patients may not exhibit any significant elevation in BNP or NT-proBNP. Therefore, BNP and NT-proBNP levels should be considered in context of the entire clinical picture, and levels in isolation are not diagnostic of heart failure.

Troponin is a sensitive and specific marker for cardiomyocyte injury; it is now routinely and widely used in the general population to assess myocardial damage from coronary artery disease. Recently, there has been significant interest in using troponin levels to assess myocardial damage from anti-cancer therapy in particular, to guide initiation of cardioprotective therapy, and also to prognosticate future cardiac events from anti-cancer therapy. Cardinale et al. 2000 and 2010 have published a significant body of work that elucidates the utility of biomarkers in patients who have received high-dose chemotherapy, anthracycline therapy, and now also trastuzumab therapy. Cardinale found that early release of troponin I after high-dose chemotherapy was correlated with increased risk of LV systolic dysfunction 9–10 months later. Furthermore, there is evidence that troponin I levels may also be useful in predicting late cardiotoxicity in patients receiving new targeted agents such as trastuzumab (Cardinale et al. 2010).

Since heart failure from anthracycline and radiation therapy is a progressive process that worsens with time, proper treatment is crucial. Thus, the goal of chronic heart failure management is symptom management, and slowing the progression of the disease, with the hope of decreasing mortality. In a patient with established heart failure from anti-cancer therapy, the medical management focuses on both life-style modification and pharmacological therapy as needed. Co-morbidities that result in additional stress to the heart should be tightly managed, i.e., thyroid dysfunction, smoking cessation, hypertension management, reduction of alcohol consumption, avoidance of recreational drug use, and maintenance of ideal body weight (Lejemtel et al. 2004). Salt and fluid restriction, along with daily weights is integral to minimizing fluid overload. Medical management of any co-occurring valvular heart disease, ischemic heart disease, cardiac arrhythmias, and renovascular disease that may worsen heart failure is also warranted.

The goals of pharmacologic management of heart failure are to improve symptoms of volume overload and improve cardiac performance. Diuretics, beta blockers, digoxin, ACE-inhibitors, and angiotensin receptor blockers are the mainstay of heart failure therapy and have been shown to prolong survival in the general population with heart failure (McCray et al. 2009). However, among cancer survivors who develop heart failure from anthracyclines or radiation therapy, it is currently unknown whether heart failure medications initiated at the time of onset of heart failure, will similarly improve long-term cardiac outcomes. Therefore, oncologists should be aware of the possible signs of heart failure or cardiac dysfunction in their patients, especially those who have received cardiotoxic anti-cancer therapy. Early referral to cardiology consultants for assessment and management may improve both the quality of life and survival for patients with heart failure.

6.2.2 Coronary Artery Disease

Severe obstructive coronary artery disease may result in acute myocardial infarction, unstable angina, or sudden death. It frequently may present with minimal or no prior symptoms, and can be rapidly fatal (Chen et al. 2011). Screening for coronary artery disease in high-risk populations is undertaken to detect subclinical disease prior to cardiac events, so that cardioprotective strategies can be implemented, and/or invasive interventions can be performed in those patients with severe obstructive disease involving the left main coronary artery. Importantly, the decision to screen asymptomatic individuals must be carefully considered after understanding the pretest probability of coronary artery disease in any specific population being screened. The probability of true coronary artery disease following a stress test is directly related to the pretest probability of cardiac risk and the results of the exercise test.

Abnormal resting ECG in asymptomatic individuals has been demonstrated to be correlated with an increased risk for cardiovascular disease as compared to those with normal ECG. However, utility of ECG screening is limited because one-half to one-third of individuals with normal coronary arteriogram have abnormal ECG, while 30 % of those with angiographically proven coronary artery disease have a normal resting ECG (Coronary Artery Surgery Study (CASS) 1983; Rose et al. 1978). Importantly, most coronary events occur in individuals who have ECG free of abnormalities.

Exercise ECG test is an important modality used to detect ischemia, as determined by ST segment depressions on ECG. However, in patients who have LBBB, and pre-existing ST changes >= 1 mm exercise testing with imaging should be considered (Klocke et al. 2003).

Stress testing with imaging can be performed with the use of echocardiography, nuclear imaging, or MRI. The choice of imaging modality to use depends on the availability, expertise at the different centers, cost, radiation exposure, and portability. In general, stress echocardiography with its portability, its wide availability and also its lack of radiation exposure, is frequently used. Computed tomography either conventional or electron beam computed tomography can measure coronary artery calcification (CAC). A high score may be indicative of heart disease in asymptomatic individuals (Haberl et al. 2001; Andersen et al. 2010). However, the additional radiation exposure to the patient that CT entails, and the lack of diagnostic cardiac data that CT provides in a known high-risk population, must be considered before ordering this test.

Angiography (or cardiac catheterization) is considered the gold standard for detecting CAD, but predictive validity is low since arteriography does not assess implications of dysfunction (e.g., detected lesions).

Coronary artery disease can be managed medically, surgically, or by some combination of both. Medical versus surgical/percutaneous management of patients with coronary artery disease is in part determined by whether patients are at low versus high risk for cardiac events. Stress testing can help risk-stratify patients. Low/intermediate risk cardiac patients are usually treated medically. Coronary angiography with percutaneous coronary intervention (PCI) or coronary artery bypass surgery is usually reserved for high-risk patients.

Medical management of CAD typically involves several simultaneous approaches: (1) ASA each day, (2) modification of cardiac risk factors, (3) reduction of other co-morbidities that increase myocardial demand, and (4) control of stable angina.

Management of cardiac risk factor is an important strategy in decreasing risk of CAD. As previously discussed, many long-term cancer survivors are at increased risk for coronary artery disease because of their anti-cancer therapy. Although cancer survivors' treatment history is an immutable cardiac risk factor, as are their age, gender, and family history of cardiac disease, the majority of cardiac risk factors can be reduced. In fact, in the general population, nine modifiable cardiac risk factors are associated with 90 % of the attributable risk of an initial myocardial infarction (Yusuf et al. 2004). Aggressive cardiac risk factor reduction including smoking cessation, lipid lowering, weight reduction, and blood pressure and glycemic control have been demonstrated to lead to improved patient outcomes. Therefore, prevention and amelioration of cardiac late effects in long-term cancer survivors, who are at risk of premature CAD, should focus on aggressive cardiac risk factor modification through diet, lifestyle modification, and medical therapy.

Another important tactic in ameliorating CAD in survivors of (childhood) cancer is to control comorbidities. Survivors who develop cardiovascular events frequently have multiple medical comorbidities such as hypertension (Aleman et al. 2007). Comorbidities that generally lead to increased myocardial demand (i.e., thyroid function, hypertension, or valvular heart disease) should be aggressively managed.

Finally, medical management of angina, if any, is generally accomplished with one or more types of anti-ischemic medications, including nitrates, beta blockers and calcium channel blockers.

6.2.3 Valve Disease

With the advent of echocardiography, valvular heart disease has become one of the more straightforward cardiovascular diagnoses. In patients who have developed cardiomyopathy and also for those that have received radiation therapy, valvular heart disease is a frequent occurrence. In patients

who have received cancer therapy, echocardiography is a Class I recommendation for screening (Cheitlin et al. 2003). Clinically, significant disease involves regurgitation or stenosis that is at least moderate in severity.

Valvular disease is known to be progressive in many patients. When the degree is severe, valve repair or replacement should be considered. Furthermore, any precipitating causes that may worsen valvular dysfunction should be corrected, if possible. The optimal timing and type of valve surgery to undertake are decisions that require integration of pathophysiology, the anatomy involved, patient preference for anti-coagulants, the patient's surgical risk, the surgeon's expertise, and valve type.

6.2.4 Conduction Block

While there is some degree of knowledge about the screening and management of heart failure and constrictive pericarditis, conduction block is a late cardiovascular effect of cancer treatment that is somewhat less well understood. Radiation fibrosis of the heart's conduction system results in electrical changes on the electrocardiogram that may be clinically silent or result in symptoms. Depending on the degree of heart block, the type, and the severity, a pacemaker may be warranted. Complete heart block may occur suddenly in long-term survivors who have received chest radiation and who develop syncope. Referral to cardiology for assessment is prudent when there is evidence of second-degree heart block on EKG, since advanced second-degree or third-degree heart block is a class I indication for a permanent pacemaker.

6.2.5 Constrictive Pericarditis

Constrictive pericarditis may be caused by radiation therapy (see above) and is an important cause of diastolic heart failure. The pericardium becomes fibrous and scarred by chronic inflammation, encasing the heart in an inflexible shell. As a result of pericardial constriction, diastolic filling of the atria and ventricle is impaired. While early diastolic filling is rapid or even normal, the pericardium constricts filling at mid-and end-diastole. Given the pericardium's rigidity, there is marked interdependence between the right and left ventricle, which can result in equalization of diastolic pressures between the left and right ventricles. Importantly, systolic function is usually preserved, until constrictive pericarditis becomes very severe. At that point, stroke volume may start to fall as the heart no longer can adequately fill.

Symptomatically, the patient may insidiously develop fatigue, dyspnea, and volume overload. Physical examination may reveal pedal edema, ascites, pleural effusions, and hepatomegaly. Since these symptoms are nonspecific, unless the suspicion for constrictive pericarditis is high, they may be misattributed to cirrhosis or liver disease (Francis et al. 2004).

Imaging studies are helpful in establishing the diagnosis of constrictive pericarditis. Echocardiography is a class I recommendation for screening in patients suspected of constriction (Cheitlin et al. 2003). Both calcification of the pericardium and pericardial thickening can frequently be seen on echocardiography. However, the gold standard for pericardial imaging is cardiac magnetic resonance (MR) imaging. Classic features on MR include increased pericardial thickening and dilation of the inferior vena cava, although the data suggest that up to 20 % of patients with constrictive pericarditis may have normal pericardial thickness (Talreja et al. 2003).

Direct measurement of intracardiac pressures on cardiac catheterization frequently is needed to make a more definitive diagnosis of constrictive pericarditis. During assessment of cardiac hemodynamics, the dip and plateau or "square root" sign in the RV and LV diastolic pressure tracings are classically seen in patients with constriction. In patients with suspected constrictive pericarditis, it is important to exclude restrictive cardiomyopathy and end-stage liver disease in the differential. In certain situations, biopsy of the endomyocardium and the pericardium is used to distinguish the constriction versus restrictive cardiomyopathy. Furthermore, noninvasive imaging, i.e., echocardiography with tissue doppler imaging, may provide some evidence of constrictive versus restrictive physiology. To complicate matters, however, most patients who have received chest radiation may develop both constrictive and restrictive physiology.

With regard to treatment, it is important to accurately distinguish constrictive pericarditis and restrictive cardiomyopathy, since the former is amenable to surgery. Constriction can be treated by surgical stripping of the pericardium, although there are risks.

Pericardiectomy is associated with significant operative mortality; current mortality rates are about 6 % in patients operated on between 1977 and 2000 at the Mayo and Cleveland clinic (Chowdhury et al. 2006; Tirilomis et al. 1994). In addition to increased mortality, patients who undergo pericardiectomy following chest radiation may also face decreased long-term survival. Seven-year survival after pericardiectomy for radiation-induced constrictive pericarditis is especially poor, reaching 27 %, as compared with other etiologies (Bertog et al. 2004). Decreased survival in this population is secondary to many other late effects of chest radiation, including restrictive cardiomyopathy, interstitial pulmonary disease, sepsis, and/or secondary neoplasms that all reduce survival (Ling et al. 1999).

7 Historic Perspective and Summary

7.1 Radiation-Associated Cardiovascular Toxicity

In the past, the heart was considered to be a relatively radioresistant organ. Since the 1960s there is, however, growing evidence of increased risks of cardiovascular diseases following exposure of (parts of) the heart to therapeutic radiation doses (Cohn et al. 1967; Brosius et al. 1981; Hancock et al. 1993a; Schultz-Hector and Trott 2007), largely in patients with Hodgkin lymphoma and left-sided breast cancer. In particular, the development of coronary pathology in young individuals following radiation who lack risk factors for atherosclerosis has raised awareness of a possible cause-and-effect relationship.

During the last decades there is also emerging evidence, especially from the Japanese LSS cohort, that radiation exposure of the heart to low doses can lead to increased risks of cardiovascular morbidity and mortality. For example, an increased risk of cardiovascular disease risk has been described in the Japanese atomic bomb survivors, who received single whole-body exposure to a range of doses less than 5 Gy (Wong et al. 1993; Shimizu et al. 1999; Preston et al. 2003; Little 2009; Little et al. 2010).

Radiation-associated heart disease includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities (Adams et al. 2003; Aleman et al. 2007; Mulrooney et al. 2009). Radiation-associated heart diseases, except for pericarditis, usually present 10–15 years after exposure, although nonsymptomatic abnormalities may develop much earlier. The long delay before expression of serious damage probably explains why the radiation sensitivity of the heart has previously been underestimated.

The risk for cardiovascular diseases might also be increased through indirect effects of radiotherapy; irradiation of the left kidney during paraaortic and spleen radiotherapy, for example, might lead to hypertension (Verheij et al. 1994).

Radiation causes both increased mortality (mainly fatal myocardial infarction) and increased morbidity from cardiovascular disease. Data on morbidity are more difficult to acquire, and therefore still more scarce than data on mortality.

7.2 Chemotherapy-Induced Cardiovascular Toxicity

Cardiotoxicity associated with anticancer drugs, including not only classical cytotoxic drugs but also newer targeted therapies, is becoming one of the most important complications of cancer treatment (Albini et al. 2010; Sereno et al. 2008). The progress in the treatment of cancer leads to large numbers of long-term survivors who are at risk for long-term cardiotoxicity.

Cardiomyopathy from anthracyclines has been recognized for many years (Lipshultz et al. 1991, 1999; Singal and Iliskovic 1998). However, cardiotoxicity from anticancer drugs can manifest itself as left ventricular dysfunction and/or heart failure, myocardial ischemia, hypertension, and interference with the cardiac conduction system causing bradycardia and heart block or QT prolongation and ventricular arrhythmias (Yeh and Bickford 2009).

The occurrence of cardiotoxicity from chemotherapeutic agents depends on a number of factors related to the oncological treatment: the type of drug, the dose administered during each cycle of treatment, the cumulative dose of the drug, the schedule of administration, the route of administration, the combination with other cardiotoxic drugs, and the combination with radiotherapy (Bovelli et al. 2010). It is also dependent on patient-related factors such as the age of the patient, the presence of cardiovascular risk factors, previous cardiovascular disease, and prior irradiation including the heart.

Heart failure has been associated with several different classes of agents, including anthracyclines, alkylating agents, antimetabolites, antimicrotubule agents, monoclonal antibodies, proteasome inhibitors, and small molecule tyrosine kinase inhibitors. Myocardial ischemia and infarction is seen after treatment with antimetabolites, antimicrotubule agents, monoclonal antibodies, and small molecule tyrosine kinase inhibitors.

Hypertension is common in the general population,and therefore occurs frequently in cancer patients. New anticancer treatments targeting angiogenesis are associated with an increased risk of hypertension, which may lead to serious complications such as hypertensive encephalopathy and cerebral hemorrhage.

Bradycardia and heart block have been associated with angiogenesis inhibitors and with antimicrotubule agents. QT prolongation has been associated with histone deacetylase inhibitors and small molecule tyrosine kinase inhibitors. Moreover, QT prolongation may also be caused by concomitant medication often used in cancer patients, such as antiemetics and certain antibiotics, and the risk may increase due to electrolyte disturbances caused by vomiting and diarrhea. QT prolongation is not symptomatic in itself. However, it is an abnormality of the electrical activity of the heart which may increase the risk for ventricular arrhythmias.

Vascular toxicity caused by anticancer drugs is primarily a local phenomenon at or near the site of infusion. However,

antineoplastic therapies may also damage the intima of the blood vessels in general, thereby activating the coagulation cascade and predisposing to thrombosis (Albini et al. 2010). In this way, peripheral circulation may be impaired.

Apart from the direct cardiovascular damage caused by cancer treatment, cardiovascular disease in cancer survivors may also result from accelerated atherosclerosis due to treatment-related cardiovascular risk factors (de Haas et al. 2010). These risk factors cluster into the so-called metabolic syndrome, whose core components are dyslipidemia, hypertension, central obesity, and insulin resistance (Alberti et al. 2006, 2009; Einhorn et al. 2003; Grundy et al. 2005). The metabolic syndrome is associated with certain cancers, e.g., colon and breast cancer, and hence patients with such malignancies have a higher risk of these risk factors even at the time of diagnosis. In survivors of adult cancer, the metabolic syndrome has been assessed in testicular cancer and after stem-cell transplantation for hematological diseases (Annaloro et al. 2008; Haugnes et al. 2007; Majhail et al. 2009; Nuver et al. 2005; Wethal et al. 2007). The reported prevalence varied between 26 and 55 %, which is significantly higher than expected in the healthy reference populations. Both local treatments (surgery and radiotherapy) and systemic treatments (chemotherapy, biologicals, and hormone therapy) can cause changes in endocrine and metabolic functions which may contribute to the development of the metabolic syndrome (de Haas et al. 2010).

7.3 Other Risk Factors for Treatment-Associated Cardiac Toxicity

General risk factors for cardiovascular diseases, such as hypertension, diabetes, hypercholesterolemia, overweight, and smoking (Miura et al. 2001; Chobanian et al. 2003; Haider et al. 2003; Kannel 1996; Bakx et al. 2001), probably also contribute to the risk for cardiovascular diseases in patients treated for malignancies (Glanzmann et al. 1994; Bowers et al. 2005; Hooning et al. 2007). The potential role of genetic variability in the pathogenesis of chronic cardiotoxicity, like congestive heart failure, remains to be elucidated. In this regard, only a few studies in humans provide evidence that genetic susceptibility may play an important role in the risk of anthracycline-associated cardiotoxicity (Wojnowski et al. 2005; Deng and Wojnowski 2007; Blanco et al. 2008).

8 Future Directions and Research

8.1 Future Directions and Research Regarding Radiotherapy

Cardiotoxicity from radiotherapy is likely to remain an important issue. Although radiation techniques have improved over time leading to less toxicity, in general the number of people treated with radiation gradually grows, in several diseases higher radiation doses are used and radiation is combined frequently with (cardiotoxic) chemotherapy. Modern radiation techniques such as intensity-modulated radiotherapy and inspiratory breathholding techniques during delivery of radiation therapy that are currently not used for many patients because of costs and lack of technical capacity to do this.

Research must focus on the following points:

- Quantifying dose- and volume effects of radiation-associated cardiotoxicity for specific cardiac sub structures.
- Evaluate possible interaction of radiation and chemotherapy with respect to cardiotoxicity.
- Evaluate whether cardiac risk may be modified by other factors such as preexisting cardiovascular disease or diabetes, lifestyle factors including smoking.
- Investigation possibilities to prevent radiation toxicity through interventions.
- Further improvement of radiation techniques minimizing radiation exposure of the heart and its particular ‘critical’ substructures.

8.2 Future Directions and Research Regarding Chemotherapy

Cardiotoxicity from systemic anti-cancer treatment is likely to become an increasing problem for a number of reasons. The number of long-term survivors increases, and hence the number of patients at risk for this complication will increase. Patients are treated with more and more systemic treatment, because they survive longer and because new drugs are being developed. These new drugs have new mechanisms of action, and hence new risks for cardiac complications.

The challenge will be to develop drugs and combinations of drugs that are more and more effective with regard to tumor response, without at the same time increasing the risk of cardiovascular complications. Research must focus on the following points:

- Elucidating the mechanisms of action on the cardiac structures of existing and new anti-cancer drugs, and if possible finding different mechanisms than the ones responsible for the anti-cancer effects, thus enabling selective blocking of cardiotoxicity without decreasing the desired effects on the tumor.
- Investigating new technologies for delivering systemic anti-cancer therapy, e.g., in nanoparticles, which may decrease cardiotoxicity of the drugs.
- Analyzing the dose and schedule dependence of the drugs, with the aim of finding the least cardiotoxic schedule with full anti-tumor effect.
- Development of new and effective drugs and classes of drugs with less or no cardiotoxicity.

8.3 Future Directions and Research Regarding Treatment and Prevention

Preventative strategies for cardiovascular health will focus on a better understanding of the temporal role of risk factors in onset of cardiovascular disease. Furthermore, there will be greater importance placed on the treatment of subclinical disease. Although novel technologies may be applied in the detection of disease, the focus should be on management rather than on detection alone. Testing that further exposes a patient to radiation should be carefully considered, and alternatives sought if possible. Given the rising cost of healthcare in all nations, the cost of tests will be greater scrutinized. Therefore, studies assessing the most cost-effective strategies to employ will be of greater import. Work and research are already underway in many groups to use electronic medical records and the Internet to enhance the interaction between patient and their healthcare providers.

Further research is also necessary to determine whether high-risk patients who undergone anti-cancer therapy should be started immediately on cardioprotective agents such as beta blockers and ACE inhibitors. Collaboration between radiation oncologists and cardiologists will allow for development of early intervention for cardiotoxicity that may arise from life-saving anti-cancer therapy.

9 Landmark Studies

Classic reports in this area include the following:

i. Carmel and Kaplan (1976): Demonstrate the strong volume dependence of pericardial injury in patients irradiated for Hodgkin lymphoma.
ii. Cuzick: Convincingly demonstrates that post-mastectomy radiation for left-sided breast cancer increases the rate of subsequent mortality (Cuzick et al. 1988), due primarily to an excess risk of cardiac events (Cuzick et al. 1994).
iii. Fajardo and colleagues: Describe the radiotherapy-induced pathologic findings (Cohn et al. 1967; Stewart et al. 1995; Fajardo et al. 2001).
iv. Sarah Darby and colleagues: Conducts a series of population studies further documenting the risk of RT-associated heart disease in patients irradiated for breast cancer (Darby et al. 2003, 2005).
v. Fiona Stewart and colleagues: Further determines the molecular mechanisms that underly RT-associated heart disease (Stewart et al. 2006).
vi. Hancock and others note increased rates of IHD in patients irradiated for Hodgkin lymphoma (Hancock et al. 1993a, b; Hancock and Hoppe 1996).
vii. van Luijk: Conducts elegant studies in animals suggesting and interaction between cardiac and pulmonary injury from radiotherapy (van Luijk et al. 2007).

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ACC/AHA guidelines on treatment of heart failure

Esophagus

Timothy N. Showalter and Maria Werner-Wasik

Contents

Abstract

- The esophagus is exposed to high radiation doses during thoracic RT, and acute esophagitis is a frequent dose-limiting toxicity of concurrent chemoradiotherapy regimens.
- Acute esophageal effects are related to damage of the basal epithelial layer, while late esophageal effects appear to be largely related to damage of the muscular wall.
- Animal models demonstrate necrosis of the muscular esophageal wall as the relevant pathway to late effects of RT on the esophagus, and associated molecular changes include oxidative stress and elevated levels of TGF-β and inflammatory cytokines.
- Esophageal peristalsis is an essential normal organ function. Disruption of esophageal motility is common after RT, as visualized by esophagograms or manometry.
- Severity of acute esophageal toxicity from RT is associated with an increased risk of late esophageal injury, suggesting a partial consequential relationship between acute and late injury.
- Late manifestations of RT-induced esophageal damage include dysphagia, dysmotility, stricture, ulceration, and fistula. The most common presentation of late esophagitis is dysphagia to solids due to focal stricture.
- The current standard instrument for scoring both acute and chronic esophagitis is the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0, which relies strongly upon patient-reported symptoms.
- Clinical parameters associated with increased risk of late esophageal injury may include concurrent chemotherapy, hyperfractionated RT, presence of dysphagia prior to RT, severity of acute esophagitis, and the addition of intraluminal brachytherapy.
- Emami et al. provided the first dose-volume recommendations for esophagitis, using the clinical endpoint of clinical stricture or perforation at 5 years, based upon expert consensus.

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- In the era of three-dimensional treatment planning, dosimetric factors that have been associated with late esophagitis include: volume and surface area exposed to >50 Gy, length of full-circumference dose >50 Gy, maximum full-circumference dose >80 Gy.
- Although data are limited, hypofractionated RT regimens for lung cancer would be expected to result in higher rates of late toxicity, based upon classic radiobiology principles.
- Recommended guideline for esophageal dose constraints in RT planning include: (1), avoiding "hot spots" above the prescription dose; (2), limiting the amount of esophagus exposed to 50–55 Gy or more; and (3), minimizing full-circumference doses to less than 80 Gy.
- Optimization of RT techniques, including intensity-modulated RT, may prevent esophagitis by reducing esophageal exposure. Radioprotective agents, such as amifostine and glutamine have been evaluated for the reduction of RT-induced esophagitis, though their clinical utility has not been clearly established.
- Preventive medical management strategies for acute esophagitis during RT have been suggested to include implementation of a bland diet, pain relief, antifungal medication, and suppression of gastric acid production, but these interventions are not evidence-based.
- Endoscopic dilatation is the primary treatment for late esophageal stricture after RT. Medical management of esophageal dysmotility involves antispasmodic therapy and metoclopramide to reduce gastro-esophageal reflux.
- Future directions to prevent late esophageal injury include a better understanding of relevant dosimetric parameters, more sophisticated techniques for RT delivery, and the development of effective radioprotective agents.

Abbreviations

AJCC	American Joint Committee on Cancer
CRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
EG junction	Esophagogastric
EB	External beam
RT	Radiation therapy
FSUs	Functional subunits
HDR	High-dose rate
LENT	Late Effects of Normal Tissues
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body RT
SOMA	Subjective Objective Management and Analytic
UNC	University of North Carolina

1 Introduction

The esophagus is a muscular, tubular structure in the alimentary tract that functions to transport food from the pharynx to the stomach. It is lined with squamous epithelium and composed of mucosa, submucosa, and a muscular layer. The esophagus is exposed to high radiation doses during therapeutic strategies that incorporate irradiation or chemo-irradiation in the management of many thoracic malignancies. Acute esophagitis is a frequent source of morbidity and potential treatment breaks for patients receiving thoracic RT. Although most of the available literature regarding radiation therapy (RT)-related esophageal injury is based upon the treatment of carcinomas of the lung or esophagus, esophagitis is also observed in patients undergoing RT for thymic neoplasms, lymphoma, or vertebral body metastases. Although late effects of esophageal injury are less frequently observed than acute esophagitis, the impact of delayed toxicity may be severe. Late manifestations of RT-induced esophageal injury include dysphagia, dysmotility, stricture, ulceration, and fistula formation (Coia et al. 1995) (Fig. 1).

The clinical effects of external beam (EB) radiation therapy (RT) on the esophagus were described prior to the 1960s (Seaman and Ackerman 1957; Engelstad 1934). As trends in therapeutic approaches for non-small cell lung cancer (NSCLC) led toward more intensive therapeutic regimens of RT and chemotherapy, rates of treatment-related acute esophagitis increased. Whereas the rate of grade 3 or higher acute esophagitis was approximately 1 % with sequential chemoradiotherapy (CRT), the rates of esophagitis are higher, around 27–40 %, with concurrent CRT (Byhardt et al. 1998; Dillman et al. 1990; Curran W Jr et al. 2000; Ball et al. 1995; Umsawasdi et al. 1985; Gagel et al. 2007). Higher rates of severe acute esophagitis have been associated with increased incidence of late esophagitis (Ahn et al. 2005), but late manifestations of esophageal injury remain less common than acute toxicity in the era of CRT. In recent reports, death due to late esophageal injury occurs in only 0.4–1 % of patients treated for NSCLC (Qiao et al. 2005; Singh et al. 2003). It is anticipated, however, that the burgeoning role of hypofractionated RT in NSCLC may result in higher rates of late esophagitis due to the administration of higher doses per fraction, based upon accepted principles of radiobiology (Onimaru et al. 2003; Timmerman et al. 2006).

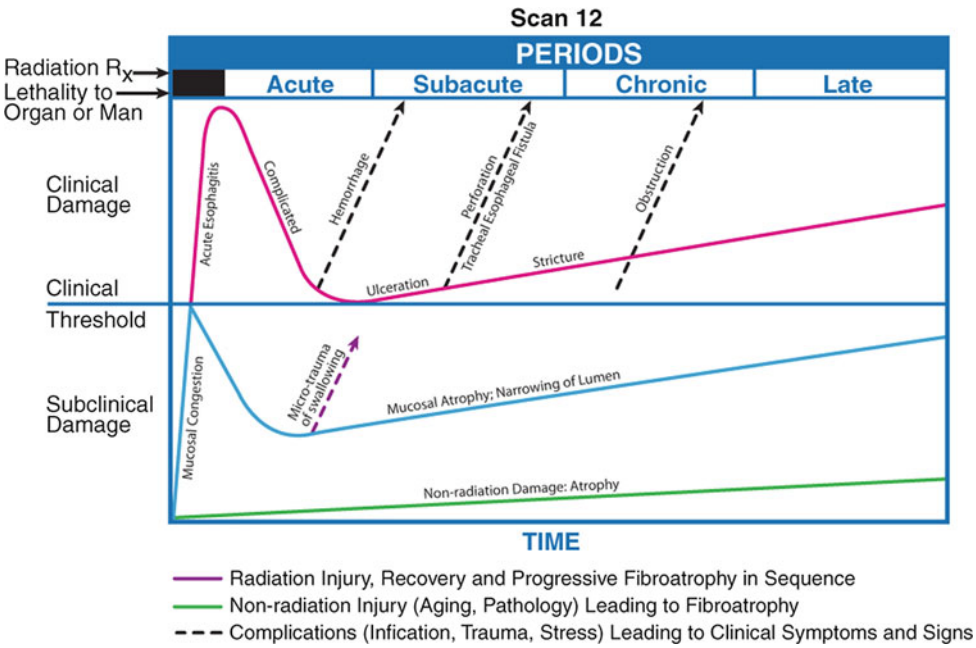

Fig. 1 Biocontinuum of adverse early and late effects of the esophagus (with permissions from Rubin and Casarett 1968)

A variety of treatment-related factors may influence the development of late effects of the esophagus after RT. An understanding of these variables will provide a foundation for efforts to limit the incidence of and to manage the symptoms of late RT-induced esophageal injury. In this chapter, we review the current understanding of RT-induced esophagitis, provide dose-volume recommendations for the clinical radiation oncologist, and describe recommendations for future directions. Bio-continuum of adverse early and late effects is shown in Fig. 1.

2 Anatomy and Histology

2.1 Gross Anatomy

The esophagus is a muscular, tubular structure that measures approximately 25 cm in length at extends from the cricoid cartilage, at the level C6 vertebral body level, to the esophagogastric (EG) junction, at the level of the T11 vertebral body level. It is located posterior to the trachea and bronchi in the posterior mediastinum. The esophagus is anterior to the spinal cord and the separation between the esophagus and spinal cord increases toward its gastric interface. The presence of an extensive network of submucosal lymphatics permits the spread of esophageal cancer several centimeters beyond the gross tumor, which is a relatively common event (Czito et al. 2008; Bradley and Mutic 2006). Sakata first demonstrated in 1903 that the submucosal lymphatics drain longitudinally, rather than in a segmental fashion (Sakata 1903). The network of lymphatics within the esophagus results in erratic spread of lymphatic metastases with frequent skip metastases to lymph nodes (van de Ven et al. 1999). Immunohistochemical analyses of surgical specimens for resected esophageal cancers have revealed a 66 % rate of skip metastases (Hosch et al. 2001). It is due to this potential for longitudinal spread that the length of longitudinal surgical margin is a predictor of outcomes after resection of esophageal cancer and that a longitudinal resection margin of 5 cm is recommended (Barbour et al. 2007) (Fig. 2).

The esophagus is generally divided into the cervical, upper thoracic, mid-thoracic, and lower thoracic regions. In the American Joint Committee on Cancer (AJCC) Staging Manual, these regions are defined as: cervical (extending from the inferior border of cricoid to thoracic inlet, at approximately18 cm from upper incisors on endoscopy), upper thoracic (extending from the thoracic inlet to level of the carina, approximately 24 cm from upper incisors), mid-thoracic (extending from the level of the carina to just superior to the EG junction, 32 cm from incisors); and lower thoracic/abdominal, the abdominal portion of the esophagus and the EG junction (40 cm from incisors) (American Joint Committee on Cancer 2002). See Fig. 2 for esophageal anatomy and index distances from upper incisors on endoscopy (Czito et al. 2008). For RT planning, the external border of the esophagus may be defined manually on axial computed tomography (CT) images. In order to obtain an accurate and informative dose-volume histogram, the esophagus should be segmented from its origin at the cricopharyngeus muscle to its termination at the gastroesophageal junction. One recent report suggests that a "correction method" for esophageal segmentation on CT images, based upon physiological principles of the normal

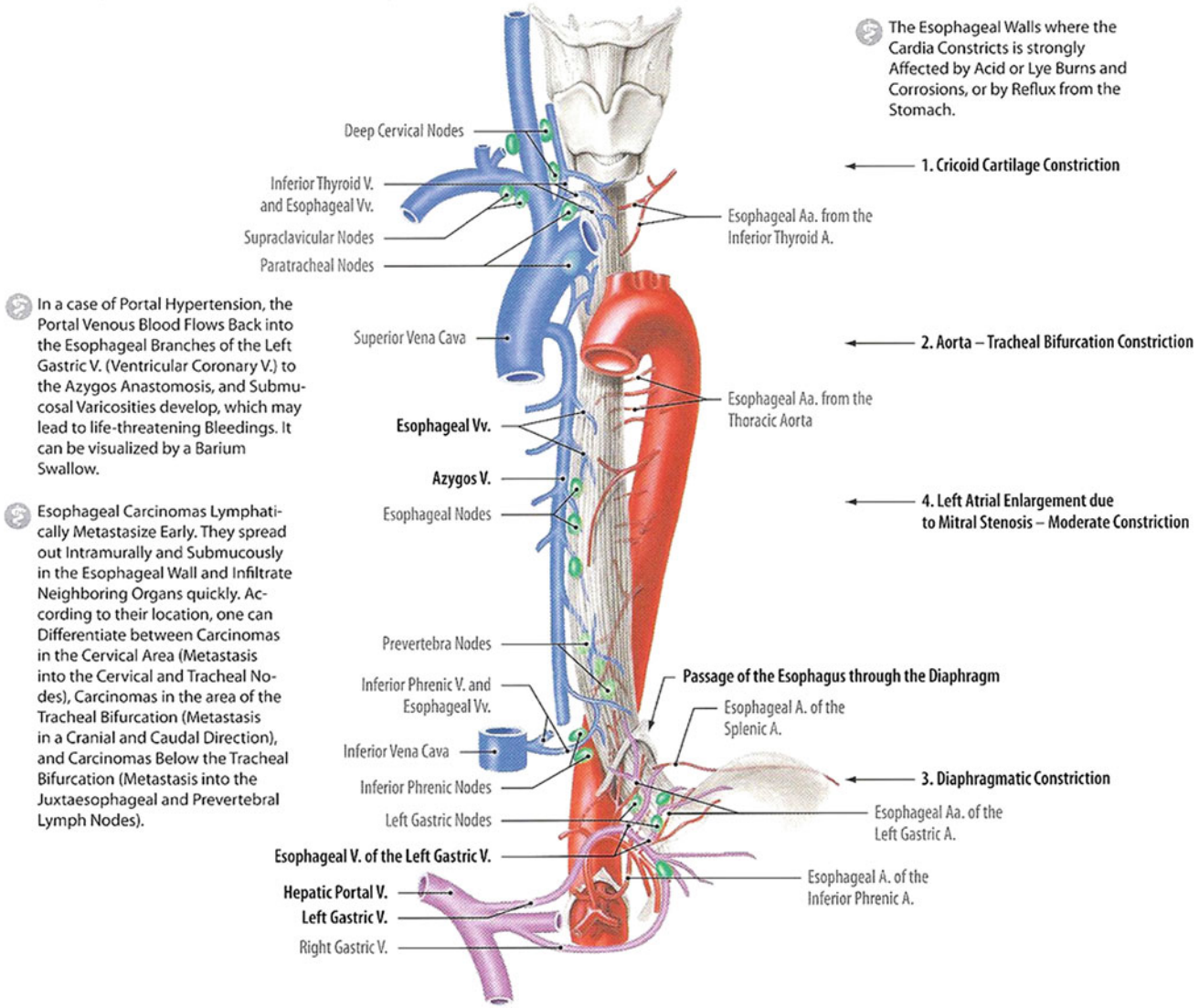

Fig. 2 Anatomy: Esophagus, Blood Supply, Lymphatic and Esophageal Sphincters: ventral view (with permission from Tillman 2007)

esophageal circumference, may improve dosimetric predictions of clinical toxicity outcomes after RT for lung cancer (Kahn et al. 2005), emphasizing the relevance of esophageal anatomy to RT planning.

2.2 Histology and the Functional Subunit

The esophageal wall contains the basic histological architecture characteristic of the gastrointestinal tract: mucosa, submucosa, two muscular layers (inner circular layer and outer longitudinal layer), and adventitia (Fig. 3a) (Rubin and Casarett 1968; Junqueira et al. 1094). It lacks serosa, a deficiency that is thought to increase the opportunity for radial extension of tumor from the esophageal wall into the periesophageal tissues. The clinical relevance, however, of the lack of serosal coverage is unclear; it is not known how much a thin serosa would protect against extramural extension for a tumor that has invaded through the muscular wall. The esophageal mucosa is composed of non-keratinized stratified squamous epithelium (Squier and Kremer 2001). The components of the esophagus may be characterized using Rubin and Casarett's classification of radiosensitivity, which is based on cellular reproductive and functional characteristics (Rubin and Casarett 1968). According to the Rubin and Casarett system, the inner germinal stratum of the esophageal epithelium contains vegetative (Group I) and differentiating (Group II) intermitotic cells, which are considered radiosensitive. The outer germinal stratum, adjacent to the esophageal lumen, is composed of fixed postmitotic cells (Group IV), which do not multiply and are considered radioresistant (Rubin and

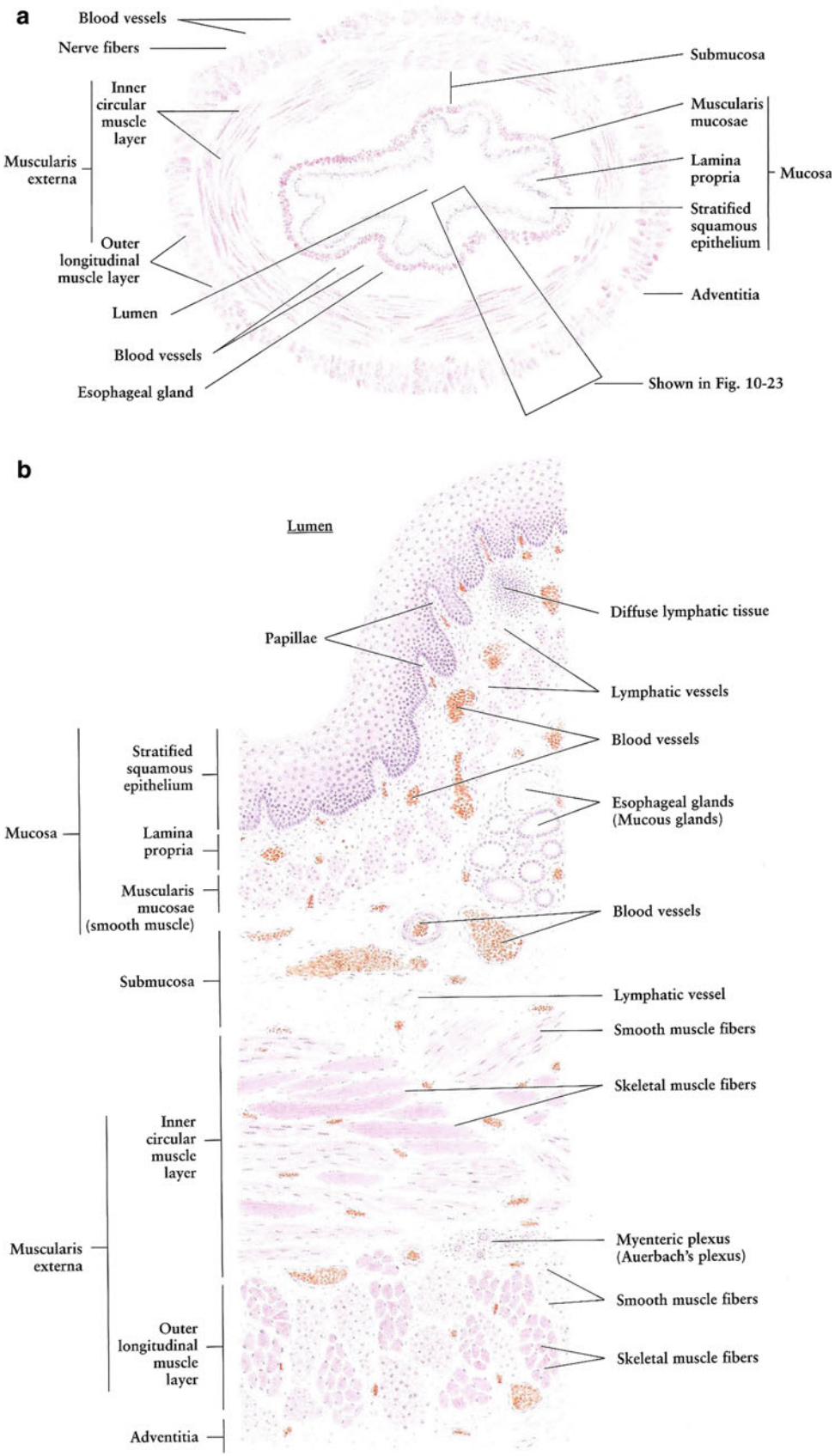

Fig. 3 **a** Histology: Esophagus cross section, very low magnification. **b** Histology: Esophagus cross section, low magnification (with permissions from Zhang 1999)

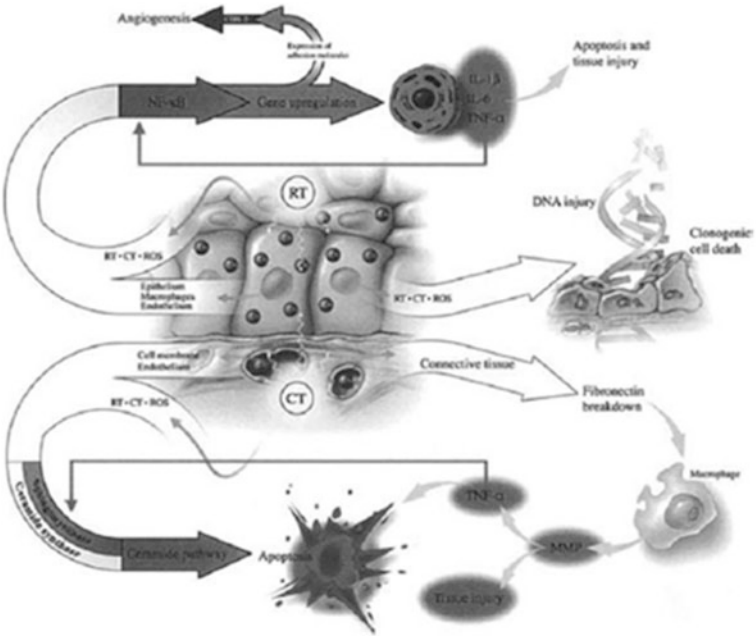

Fig. 4 Radiotherapy (RT) and chemotherapy (CT) generate ROS resulting in direct DNA injury as well as stimulation of secondary mediators leading to apoptosis. Other genes are also up regulated leading to angiogenesis. (Reprinted from Sonis ST et al. 2004; with permission)

Casarett 1968; Hall and Giaccia 2006). Although the mucosal epithelium is avascular, it receives nutrients by diffusion from capillaries contained in the lamina propria, which is also the site of venous and lymphatic drainage (Rubin and Casarett 1968). Small mucous glands, whose functions are to protect mucosa and facilitate food transport, are present within the submucosa throughout the esophagus ("esophageal glands") and within the lamina propria in the distal esophagus near the stomach ("esophageal cardiac glands") (Junqueira et al. 1094). The muscular components of the esophageal wall, governed by both reflexive and autonomic nervous system mechanisms, are responsible for the peristalsis and sphincter regulation necessary for food transport. When considered as an organ using the Michalowski classification, the esophageal radiosensitivity is in agreement with hierarchical (H-type) tissues, which are early-responding cell lines (Michalowski and Hornsey 1986; Wheldon et al. 1982). The esophagus is comprised of structurally undefined functional subunits (FSUs), in contrast to the lung, which implies that repopulation after RT may result from the migration of clonogenic cells from one FSU to another (Hall and Giaccia 2006) (Fig. 3a, b).

3 Physiology, Biology, and Pathophysiology

A series of molecular mechanisms (Fig. 4) lead to the clinical RT-induced esophageal injury that has been often divided into two phases: the acute phase, associated with mucosal damage, and the late phase, associated with harm to the muscular wall (Fig. 5a, b). There is significant overlap between the two phases, and the strong predictive association between the severity of acute esophagitis and the development of late toxicity (Fig. 5c) (Ahn et al. 2005) suggests a causative relationship. In their 1968 text, Rubin and Casarett wrote, "The radiation-induced responses and lesions in the esophagus and stomach are basically similar in principle and mechanism to those which have been described for the skin and oropharyngeal mucosa" (Rubin and Casarett 1968). This early statement has been confirmed by subsequent literature describing the pathophysiology of the acute and late effects of esophageal irradiation, both in animal models and in humans (Seaman and Ackerman 1957; Engelstad 1934; Rubin and Casarett 1968; Northway et al. 1979; Phillips and Margolis 1972; Phillips and Ross 1974; Novak et al. 1979; Gilette et al. 1998) (Figs. 4 and 5a, b, c).

3.1 Physiology

The principal function of the esophagus is to deliver food from the pharynx to the stomach, and this rapid transfer requires complex coordination to ensure proper timing and anterograde direction. Although swallowing is initiated voluntarily, esophageal motility is largely under automatic control that consists of input from the brainstem and involvement of vagal parasympathetic, efferent nerve fibers and the enteric nervous system. The upper and lower esophageal sphincters must be relaxed at the appropriate time during swallowing, as these structures are closed at rest in order to prevent retrograde movement of digestive contents. Esophageal peristalsis is activated by the stimulatory effects of distention on mechanoreceptors, triggering a

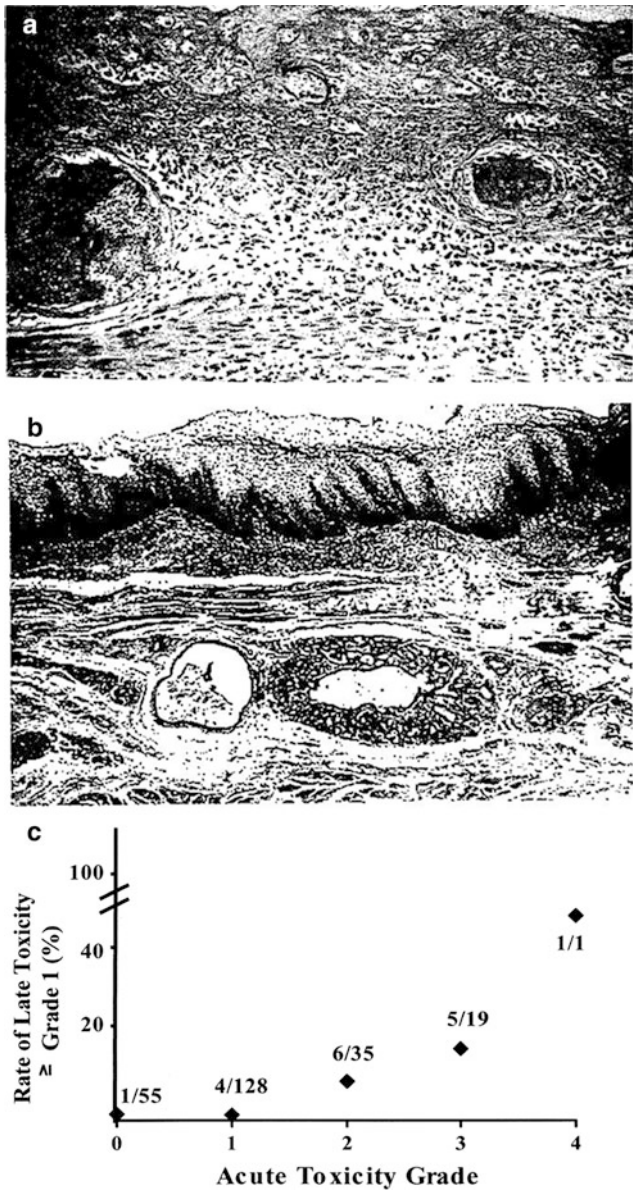

Fig. 5 **a** Acute: One-year earlier, this patients received 30 Gy to the esophagus for metastatic bone malignancy from breast carcinoma, and 20 days before death she received 30 Gy for sternal and cervical spine metastases. This photomicrograph shows acute necrosis of the esophageal mucosa (*upper*) and intense submucosal inflammation in which two thin-walled vessels are seen containing fibrin thrombi. High power. **b** Fibrosis: Postradiation esophageal squamous epithelial hyperplasia and parakeratosis are seen over submucosal fibrosis, distorted and atrophic esophageal mucosal glands, and several small blood vessels with fibrosed walls and narrow lumens. Low power. (with permission from Fajardo 2001). **c** The severity of acute esophagitis is associated with incidence of late esophageal toxicity for NSCLC patients receiving RT *With permission* (Ahn et al. 2005)

vagovagal reflex that is responsive to food bolus volume and temperature (Barrett 2307). The delivery of a food bolus from the oropharynx to the stomach is a complex, coordinated process dependent upon adequate function of multiple autonomic and reflexive processes.

Disruption of esophageal motility is a frequent occurrence after RT. Goldstein et al. used esophagograms to study RT-induced changes. They found motility disorders to be the most common RT-induced problem and reported loss of peristalsis in the irradiation portion of the esophagus, with adjacent areas of rhythmic, but uncoordinated, contraction after an average 50 Gy of RT (Goldstein et al. 1975). Lepke and Libshitz observed similar dysmotility after RT, which they described as developing 4–12 weeks after RT (Lepke and Libshitz 1983). Technetium scintigraphy has also been used to visualize temporarily prolonged esophageal transit times in most patients after RT doses higher than 40 Gy (Lamanna et al. 1985). Impaired esophageal motility may also be observed by manometry (Kaplinsky et al. 1991). The impaired motility may be related to neuronal and/or muscular injury (Coia et al. 1995; Kaplinsky et al. 1991). Due to the tubular geometry of the esophagus, the development of mural thickening or stricture may severely impair the transit of food (Coia et al. 1995; Fajardo et al. 2001). Esophageal dysmotility and stricture is a serious late morbidity for patients after RT.

3.2 Biology (Molecular Mechanisms of RT-Induced Esophageal Injury)

Although the pathologic response of the esophagus to radiation injury has been characterized (Rubin and Casarett 1968), the molecular events responsible for the late effects of radiotherapy are complex and not resolved fully (Stone et al. 2003; Brush et al. 2007; Denham and Hauer-Jensen 2002). The response of normal tissue to RT involves a sequence of steps intended to promote healing, including inflammation, epithelial proliferation, collagen deposition, and remodeling (Denham and Hauer-Jensen 2002). When compared to wound healing after non-RT tissue damage, the injury response is often dysregulated after RT. Whereas the tissue-damage response functions to promote successful wound healing in response to other insults, this response contributes to chronic damage after RT. It is possible that cytokine-mediated damage in response to RT is due to changes in the microenvironment, the influence of cell death on nearby tissues, or DNA damage (Brush et al. 2007). Pro-inflammatory mediators, such as chemokines and cytokines, are expressed in tissues, including the esophagus after RT (Vujaskovic et al. 2007; Brush et al. 2007). The significance of oxidative stress and integrin $\alpha v6\beta$-mediated stimulation of TGF-β is supported by preclinical work with amifostine in a rat model. Vujaskovic et al. showed that amifostine reduced acute and late pathologic changes after RT with associated decreases in oxidative stress and levels of integrin$\alpha v6\beta$ and TGF-β (Vujaskovic et al. 2007). It has been shown that manganese superoxide dismutase gene therapy

can ameliorate acute and late esophageal injury via modulation of RT-induced elevation of inflammatory cytokines (Epperly et al. 2001). These animal model studies of radioprotective agents for esophageal injury emphasize the relevance of pro-inflammatory mechanisms in the development of late effects after irradiation of the esophagus. In summary, the late clinical effects of esophageal irradiation appear to be initiated by oxidative stress, mediated by cytokines, and guided by end-pathway damage to the muscle wall and submucosal thickening (Fig. 4).

3.3 Pathophysiology (The Radiation Response of the Esophagus)

3.3.1 Pathologic Response to Radiation Therapy

The acute effects of RT on the esophagus are related primarily to damage of the basal epithelial layer (Phillips and Ross 1974), and late effects are associated with RT-induced changes in the submucosa and muscular tissue of the esophageal wall (Northway et al. 1979; Fajardo et al. 2001). The pathologic changes observed during RT-induced acute esophagitis are similar to findings in acute dermatitis or mucositis (Rubin and Casarett 1968; Fajardo et al. 2001). During the course of therapy, RT limits the proliferation of the basal cell layer, with degenerative changes and failure of cellular renewal. Characteristic morphologic changes include epithelial swelling, focal necrosis of the basal cell layer, and nuclear hyperchromasia. The basal cell layer may be considered the target for acute RT-induced esophagitis, as this is the region of rapid mitosis and multiplication (Fajardo et al. 2001). Dilatation of capillaries is also observed early in the course, with erythema and increased interstitial edema. The destruction of the basal cell layer results in mucosal thinning or ulceration and may culminate in esophageal mucosal denudation (Rubin and Casarett 1968; Squier and Kremer 2001; Fajardo et al. 2001) (Fig. 5a, b and c).

Although regeneration of the esophageal mucosal epithelium starts during RT, this period may also include the start of progression toward fibrosis of the esophageal wall. During the subacute period after RT, subepithelial fibrosis may become apparent. The chronic period may be viewed as a continual progression of pathologic changes observed during the subacute period, with increased thickening of the esophageal wall (Rubin and Casarett 1968; Fajardo L-G 1982). Stricture is the most common delayed sequela of esophageal irradiation (Coia et al. 1995; Fajardo et al. 2001; Fajardo L-G 1982). Morphologic findings at the stricture site include severe submucosal fibrosis, atrophic epithelial layer, and telangiectatic vessels within the lamina propria (Fajardo et al. 2001). Esophageal ulcers may develop as a delayed toxicity after RT and are usually solitary, round lesions with well-defined, raised borders. Ulceration typically involves the lamina propria and/or submucosa, but the muscularis propria is occasionally eroded. Microscopically, late esophageal ulcers characteristically contain a base of necrotic tissue with acute granulation tissue underneath, as well as chronic granulation tissue below. Chronic ulceration is associated with extensive fibrosis, and esophageal ulcers are often thought to be due to RT-induced vascular insufficiency (Fajardo et al. 2001).

Esophageal motility disorders are a significant feature of late esophagitis. Dysmotility after RT has also been attributed to neuronal injury, based upon findings of manometry and dynamic isotope studies (Kaplinsky et al. 1991). However, morphologic evidence of neuronal damage is *not* commonly found in pathologic specimens after RT (Fajardo et al. 2001), thus suggesting an alternative mechanism. Nevertheless, it is possible that there are neuronal effects that without detectable abnormalities being seen on light microscopy (Fajardo et al. 2001). It has also been suggested that motility changes after RT may be related to muscularis propria damage (Seaman and Ackerman 1957).

3.3.2 Insights from Animal Models

Animal models of esophageal injury after RT have provided important clues to the pathogenesis of acute and chronic esophagitis, beginning in 1921 with the experiments by Lacassagne involving radium exposure of the rabbit esophagus (Lacassagne 1921). After a single, large-dose RT fraction, characteristic pathologic changes in the mucosa occur that correspond to acute effects (Engelstad 1934; Phillips and Ross 1974; Lacassagne 1921). Phillips et al., using a mouse model, observed vacuolization and absence of mitoses within the basal level and thinning of the squamous surface by the third day after RT, followed by areas of basal cell proliferation during the second week, and regeneration of the mucosal lining by the end of the third week (Phillips and Ross 1974). These findings have been confirmed by pathologic studies of acute esophagitis in humans (Seaman and Ackerman 1957; Mascarenhas et al. 1989). In a more recent study, designed to evaluate amifostine in a rat model of RT injury, Vujaskovic et al. administered a single fraction of 9 Gy and observed increased esophageal mucosal thickness within 5 days of irradiation. They reported decreased acute pathologic radiation response in rats receiving amifostine (Vujaskovic et al. 2007).

Animal models have also contributed to our understanding of late pathologic changes of the esophagus after RT. Because the opossum esophagus is comprised of a muscular wall with architecture similar to the human esophagus, this has been used as a model of late RT-induced pathologic change. After a single dose of 22.5 Gy to the opossum, Northway et al. reported necrosis of the muscularis propria

and deep musculature, as well as the presence of inflammatory cells surrounding the mesenteric plexus (Northway et al. 1979). These findings have been confirmed in humans (Fajardo et al. 2001; Fajardo L-G 1982; Papazian et al. 1983) and implicate the muscular component of the esophagus as the relevant target for late esophageal injury after RT. Northway et al. also observed peristalsis abnormalities and impaired esophageal sphincter function in opossum 1–8 months after RT (Northway et al. 1979).

Michalowski and Hornsey demonstrated a dose/length effect for ulcerative esophagitis after RT, reporting that the mean effective dose for single-fraction RT decreased only slightly, from 24.5 to 22 Gy, when length of irradiated esophagus was doubled in a mouse model (Michalowski and Hornsey 1986). This weak volume effect suggests that the esophagus is a "parallel" organ. In a recent study of RT-induced esophageal injury in rodents, a single fraction of 9 Gy resulted in damage to the tunica muscularis, higher submucosal deposition of collagen, and increased presence of macrophages. These findings were associated with oxidative stress and elevation of TGF-β levels (Vujaskovic et al. 2007).

4 Clinical Syndromes (Endpoints)

For patients receiving RT for thoracic malignancies, acute esophagitis is a common treatment-related toxicity. After 2 weeks of daily standard irradiation to portals that encompass the esophagus, dysphagia, and odynophagia are commonly reported. Morbidity may be severe enough to create treatment interruptions due to consequential dehydration and weight loss. Rates of severe ($\geq$ grade 3) acute esophagitis increased from 1 % with sequential chemotherapy and RT for NSCLC (Byhardt et al. 1998; Dillman et al. 1990) to 15–46 % with concurrent chemoradiation treatment strategies (Byhardt et al. 1998; Curran et al. 2000; Choy et al. 1998) (Fig. 6, Tables 1 and 2).

Late esophagitis, which is less commonly observed than acute esophagitis, develops in <10 % of NSCLC patients receiving contemporary chemoradiotherapy (Byhardt et al. 1998). It is possible that late esophagitis will increase in frequency as hypofractionated RT becomes more prevalent for NSCLC treatment (Onimaru et al. 2003; Timmerman et al. 2006). Rates of late esophagitis are high among patients who receive large fractions of intraluminal brachytherapy in addition to external beam RT and chemotherapy, with a 12–17 % rate of fistulas and 24 % rate of strictures (Gaspar et al. 1997; Sharma et al. 2000). The late effects of RT on the esophagus generally manifest as dysphagia and odynophagia, which may be associated with stricture formation due to fibrosis of the muscular wall. Defects in esophageal motility are characteristic of late RT

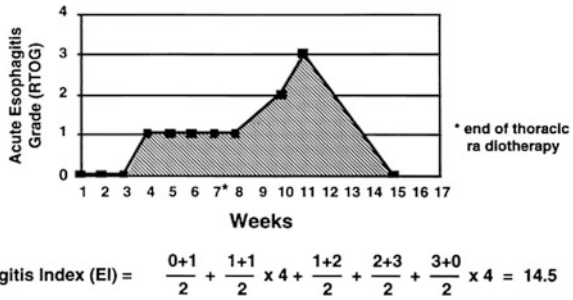

Fig. 6 Esophagitis Index is a measure of toxicity that uses an area-under-the-curve calculation to quantify the esophagitis grade over time (with permission from Werner-Wasik et al. 2000, 2002)

damage and may be observed on barium swallow (Lepke and Libshitz 1983; Goldstein et al. 1975), scintigraphy (Lamanna et al. 1985), or manometry (Coia et al. 1995; Kaplinsky et al. 1991). Strictures may develop 3 or more months after RT, with a median time of $\approx$6 months (O'Rourke et al. 1988). Barium swallow may demonstrate esophageal stricture, and endoscopy allows both visualization and potential for dilatation (Wax et al. 1997; Swaroop et al. 1994; Siersema 2008). In order to evaluate treatment-related esophagitis, several approaches have been utilized for standardized assessment of both acute and late findings.

The RTOG/EORTC developed the Subjective Objective Management and Analytic (SOMA) scale was published in 1995, as a product of the Late Effects of Normal Tissues (LENT) Conference, and provides a standard, consensus-based instrument for scoring late esophagitis (No Authors Listed 1995) (Table 1a and b).

The current version of the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) for Adverse Events (AE), CTC version 4.0 (CTCAEv4.0), and the immediately prior version (CTCAEv3.0), differ from previous versions by relying more strongly upon patient symptoms. Prior criteria, including the RTOG scale and the CTCv2.0, were based more strongly upon the clinician's assessment of the patient's symptoms, dietary changes, analgesic requirement, weight loss, and need for IV fluids and/or non-oral nutritional supplementation. The CTCAE v4.0 criteria, which are designed for both acute and late effects can be found online. Late effects of esophageal RT may also be scored using the CTCAEv4.0 GI stricture criteria. The CTCAEv4.0 is currently considered the standard instrument for evaluating both acute and chronic esophagitis. The scale is meant to incorporate symptoms due to gastroesophageal reflux, but esophagitis symptoms attributable to infection (most commonly candidiasis) must be excluded when determining a score. Toxicity scores apply to only one point in time, without information regarding the duration of suffering. For patients receiving CRT for thoracic malignancies, symptoms of acute esophagitis develop after the second week of RT

Table 1 Late effect of normal tissues for the esophagus. LENT SOMA

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dysphagia	Difficulty eating solid foods	Difficulty eating soft foods	Can take liquids only	Totally unable to swallow
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective				
Weight loss from time of treatment	≥5–10 %	>10–20 %	>20–30 %	>30 %
Stricture	>2/3 normal diameter with dilatation	>1/3–2/3 normal diameter with dilatation	<1/3 normal diameter	Complete obstruction
Ulceration	Superficial ≤1 cm^2	Superficial >1 cm^2	Deep ulcer	Perforation, fistulae
Bleeding (melena or hematemesis)	Occult	Occasional, normal Hb	Intermittent, 10–20 % decrease in Hb	Persistent, >20 % decrease in Hb
Anemia		Fatigue	Exhaustion	
Management				
Dysphagia/Stricture	Diet modification or antacids	Diet modification and occasional dilatation	Temporary NG tube or regular dilatation	Parenteral feeding, prosthesis, gastrostomy or permanent NG tube
Weight loss	Diet modification	Nutritional supplements	Tube feeding	Surgical bypass, PEG
Pain/Ulceration	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Analytic				
Barium esophagram	Assessment of esophageal lumen, stricture, dilatation			
Endoscopy	Assessment of esophageal lumen, mucosal integrity, ulceration			
CT	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
MRI	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
Ultrasonography	Assessment of esophageal wall thickness, lumen, stricture, dilatation			
Mobility esophagram	Assessment of motility of bolus and peristalsis			
Electromyogram	Assessment of motility of bolus and peristalsis			

and increase to peak severity during the treatment course (Wei et al. 2006). Acute esophagitis symptoms commonly resolve within 2–3 weeks after RT, but late symptoms of esophageal damage may develop 3–8 months afterwards. The most common presentation of late esophagitis is solid food dysphagia due to focal esophageal stricture. In the study by Ahn et al., the median time to onset of late esophageal toxicity was 5 months (maximum, 40 months) (Ahn et al. 2005). In addition to stricture formation, deficits in esophageal motility are also observed frequently, with occurrence typically within 1–3 months after RT alone or within 1 week from the start of concurrent CRT (Coia et al. 1995; Goldstein et al. 1975).

It is challenging to score the severity of acute esophagitis as the severity of symptoms varies over time. Is 1 day of severe symptoms 'better or worse' than a week of moderate symptoms? The Esophagitis Index has been suggested as a reasonable manner to generate a single quantity (area under the curve) to reflect the severity and duration of symptoms (Fig. 6) (Werner-Wasik et al. 2000, 2002). The potential advantage of this approach is that it quantifies the degree of toxicity over time, but its calculation requires the collection of toxicity scores at specific points in time (Werner-Wasik et al. 2000).

A variety of endpoints that can be used to describe late esophageal injury are presented in Table 2.

4.1 Detection: Endoscopy

In the assessment of RT-induced esophagitis, endoscopy, and imaging studies provide important information. During the acute phase, endoscopic findings of esophagitis include mucosal erythema, erosion or ulceration (Mascarenhas et al.

Table 2 Endpoints for late esophageal toxicity may be broadly divided into categories of subclinical versus clinical, and focal versus global, with corresponding examples as shown

	Focal	Global
Subclinical	1. Endoscopically detected mucosal changes (e.g., telangiectasias, ulcer, bleeding)	1. Asymptomatic dysmotility on swallowing study
	2. CT-defined thickening	2. Weight loss
	3. Stricture observed on endoscopy or swallowing study	
Clinical	1. Bleeding/ulceration	1. Dysphagia
	2. Stricture	2. Weight loss

1989; Hirota et al. 2001). Hirota et al. performed endoscopic examination during or soon after RT for patients with NSCLC, most treated with concurrent chemoradiotherapy, and found a good correlation between endoscopy-measured esophagitis grade and RTOG toxicity score (rank correlation coefficient = 0.428, $p < 0.0001$) (Hirota et al. 2001). Endoscopic findings of acute esophagitis from Hirota et al., along with the accompanying score, are displayed in Fig. 7a (Hirota et al. 2001). The agreement between endoscopic appearance of the esophagus during the acute phase and the reported RTOG toxicity score is supportive of the scoring system's validity (Werner-Wasik et al. 2004). In some instances, however, endoscopic findings of esophagitis may not be confirmed by histology when biopsied (Mascarenhas et al. 1989), producing some false-positive results. Although endoscopy may be useful in the management of esophagitis, endoscopic findings are not a primary determinant of toxicity grade in standard practice. The current CTCAE criteria emphasize patient symptoms of esophagitis, but the description of CTCAEv4.0 Grade 1 esophagitis does include asymptomatic findings on endoscopy or radiography.

Although most endoscopic findings of acute esophagitis resolve without the development of chronic effects, some damage that is evident during the acute period may progress to late esophagitis (Hirota et al. 2001). Endoscopy permits the visualization of strictures that occur as a late effect after RT (Fig. 7b) and provides an opportunity for dilatation by bougie or balloon, the standard therapeutic approach for post-RT benign esophageal stricture (Siersema 2008; Raymondi et al. 2008). Many strictures require more than one dilatation, with a reported median number of 2.5 dilatations delivered after a median time of 5 months between procedures (O'Rourke et al. 1988). The likelihood of requiring more than one dilatation for esophageal stricture is higher for complex versus simple strictures, which may be

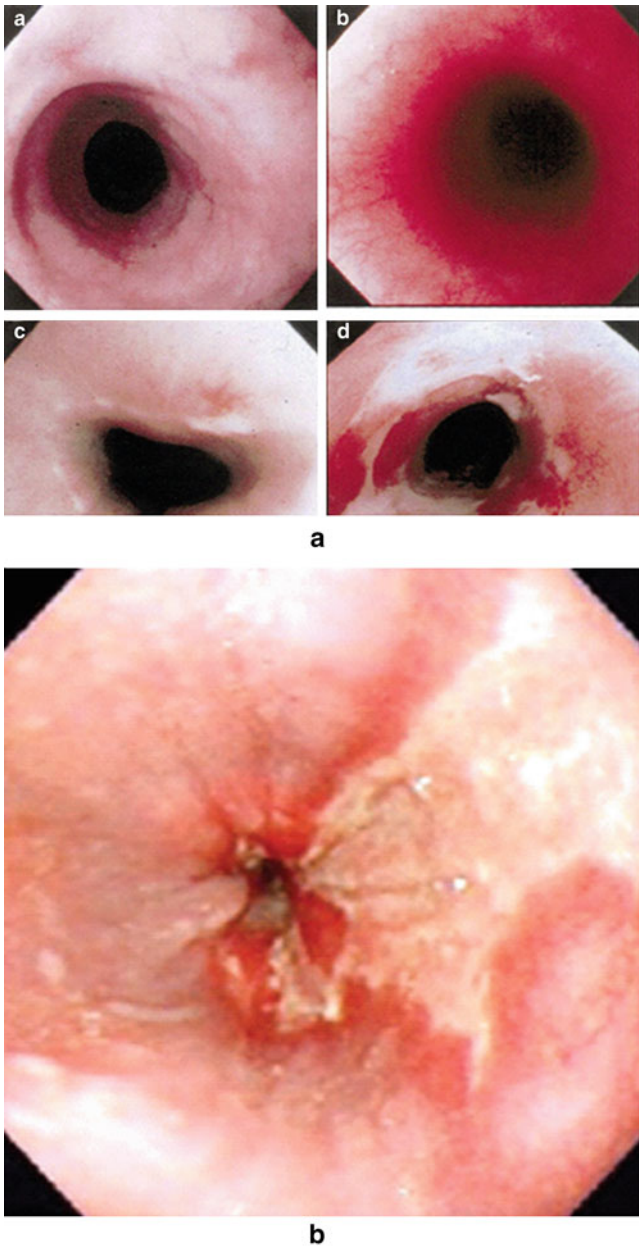

Fig. 7 Endoscopically assessed score used by Hirota et al. 2001 **a** Grade 0 for normal mucosa. **b** Grade 1 for mucosa with erythema. **c** Grade 2 for mucosa with erosion. **d** Grade 3 for mucosa with thickly-coated ulcer *Adapted with permission.* Endoscopic appearance of esophageal stricture as a late effect after RT *With permission*

determined by endoscopy. Simple strictures are short, straight, and wide enough to permit passage of a standard-diameter endoscope. Longer (>2 cm), tortuous strictures, through which a standard endoscope may not be advanced, are categorized as complex and are a challenge for endoscopic visualization and dilatation (Siersema 2008; Giever et al. 2008; Lew and Kochman 2002). Endoscopic dilatation

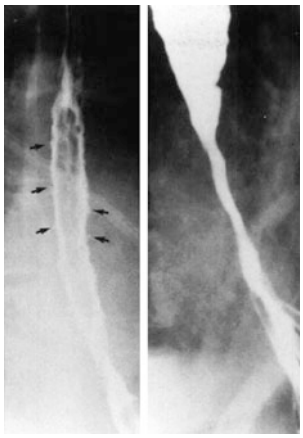

Fig. 8 Double-contrast esophagograms show the presence of multiple, small ulcers in the acute period (*left*) and the development of stricture at the site of radiation injury as a late effect (*right*). *With permission* (Collazzo et al. 1997)

is discussed in further detail below in Sect. 8.2 along with other aspects of management of RT-related esophagitis.

4.2 Diagnosis: Imaging (Radiology)

Radiological studies may complement endoscopy and clinical evaluation in the assessment of esophagitis after RT. The esophagogram may be used to demonstrate esophageal stricture and dysmotility after RT (Lepke and Libshitz 1983; Goldstein et al. 1975; Ellenhorn et al. 1993). Goldstein et al. observed deficiencies in peristaltic waves on esophagograms in patients who received mediastinal RT (Goldstein et al. 1975). Double-contrast esophagograms may demonstrate the presence of multiple ulcers or granular mucosa as an acute effect of RT, as well as stricture as a late effect after RT, as shown in Fig. 8 (Collazzo et al. 1997). Manometry and technetium transit scintigraphy may also be used to demonstrate abnormal esophageal motility after RT (Kaplinsky et al. 1991; Lamanna et al. 1985). Findings on esophageal manometry after RT that support the diagnosis of esophagitis include low-amplitude, weakened or absent peristaltic contractions (Collazzo et al. 1997). Among 25 patients who received RT, Lamanna et al. observed protracted transit times using technetium transit scintigraphy in nearly all patients after more than 40 Gy, and some patients displayed transit abnormalities at >2 months after RT (Lamanna et al. 1985). During the initial evaluation of esophageal stricture after RT, esophagography may be helpful in defining the location and extent of stricture. Other modalities, such as manometry or scintigraphy, may provide complementary information regarding esophageal motility. In appropriate cases, endoscopy would then be performed, with biopsy or dilatation as appropriate. In summary, radiography can demonstrate RT-induced esophageal injury and complements endoscopy in the evaluation of acute and late esophagitis.

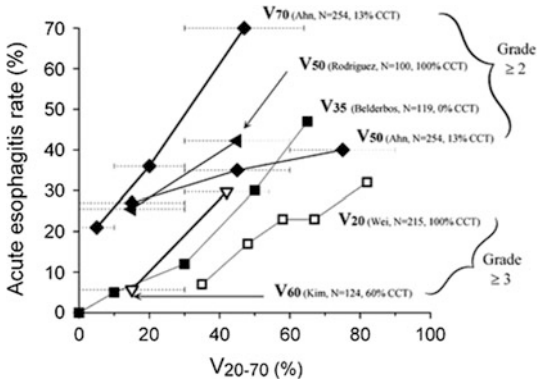

Fig. 9 The QUANTEC review analyzed the associations among dose-volume parameters and risk of acute toxicity. Incidence of acute esophagitis (y-axis) versus Vx (volume receiving more than x Gy). x-Axis values estimated according to range of doses reported. Each curve annotated as follows: Vdose (investigator, number of patients, percentage with concurrent chemotherapy (CCT). Dashed horizontal lines reflect dose ranges ascribed to each data point. Upper x-axis range of greatest data point for V50, are indefinite according to data (*light-gray dotted bars*). Solid and open symbols represent reported rates of Grade 2 or greater acute esophagitis and Grade 3 or greater acute esophagitis, respectively. Thicker and thinner solid lines represent higher and lower doses of Vx, respectively (i.e., thicker line for V70 and thinner line for V20) *Reproduced with permission* (Werner-Wasik et al. 2010)

5 Radiation Tolerance (Predicting Radiation-Induced Esophageal Injury)

Rates of late esophageal complications after RT have been associated with RT dose, with evidence of a relatively-steep dose–response curve (Morichau-Beauchant et al. 1983; Phillips and Margolis 1972). Analyses of associations between dosimetric parameters and late esophagitis have provided insight into dose-volume aspects of delayed esophageal injury after RT (Ahn et al. 2005; Qiao et al. 2005; Kahn et al. 2005; Maguire et al. 1999; Rose et al. 2008). In their seminal publication of estimated normal tissue dose limits, Rubin and Emami, Lymen, et al. suggested that the doses for whole-esophagus RT that result in a 5 and a 50 % rate of stricture or perforation at 5 years are 55 and 68 Gy, respectively, in standard fractionation (Emami et al. 1991). In the following section, we review factors associated with risk of radiation-induced esophageal injury (Fig. 9, Tables 3 and 4).

5.1 Dose Time Fractionation (Dosimetric Parameters)

Although threshold doses for RT-induced esophageal injury had been described earlier (Roswit 1974), Emami et al.

Table 3 Normal tissue tolerance estimates for esophagus, proposed by Emami et al. based upon clinical experience and review of the literature. TD5/5 and TD50/5 represent the dose that results in 5 risk and 50 % risk, respectively, for the selected endpoint of clinical esophageal stricture or perforation at 5 years

Risk	Estimated tolerance doses for esophageal irradiation			Endpoint
	1/3 Volume	2/3 Volume	3/3 Volume	
TD5/5	6000	5800	5500	Clinical stricture/perforation
TD50/5	7200	7000	6800	Clinical stricture/perforation

From Emami et al. (1991) with permission

Table 4 Example dosimetric factors that have been associated with late esophagitis in the medical literature

Author	Years	N	Dosimetric parameter
Maguire et al. (1999)	1999	91	Volume tx >50 Gy
			Surface area tx >50 Gy
			Length of 100 % circumference tx >50 Gy
			Length of 100 % circumference tx >60 Gy
			Maximum % circumference tx >80 Gy
Ahn et al. (2005)	2005	196	Length of 75 % circumference tx ≥70 Gy
			Length of 100 % circumference tx ≥50 Gy
			Length of 100 % circumference tx ≥55 Gy
			Maximal percentage of circumference tx ≥70 Gy
Kahn et al. (2005)	2005	236	Volume tx ≥60 Gy
Qiao et al. (2005)	2005	208	Mean esophageal dose ≥40 Gy
			Maximal dose point ≥60 Gy

provided the first dose-volume recommendations for esophagitis, using the endpoint of clinical stricture or perforation at 5 years, based upon the authors' clinical experience and review of the literature (Emami et al. 1991) (Table 3). Subsequently, the widespread availability of three-dimensional RT planning has provided informative data for the prediction of esophagitis. The length of irradiated esophagus has been reported to impact esophagitis, as suggested by animal studies that demonstrated that increasing the length of irradiated esophagus lowers the mean effective dose for ulcerative esophagitis (Michalowski and Hornsey 1986). However, findings in clinical studies are contradictory and do not confirm the presence of such a relationship between length or irradiation esophagus and esophagitis in NSCLC patients (Ball et al. 1995; Werner-Wasik et al. 2000; Werner-Wasik et al. 2004; Choy et al. 1999; Langer 1999). Dosimetric parameters have been associated with both acute and late esophagitis in published reports, and are reviewed below (see Tables 3, 4 and 5).

Direct associations between dosimetric factors and chronic esophagitis after RT have been described by several groups (Ahn et al. 2005; Qiao et al. 2005; Kahn et al. 2005; Maguire et al. 1999). Qiao et al. evaluated the influence of clinical and dosimetric factors upon the occurrence of esophageal injury, combining acute and late esophagitis in their analysis. In their cohort of 208 consecutive patients who received RT for NSCLC, only concurrent chemotherapy and maximal organ point dose ≥60 Gy were significant predictors of esophagitis (acute or chronic) in multivariate analysis. Late esophagitis was not evaluated separately in this paper to determine its association with the parameters studied (Qiao et al. 2005).

Investigators from the Duke University Medical Center have provided insight into the associations among clinical and dosimetric parameters and the incidence of late esophageal toxicity after RT. They also tried to consider the spatial distribution of dose to the esophagus (i.e., its longitudinal and circumferential character). The following three studies summarize their findings (Ahn et al. 2005; Kahn et al. 2005; Maguire et al. 1999). Maguire et al. evaluated the associations among incidence of late toxicity with the esophageal volume or surface area exposed to RT doses above 50, 60, and 70 Gy. In their series of NSCLC patients published in 1999, both the volume and the surface area of esophagus receiving >50 Gy (but not >60 or >70 Gy) were significant predictors of late esophageal toxicity. RT plans that delivered 50 Gy or higher to more than 32 % of the esophageal volume or surface area resulted in a threefold higher rate of late esophagitis (Maguire et al. 1999). The length of full-circumference esophageal irradiation was a significant predictor of late toxicity at a threshold dose of 50 Gy. Lengths >3.2 cm of full-circumference irradiated to beyond 50 Gy were associated with a

Table 5 Summary of large published series investigating treatment-related esophagitis in patients with non-small cell lung cancer *Reproduced with permission* (Werner-Wasik et al. 2010)

Series Institution (Author, Year)	Patient number	Prescription dose range [Median][a] in Gy (special fractionations)	% with CCT	Endpoint[b] (rate)	Univariate significant factors	Multivariate significant factors:
Duke (Maguire et al. 1999)	91	64-86 (Collazzo et al. 1997)[d] (64 % BID, 1.25−1.6 Gy/fx)	47	Acute grade ≥3 (Gr 3: 11 % Gr 4 and 5: 0 %)	None	None
				Any late:[d]18 % (Gr 1: 9 % Gr 2: 6 % Gr 3: 3 %)	V50; A50; Length of 100 % circumference >50 Gy	Gender; pre-RT dysphagia; V50; maximum % of circumference >80 Gy
Thomas Jefferson (Werner-Wasik et al. 2000)[d]	105	45–70 (Barrett 2307) (7 % BID)[f, g]	55	Acute Grade ≥3 (Gr 3: 12 % Gr 4: 1 %)	CCT; BID treatment; female gender	CCT; BID treatment
Wash Univ (Singh et al. 2003)	207	60–74 (Wei et al. 2006)[n]	25.6	Acute Grade ≥3 (Gr 3: 4.3 % Gr 4: 0.5 %)	CCT; Dmax ≥58 Gy; Mean Dose >34 Gy; Subcarinal nodes; Race	CCT; Dmax ≥58 Gy
				AND/OR[i]		
				Late Grade ≥3 (Gr 3: 4.8 % Gr 4: 0.5 % Gr 5: 0.5 %)[j]		
Wash Univ (Bradley et al. 2004)[k]	166	60–74 (Wei et al. 2006)[k]	24.7	Acute Grade ≥2 (Gr 2: 22.3 % Gr 3: 4.2 % Gr 4: 0.6 %)	CCT; aA range (aA5-aA70); aA55[m]; aV range (aV5-aV70); aV60[m]	CCT and aV60; CCT and aV60 and aV80; CCT and aA55; CCT and aA55 and aA80 "volume and area equally predictive"
Duke (Ahn et al. 2005)[n]	254	30–86 (Wax et al. 1997)[l] (39 % BID, 1.25−1.6 Gy/fx))	12.6	Acute Grade ≥3 (Gr 3: 8.7 % Gr 4: 0.4 %)	BID; nodal stage; pre-treatment dysphagia; Dmax; Mean dose; V50 Length of 50 %, 75 % or 100 % circumference ≥50 Gy; Max % circumference. ≥50, 60, 70 Gy	BID RT; nodal stage; pre-treatment dysphagia
				Any late[d] (Gr 2: 2 % Gr 3: 2 % Gr 4: 1 %)	Length with 75 % circ ≥70 Gy; Length with 100 % circ. ≥50, 55 Gy; Max % circ. ≥60−80 Gy	Prior acute toxicity dominates all dosimetric factors
NKI (Belderbos et al. 2005)	156	Group 1 (88 pts) 50−95 at 2.25/fx[o, g,o] Group 2 (68 pts) 66 at 2.75/fx [o, g]	23.7[q]	Acute Grade ≥2 (Gr 2: 20 % Gr 3: 6 % Gr 4: 0.6 %)	Lyman NTCP[r],V range (V20-V60); 35[m] % Length 100 % circumference ≥40 Gy or ≥66 Gy; Treatment group (column 3 of table); CCT worse than sequential C/RT or RT only; Sequential C/RT worse than RT alone; T Stage and Nodal stage; Age[s]	V35; CCT
Univ Michigan (Chapet et al. 2005)	101	65–103[o,g,p]	0	Acute Grade ≥2 (Gr 2: 13 % Gr 3: 3 %)	Nodal stage; V range (V40-V70); Dose- % volume range (D5-D60), D30[m];D1 cc, 2.5 cc, 5 cc	Lyman model NTCP with study-specific parameters
Goyang (Kim et al. 2005)	124	54−66 (Barrett 2307) [o,g]	60	Acute Grade ≥3–4 (G3: 12 % G4: 0.8 %)	CCT; V range (V58-V63); Dmax Lyman Model NTCP (Burman (24) parameters)	CCT; V60 (in pts with CCT)

(continued)

Table 5 (continued)

Series Institution (Author, Year)	Patient number	Prescription dose range [Median][a] in Gy (special fractionations)	% with CCT	Endpoint[b] (rate)	Univariate significant factors	Multivariate significant factors:
Harbin Univ., (Qiao et al. 2005)	208	60–72 (Wei et al. 2006)[h]	26	Acute Grade ≥3 (Gr 3: 5 % Gr 4:0.5 % Gr 5: 1 %) AND/OR[i] Late Grade ≥3 (Gr 3: 5 % Gr 4: 0.5 %)	CCT; Dmax ≥60 Gy; Mean dose ≥40 Gy; Subcarinal lymph nodes	CCT; Dmax ≥60 Gy
MDACC (Wei et al. 2006)	215	60–70 (Choy et al. 1998)[n] (16 % BID, 1.2 Gy/Fx)	100	Acute Grade ≥3[t] (Gr 3: 20 % Gr 4: 0.5 %)	aV range (aV15-V45); V range (V10-V45); Mean dose ≥34.5 Gy	V20
Barcelona (Rodriguez et al. 2009)	100	55–65 (Lamanna et al. 1985)	100	Acute Grade ≥1 Gr 2: 29 %Gr 3: 4 % Esophagitis Index[u]	V50–V55	n/a

Std Fx: five-daily fractions of 1.8–2.2 Gy/fraction per week, unless otherwise noted. *BID*: two fractions/day. *CCT*: concurrent chemotherapy
Dmax: maximum dose
Vdose (e.g., V20): relative volume receiving ≥ specified dose (e.g., ≥20 Gy). *Adose*: relative surface area receiving ≥ specified dose
aVdose, aA dose: absolute volume (V) or area (A) receiving ≥ specified dose
D#: Dose encompassing hottest # % of the esophagus. *D #cc*: Dose encompassing hottest #cc of esophagus
[a] All doses at standard fractionation 1.8–2.2 Gy/day, 5 days per week unless otherwise stated
[b] Unless otherwise specified, RTOG grading was used
RTOG Grade 2: Moderate dysphagia or odynophagia, requiring narcotic agents or liquid diet
RTOG Grade 3: Severe dysphagia or odynophagia with dehydration or weight loss, requiring nasogastric feeding
[c] Clinical calculations and prescriptions done without inhomogeneity correction. Doses for the study retrospectively corrected for inhomogeneity and are tabulated above
[d] Late complications based on fraction of patients assessable for late toxicity
[e] No 3D CRT but correlation with irradiated esophagus length as inferred from length of spine in field was investigated
[f] All the BID patients also had CCT
[g] Doses are fraction-size corrected using the LQ model and $\alpha/\beta = 10$ Gy
[h] Doses reported without tissue heterogeneity correction
[i] Acute and Late complications analyzed together
[j] Percent late complications from raw numbers (e.g. 4.8 % = 10 pts/207 pts)
[k] Same patients analyzed by El Naqa et al. (2006)
[l] Various treatment techniques and fractionation schedules used. Most common was standard fractionation for 45 Gy to the CTV with cone down to 66 Gy total to the GTV. The dose range quoted above is overall dose to isocenter, corrected for tissue heterogeneity
[m] Lowest p value
[n] Some patients analyzed by Ahn et al. (2005) were also analyzed by Maguire et al. (1999)
[o] Doses are heterogeneity corrected
[p] Esophagus constraint on treatment plan
[q] All CCT patients were in the 66 Gy group, a randomized trial of concurrent versus sequential chemotherapy; they were 54 % of that group but only 23.7 % of the total
[r] Found Lyman NTCP model parameters that gave visually good fit to data; significance not stated
[s] Not specified whether toxicity is more likely at older age
[t] Grading by institutional modification of RTOG
[u] See reference 123 for definition

threefold higher risk of late esophagitis. Similar findings were not observed at the higher dose levels, >60 Gy or >70 Gy. The administration of more than 80 Gy to any portion of the full esophageal circumference was also linked to a higher incidence of late esophagitis. In their multivariate analysis of clinical and dosimetric parameters, Maguire et al. found that significant predictors of late esophagitis were volume irradiated to >50 Gy (OR 1.10, $p = 0.02$) and maximum circumference treated to >80 Gy (OR 1.09, $p = 0.02$), as well as gender and pre-RT dysphagia (Maguire et al. 1999). This study suggested that a dose-volume effect exists for late toxicity of the esophagus after RT to a modest dose, 50 Gy, but that delayed damage may also develop after full-circumference irradiation to a higher dose, 80 Gy.

In their series of 254 NSCLC patients treated at Duke, Ahn et al. found a strong relationship between the occurrence and the severity of acute esophagitis and the subsequent development of late esophageal toxicity. In multivariate analysis of a multitude of clinical parameters, only the presence of grade 2 or worse, and grade 3 or worse, acute esophagitis were associated with late esophagitis. Seven-percent of patients developed late esophageal toxicity, and the severity of acute esophagitis was a significant predictor of late effects ($p < 0.0001$). Late esophagitis was observed in 2, 3, 17, 26, and 100 % of patients with Grade 0, 1, 2, 3, and 5 acute esophageal toxicity, as measured by the RTOG scoring criteria. Dosimetric parameters that were associated with the subsequent development of late esophagitis included length of 100 % organ circumference receiving ≥50 Gy ($p = 0.05$) and ≥55 Gy ($p = 0.05$), as well as maximum percentage of organ circumference receiving ≥60 Gy ($p = 0.03$), ≥70 Gy ($p = 0.01$), and ≥80 Gy ($p = 0.02$). The strong relationship observed in this study between the severity of acute esophageal toxicity and the incidence of late esophagitis may suggest a "consequential components" of late radiation effects, as suggested by the authors (Ahn et al. 2005).

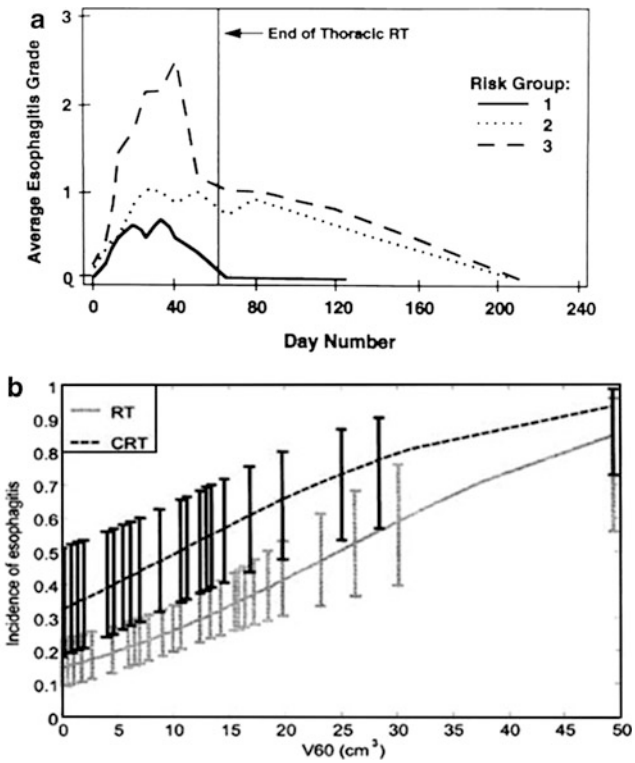

Fig. 10 The time course of acute and chronic esophagitis, as measured by the Esophagitis Index (Group 1 = standard thoracic RT alone or with induction chemotherapy. Group 2 = standard thoracic RT with concurrent chemotherapy. Group 3 = twice daily RT with concurrent chemotherapy) *With permission* (Werner-Wasik et al. 2000). Rate of ≥ grade 1 acute esophagitis as a function of the volume of esophagus receivinf ≥60 Gy (V_{60}). 95 % confidence intervels are reperesented by error bars; $p < 0.0004$ RT versus CRT. RT, radiation therapy or sequential chemotherapy followed by radiation theraphy; CRT, concurrent chemoradiation. (Reprinted from Elsiever, with permission Rubin et al. 1968)

5.2 Dose-Volume Histogram

Kahn et al. developed a "correction" method in order to produce esophageal Dose-Volume Histograms (DVHs) that reflect anatomic realities of the esophagus. That study illustrated that the circumference of the esophagus as segmented on serial axial CT images is usually variable, while the anatomic reality is that the majority of the esophagus has a fairly uniform circumference. The correction applied in that study forced a uniform "weight" to be given to each axial level in the Dose-Volume Histogram (DVH) computation. This was adopted to assess if the correlation of dosimetric factors with clinical outcomes could be improved by this "correction." It is important to emphasize that this was *not* a correction in the contouring/segmentation. Rather, it was an adjustment to the *weight* applied to each contour/segment used in computing the DVH. For 236 patients treated with RT for NSCLC, both corrected and uncorrected esophageal DVHs were analyzed with respect to both acute and late esophagitis. The correction method appeared to strengthen the associations between dosimetric parameters and the incidence of grade 1 or higher late esophagitis. Whereas the uncorrected volume of esophagus exposed to ≥60 Gy was not predictive of late esophagitis ($p = 0.091$), the correction method resulted in a significant relationship for this dosimetric factor ($p = 0.05$). A similar trend was observed for mean esophageal dose and volume receiving ≥50 Gy, but statistical significance was not observed. These findings suggest that anatomic correction of esophageal DVHs may improve the correlation between selected dosimetric parameters and observed toxicity (Kahn et al. 2005). This observation highlights a potential shortcoming of traditional DVHs, and illustrates that a modest "correction", to consider anatomic factors, may improve dose/volume/outcome correlations (Fig. 9 and Table 5).

The QUANTEC review summarized the findings from several studies that identified dosimetric and/or clinical factors as being associated with esophagitis (Table 5) (Werner-Wasik et al. 2010). The review by the QUANTEC group suggested that there is a dose response for acute esophagitis, with V70 > 20, V50 > 40, and V35 > 50 % associated with a >30 % rate of acute Grade ≥2 esophagitis. Metrics that consider the circumferential/longitudinal character of the dose (e.g., esophageal length receiving full circumference dose >40–66 Gy or 50–65 Gy) have also been reported to be associated with the risk of acute esophagitis. Other parameters including maximal esophagus dose, absolute area receiving 55 Gy (aA55) 80 Gy (aA80),

absolute volume (aV60 and aV80) have also been suggested to be predictive (Werner-Wasik et al. 2010).

Several general conclusions may be reached regarding analyses of the associations among dosimetric parameters and late esophagitis. There appears to be a dose-volume effect for the esophagus at approximately 50 Gy, as suggested by Maguire et al. and confirmed by Ahn and coworkers, who reported a predictive association between the length of 100 % circumference receiving ≥50 and ≥55 Gy the occurrence of grade 1 or greater late toxicity (Ahn et al. 2005; Maguire et al. 1999). In addition, the delivery of higher RT doses (more than 70 or 80 Gy) to an increasing portion of the organ circumference may predict for higher risk of grade 1 or higher late esophageal toxicity (Ahn et al. 2005; Maguire et al. 1999). The QUANTEC review analyzed the associations among dose-volume and clinical parameters for both acute and late toxicity (Table 5), and provided some dose-response data for acute toxicity (Fig. 9). Some of the dosimetric parameters that are associated specifically with increased risk of late esophagitis are summarized in Table 4.

5.2.1 Recommended Dose/Volume Constraints

In 1991, Emami, Lymen and others published consensus dose/volume recommendations for the tolerance of the esophagus to irradiation, using stricture and perforation as the endpoint (Table 3) (Emami et al. 1991). Although there has been a proliferation of published dose/volume guidelines for esophageal irradiation, the wide range of reported parameters and variety of clinical protocols (e.g., fractionation and chemotherapy) precludes the identification of an optimal dose/volume threshold. As a general rule of thumb during RT planning, it is essential that the maximum dose to the esophagus does not exceed the prescription dose. This consideration may be particularly relevant for radiation oncologists who plan to utilize IMRT or hypofractionated RT to treat thoracic malignancies. In designing the protocol for the current study of CRT with dose-escalated, conventionally fractionated RT in Stage III NSCLC (RTOG 06-17), the RTOG investigators elected to recommend, but not mandate, that the mean dose to the esophagus be kept below 34 Gy and that the V60 Gy be calculated and recorded. The parameters are computed with the esophagus contoured from the bottom of the cricoid to the gastroesophageal junction (Radiation Therapy Oncology Group. RTOG 0617 Protocol). Based on the authors' interpretation of the literature regarding late esophagitis (Ahn et al. 2005; Qiao et al. 2005; Kahn et al. 2005; Maguire et al. 1999), the most relevant dosimetric parameters to consider include the amount of esophagus, by volume or by full-circumference length, exposed to 50–60 Gy, as well as the maximum amount of esophagus treated to very high doses (around 70–80 Gy). Threshold values or cut-points for these dosimetric parameters cannot be recommended based on the available literature. However, it seems prudent to consider these factors during radiation planning and to make efforts to limit them in order to minimize risk of late esophagitis. Perhaps future research on the association between dosimetric factors with late esophagitis will provide specific dose-volume threshold recommendations that can be applied to clinical practice. The QUANTEC group review did not identify a single dose-volume threshold for irradiation of the esophagus, but concluded that volumes receiving >40 Gy are associated with acute esophagitis, and that RT doses above the prescription dose should be avoided to even small volumes of the esophagus (Werner-Wasik et al. 2010).

6 Chemotherapy Tolerance

It is generally accepted that concurrent chemotherapy results in higher incidence of acute esophagitis (Byhardt et al. 1998), but its relationship to late esophagitis is not as well-described in the literature. Chemotherapy, when delivered concomitant with RT, may contribute to slight increases in rate of late esophagitis (Lepke and Libshitz 1983; Greco et al. 1976). The University of North Carolina (UNC) reports do not demonstrate a correlation between late esophagitis and concurrent chemotherapy (Ahn et al. 2005; Maguire et al. 1999). However, other authors have described increased rate of esophagitis with concurrent chemotherapy. For example, the long-term results of the RTOG 92-04 trial revealed an increase in grade 3–4 late esophageal toxicity from 4 % with *sequential* chemotherapy and RT, to 17 % with *concurrent* chemotherapy and hyperfractionated RT (Komaki et al. 2002). Werner-Wasik et al. showed that concurrent chemotherapy and twice-daily RT are associated with higher Esophagitis Index in patients with NSCLC (Fig. 10a) (Werner-Wasik et al. 2000), compared to RT alone or to once-daily RT with concurrent chemotherapy. Rate of ≥grade 1 acute esophagitis as a function of the volume esophagus receiving ≥60 Gy (V60) is shown in Fig. 10b (Bradley et al. 2004). In a review of 207 NSCLC patients who received RT at Washington University, concurrent chemotherapy was a significant predictor of grade 3 or greater acute or chronic esophagitis (Singh et al. 2003). In short, the intensification of chemoradiotherapy by utilizing concurrent chemotherapy and twice-daily RT is associated with an increased incidence of late esophageal toxicity.

Maguire et al. reported an 18 % incidence of grade 1–3 late esophagitis after RT for NSCLC. Among the clinical variables analyzed, only the presence of dysphagia prior to RT showed a trend toward a significant association with the development of esophagitis on univariate analysis ($p = 0.06$). Other clinical variables evaluated include

gender, age, twice-daily RT fractionation, and concurrent chemotherapy (Maguire et al. 1999). In a subsequent publication by Duke investigators, Ahn et al. showed that, among all clinical variable studies, only severity of acute esophagitis was associated with increased risk for late esophageal toxicity (Ahn et al. 2005) (Fig. 5c). In a recent analysis of RTOG trials of patients with locally advanced NSCLC, the majority of patients developed acute esophagitis from concurrent CRT, and hyperfractionated RT was associated with more severe esophagitis (Werner-Wasik et al. 2011).

6.1 Clinical Parameters Including Chemotherapy Tolerance

A variety of clinical factors have been associated with increased risk of late esophageal toxicity after RT, (some information regarding clinical factors is also included in Table 5 summarizing the dosimetric predictors). Patient age has been reported to be a predictor for development of late esophagitis, with esophageal strictures reported after modest RT doses (<40 Gy) in pediatric patients exposed to RT (Mahboubi and Silber 1997). However, the administration of radiosensitizing chemotherapy confounds interpretation of the few, small reports pertaining to pediatric patients (Kaplinsky et al. 1991; Ellenhorn et al. 1993; Mahboubi and Silber 1997) (Table 5).

7 Special Topics

7.1 Hypofractionated Radiation Therapy

The incidence of late esophageal toxicity with hypofractionation has not been well studied/reported. Nevertheless, it is expected that large fractions sizes utilized in stereotactic body RT (SBRT) for lung cancer may result in higher risk of late effects, if indeed meaningful portions of the esophagus are irradiated at high fraction sizes. In a series of 70 NSCLC patients who received hypofractionated SBRT to 60–66 Gy in 3 fractions, published by Timmerman et al., no cases of acute or late esophagitis were observed at a median follow-up time of 17.5 months (Timmerman et al. 2006). Similarly, Nagata et al. reported no acute or late esophagitis in their experience of 45 patients receiving SBRT to 48 Gy in 4 fractions, with a median follow-up time of 30 months. The maximum point dose to the esophagus in this study was low, 1.9 Gy (Nagata et al. 2005). Thus, a lack of toxicity may be an expected observation. Onimaru et al. administered SBRT to 45 patients with NSCLC, prescribing 60 Gy for peripheral tumors and 48 Gy for central tumors in a total of 8 fractions. The dosimetric dose constraint used for esophageal dose in RT planning was 40 Gy in 8 fractions. One case of grade 5 esophagitis occurred in a patient with metastatic NSCLC who received 48 Gy for a 3.5 cm tumor in central location adjacent to the right main bronchus. Following the resolution of grade 1 esophagitis shortly after RT, the patient developed odynophagia 3 months after RT. Death occurred 5 months after RT due to a bleeding esophageal ulcer. When the esophageal segmentation was reviewed retrospectively, a region of the esophagus near the ulcer was found to have received a maximum dose of 50.5 Gy (in 8 fractions). The highest dose administered to 1 cubic centimeter of esophagus in this region was 42.5 Gy. In their analysis of the toxicity for this patient, the authors suggested that special attention be paid to esophageal segmentation during planning and to setup uncertainty during delivery for hypofractionated RT of central lung lesions. More stringent dose constraints for the esophagus were also recommended, and the investigators planned to revise their guidelines before initiating additional trials (Onimaru et al. 2003). Although dosimetric parameters for hypofractionated RT may not be extrapolated from the above studies, it seems prudent to limit maximum esophageal dose and to exercise caution during RT planning and delivery. In the protocol for the ongoing RTOG trial of SBRT for patients with operable Stage I/II NSCLC (RTOG 0618), in which 60 Gy is delivered in 3 fractions, the maximum permitted dose to any point within the esophagus is 27 Gy (9 Gy per fraction). Exceeding this maximum dose constitutes a major protocol violation (Radiation Therapy Oncology Group. RTOG 0618 Protocol). The RTOG has developed a Phase I/II trial to evaluate SBRT for early-stage NSCLC in medically inoperable patients with centrally located tumors (RTOG 0813) (Radiation Therapy Oncology Group. RTOG 0813 Protocol). In this protocol, it is anticipated that target volumes will be adjacent to the esophagus and other midline critical structures at risk for radiation injury. For RTOG 0813, the dose constraints chosen for the esophagus, with endpoints for avoidance of stricture and fistula, are: less than 5 cc receiving a dose of 27.5 Gy (5.5 Gy per fraction), and maximum point dose of 105 % the prescription dose. Exceeding the maximum dose point limits by 2.5 % constitutes a minor, and by 5 % a major, protocol violation (Radiation Therapy Oncology Group. RTOG 0813 Protocol). Data are still emerging regarding the risk of late esophagitis after hypofractionated RT for lung cancer. Presently, the careful evaluation of doses delivered to the esophagus, and adherence to constraints employed by the RTOG, seem to be prudent to reduce the risk of late toxicity.

Table 6 Dietary rules recommended in the prospective clinical trial by Sasso et al. *Adapted by permission* (Sasso et al. 2001)

Dietary rules	
Avoid	Smoking, alcohol, citrus fruit juices, coffee, acidic foods and drinks, spicy foods, chips, crackers and other similar hard breads, chocolate, mint, fatty foods or indigestible foods
Suggested	Drink between meals. Have six light meals a day (especially liquids). Consume semisolid foods like semolina, pastina (small pasta), soup, finely diced or ground food, puree of legumes and vegetables and fresh food with high liquid content such as puddings, melon, grapes, butter, cream milk, custard, milk, and biscuits. Add to any solid food sauces, gravies, clear soups, melted butter, mayonnaise, yogurt. Take a teaspoon of olive oil before every meal

7.2 Brachytherapy

The use of endoluminal brachytherapy in the treatment of esophageal cancer has been associated with increased incidence of esophageal stricture and ulceration. When a single fraction of 20 Gy was administered via high-dose rate (HDR) brachytherapy after external beam RT, a 90 % rate of esophageal ulceration was reported (Hishikawa et al. 1985, 1987, 1991). In order to reduce incidence of late esophageal toxicity after intraluminal brachytherapy for esophageal cancer, fractionated regimens, which deliver 2–3 fractions of 5–6 Gy, have been investigated. RTOG 9207, a phase I/II trial of 49 patients with esophageal carcinoma, delivered concurrent 5-fluorouracil and cisplatin with external beam RT to 50 Gy, and a brachytherapy boost. Patients received HDR brachytherapy, consisting of three 5 Gy fractions, or low-dose rate brachytherapy to 20 Gy. Significant, life-threatening toxicities were observed, including esophageal strictures (3 patients) and fistulas (6 patients). Three patients with fistulas died due to esophageal toxicity. The cumulative yearly incidence of esophageal strictures was 17.5 % per year. Due to the significant treatment-related toxicity for patients enrolled on RTOG 9207, brachytherapy was not recommended in combination with external beam RT and concurrent chemotherapy (Gaspar et al. 1997, 2000).

8 Prevention and Management

8.1 Prevention

Dietary rules are the simplest and effective elements in avoiding the enhancement of esophagitis. The most important factors: no smoking or imbibing alcohol. These are usually the inciting elements that have initiated the carcinogenesis process (Table 6).

8.1.1 Physical Efforts to Prevent Esophagitis

During the planning of RT, several considerations may help prevent late esophageal toxicity, in addition to the dose-volume recommendations above. One obvious tactic is to limit the volume of the esophagus contained within the irradiated volume. This approach is limited directly by the anatomic location and size of the clinical target volume to be treated. Sparing of part of the esophageal circumference should be attempted if the entire esophagus cannot be avoided, which would presumably limit the risk of stricture by maintaining a portion of pliable, non-fibrotic tissue. IMRT is a potentially useful technique and has been used to avoid a portion of the esophageal circumference by creating a concave dose distribution for treatment of lung cancer (Xiao et al. 2004). It has been shown that beam weight optimization and intensity-modulation in RT planning can produce improved dose to central normal tissue structures, including the esophagus (Derycke et al. 1998; De Gersem et al. 2000). Improved understanding of esophageal motion during treatment may enhance the ability to reduce esophageal dose when using highly conformal RT. Using data obtained from four-dimensional CT scans in 29 patients, Dieleman et al. described a differential margin of 5–9 mm to account for esophageal mobility during thoracic RT Dieleman et al. 2007. Careful RT planning using contemporary techniques may improve dosimetric concerns regarding the esophagus, with reasonable, but unproven, potential for clinical enhancement. It is important that one should be careful not to compromise target coverage with modern "esophagus sparing" approaches, as the target is often exceedingly close to the esophagus. Thus, in many patients with unresectable lung cancer, incidental irradiation of the esophagus is necessary to achieve the desired target coverage.

8.1.2 Radioprotective Agents to Reduce the Risk of Esophagitis

The radioprotecting agent, amifostine, has been studied extensively for the prevention of acute esophagitis. This approach is based upon reducing oxidative stress, which is considered an initiating factor for RT injury. Given the shared pathophysiology and the clinical correlation between acute and late esophagitis, it is logical that amelioration of acute esophageal injury may reduce delayed effects after RT (Ahn et al. 2005). Amifostine (Ethyol; WR-2721) possesses a thiol group that allows it to scavenge free radicals generated by RT in an aerobic environment. The clinical trials of amifostine have produced mixed results. Institutional trials by Antonadou and coworkers, and by Komaki et al., suggested that amifostine

Table 7 Randomized trials assessing the efficacy of amifostine on RT-induced injury in patients with lung cancer (Mao et al. 2008)

First author year	Institution	Number of patients	RT dose (Gy)	Chemotherapy	Amifostine usage		Acute grade >2 pneumonitis rate (%)			Lung fibrosis rate (%)			Severe esophagus toxicity rate (%)		
					Dose (mg)	Timing (min)	Amif	Contr	ρ	Amif	Contr	*P*	Amif	Contr	*P*
Movsas et al. 2005	RTOG	242	69.6 (1.2 bid")	ind + conc	500 IV Mon.-Thu.	Pre-afternoon RT	27	28	NS	–	–	–	30[a]	34[a]	NS
(Komaki 2004)	MD Anderson cancer center	62	69.6	conc	500 *IV* 500 *IV*	20–30 pre-ChT 20–60 pre-ChT	0[a]	16[a]	0.02	–	–	–	16[a]	35[a]	0.02
Antonadou et al. 2003	Metaxa cancer, greece	73	60−67 (2 qd)	conc	300/ m^2IV	15 pre-ChT/RT	30	67	0.009	29	50	0.16	39[a]	84[a]	<0.001
Leong 2003	Singapore	60	60−66 (2 qd)	ind + conc	740/ m^2 IV	pre-ChT	–	–	–	–	–	–	43[b]	70[b]	<0.08
Senzer	Sammons	100	64.8	conc +	500 IV	15–30	–	–	–	–	–	–	11′	12·	NS
Antonadou	Metaxa Cancer	146	55–60	none	340/ m^2IV	15 pre-RT	12	52	<0.001	28	53	<0.05	$_4$t	42[b]	<0.0001
Koukourakis	University	60	50–64 (2 qd)	not specified	500 SC	20 pre-RT	–	–	–	–	–	–	20[t]	54[b]	0.05[b]

RTOG Radiation Therapy Oncology Group; *ind* induction, *conc* concurrent; *ChT*chemotherapy; *Amif* amifostine group; *Contr* control group; *NS* nonsignificant

[a] Grade 3 or greater

[b] Grade 2 or greater

[c] Three patients with thymoma and one with neuroendocrine tumör included

Table 8 Medical management guidelines for the treatment of acute esophagitis, as recommended for use in patients treated on an RTOG trial of chemoradiotherapy for non-small-cell lung cancer (0617) (Mao et al. 2008)

Suggested management of acute esophagitis (RTOG 0617)
Ketoconazole 200 mg *po* daily OR
Fluconazole 100 mg *po* daily until the completion of RT
Mixture of
2 % viscous lidocaine: 60 cc
Mylanta®: 30 cc
Sucralfate (1 g/cc): 10 cc
*Take 15–30 cc *po* q3–4 h PRN
(Contraindications: Patients on dilantin, ciprofloxacin, or digoxin)
Ranitidine 150 mg *po* BID (or other H2 blocker or proton-pump inhibitor) until the completion of RT
Grade 4 esophagitis: Hold RT and chemotherapy until grade 2 or less

may reduce acute esophagitis (Antonadou 2002; Antonadou et al. 2003; Komaki et al. 2002). In the largest published study, amifostine was evaluated in a Phase III, randomized, cooperative group trial (RTOG 98-01) of 243 patients undergoing RT, with induction and concurrent carboplatin/paclitaxel chemotherapy, for locally advanced NSCLC. The rate of grade ≥3 esophagitis in the experimental arm (intravenous amifostine), 30 %, was not significantly lower than in the control arm (no amifostine), 34 % (Movsas et al. 2005). Although amifostine did not influence the rates of esophagitis, analyses of secondary endpoints demonstrated improvements in patient-rated dysphagia and pain, as well as weight loss (Movsas et al. 2005; Sarna et al. 2008). Further, in this study, the amifostine was given only once daily, while the RT was given twice daily. Thus, "optimal potential protection" was likely not achieved. Nevertheless, taken as a whole, the prospective data do not clearly support the routine use of amifostine to prevent esophagitis in patients receiving RT for thoracic malignancies. The patient-reported outcomes, as well as potential advantages to subcutaneous administration (Koukourakis et al. 2000), may encourage further trials of amifostine, but it is not clear whether a clinically meaningful benefit will be attained. The published results of randomized trials of amifostine for the prevention of RT-induced injury in the treatment of lung cancer are summarized in Tables 6 and 7).

Other agents have been evaluated as potential radioprotective agents to prevent esophagitis, without clear demonstration of efficacy. Glutamine supplementation has been investigated as a way to prevent esophagitis. The rationale is based upon the prevalence of glutamine deficiency among cancer patients and the positive effects of glutamine on the immune system with reduction of bacterial translocation in the gastrointestinal tract. Some promising results have been obtained in prospective, non-randomized studies (Algara et al. 2007). However, there is a lack of Level I evidence to support its routine use for patients receiving RT. An oral form of sucralfate was the subject of a randomized trial of 97 patients receiving thoracic RT, but no benefit was observed in the reduction of acute esophagitis (McGinnis et al. 1997). In a double-blinded study of naproxen versus placebo in patients receiving RT, prophylactic naproxen failed to reduce acute esophagitis (Soffer et al. 1994). Another strategy that is currently under preclinical investigation is gene therapy using a human manganese superoxide dismutase plasmid, which has been effective in rodents (Epperly et al. 2001, 2002). In a small, prospective clinical trial of 29 patients, Sasso et al. evaluated a cost-effective protocol of dietary and pharmacological prophylaxis, using standard medications, to prevent acute esophagitis (Sasso et al. 2001). The dietary recommendations from this study are displayed in Table 6. Pharmacological therapy consisted of nimesulide (nonsteroidal anti-inflammatory), an antacid suspension, ranitidine (H_2-receptor blocker), domperidone (eucinetic), and sodium bicarbonate solution (alkalinizing agent). All patients tolerated the prophylactic regimen, and no patients exhibited grade 2 or higher esophagitis after a moderate dose (median, 46 Gy) of mediastinal RT without chemotherapy (Sasso et al. 2001). Though small and poorly representative of NSCLC patients, this study does demonstrate the potential impact of careful preventive management, using conservative dietary and pharmacological interventions, in the reduction of acute esophagitis during RT. The influence of these measures on the incidence of late esophageal is not known. Continued efforts are needed in order to develop novel, effective strategies to minimize acute esophagitis and to decrease the late esophageal effects of thoracic RT.

8.2 Management

8.2.1 Acute Esophagitis

Medical management of acute esophagitis centers upon supportive care with pain relief and nutritional supplementation. Topical anesthetics, opiate analgesics, sucralfate, antacids, prokinetic agents, H_2-blockers, proton-pump inhibitors, and antifungal medications are commonly prescribed (Coia et al. 1995; Choy et al. 1999; Sasso et al. 2001; Bradley and Movsas 2004; Bradley et al. 2002). Dietary recommendations typically consist of a bland diet of soft foods, with avoidance of spicy, hot or cold foods, as well as tobacco and alcohol (Choy et al. 1998). A liquid mixture ("Magic Mouthwash") commonly used in the radiation oncology clinic is composed of viscous lidocaine (2 %), benadryl elixir, saline, and baking soda. This may be used liberally by patients to ease swallowing, particularly around meal time (Werner-Wasik et al. 2004). If conservative interventions fail, a gastrostomy tube may be necessary to provide adequate nutrition during RT (Bradley

Table 9 Timeline of Literature Landmarks: A chronological summary of selected, important published contributions to the development of our contemporary understanding of the late effects of radiation on the esophagus. *Adapted from Rubin and Casarett* (Rubin and Casarett 1968) *with permission*

Years	Author	Comments
1931	Desjardins	Presented a general review of the depressive and injurious effects of irradiation reported up to that time
1934	Engelstad	Studied histologic changes in the esophagus following varying doses of irradiation
1957	Seaman and Ackerman	Presented a clinical study of radiation effects in the esophagus produced by the betatron
1960	Jennings and Arden	Conducted a serial histopathologic study of radiation changes in the esophagus of rats following single dose exposure 3000 R
1962	Skarloff and Karayannis	Found that oxethazaine in alumina gel palliated esophageal irritation due to radiation in 51 cases
1968	Rubin and Casarett	Presented a comprehensive textbook to summarize contemporary understanding of clinical radiation pathology
1979	Northway	Described radiation dose-related pathologic changes in the muscle wall of the opossum esophagus, as a model for late esophageal complications
1991	Emami	Estimated clinical stricture or perforation rate following esophageal radiation based upon dose and volume of irradiation

et al. 2002). Intravenous hydration may be necessary if oral intake of fluids is insufficient. Hospitalization is generally required if prolonged intravenous hydration and/or pain control is needed. Although acute esophagitis is usually reversible, it is a frequent cause of treatment breaks during thoracic RT. In many patients, rapid improvement occurs after a 1–3 day treatment break. In general, it is recommended that RT is interrupted after the development of grade 4 esophagitis and is not resumed until esophagitis returns to grade 2 or less. After sufficient time for healing, most cases of acute esophagitis resolve without development of chronic effects (Rubin and Casarett 1968). In the protocol for RTOG 06-17, the randomized trial of dose escalation for locally advanced NSCLC, suggestions for management of esophagitis included: an antifungal medication (ketoconazole or fluconazole); a topical anesthetic mixture consisting of lidocaine, Mylanta, and sucralfate; and a proton-pump inhibitor or an H_2-blocker such as ranitidine (Table 8) (Radiation Therapy Oncology Group. RTOG 0617 Protocol).

8.2.2 Late Esophageal Injury

The principal management approach for late esophageal stricture after RT is endoscopy with dilatation. Esophageal dilatation is generally successful at improving patients' symptoms from esophageal stricture (Zhang and Trillis 2008). When dilatations are required, the median number of dilatations performed in 2.5 per patient at a median interprocedural interval of 5 months (O'Rourke et al. 1988). For simple strictures that are focal and of sufficient diameter to allow passage of a standard endoscope, balloon dilation using normal techniques is usually possible (Lew and Kochman 2002). Dilatation may be accomplished using bougie or balloon dilatation. The primary difference between these tools is the use of longitudinal shearing force in the former, though no clear advantage has been demonstrated for balloon versus bougie dilatation (Siersema 2008). Most simple strictures resolve permanently after one to three dilatations (Siersema 2008; Raymondi et al. 2008). Dilatation is associated with a small risk of perforation or bleeding, around 0.3 %, and this rate may increase with complex strictures (Hernandez et al. 2000). In some cases of long, complex strictures or complete stricture, a "rendezvous" approach may be utilized, which involves both antegrade and retrograde endoscopic pathways to allow for dilatation (Siersema 2008; Giever et al. 2008). For patients with strictures that are refractory to multiple dilatations, endoscopic stent placement may be an appropriate step (Siersema 2008). Esophageal stents composed of silicone and polyester have been developed to prevent growth of granulation tissue and obstruction for post-RT stricture, but results have been mixed (Siersema 2008; Repici et al. 2004; Holm et al. 2008).

Esophageal dysmotility is also observed after RT (Lepke and Libshitz 1983). Currently, there are no effective methods to restore peristalsis. Metoclopramide, which increases the rate of gastric emptying, is sometimes prescribed to reduced reflux of gastric contents into the esophagus (Ramirez-Mata et al. 1977). Diffuse esophageal spasms after RT can be treated with antispasmodics such as nitrates, anticholinergics, and calcium-channel blockers (Blackwell et al. 1981; Orlando and Bozymski 1973).

9 Future Direction and Research

Significant progress has been made in our understanding of the dosimetric parameters associated with late esophagitis, and sophisticated RT techniques such as IMRT offer the

potential to avoid delivering high radiation doses to the esophagus. Future efforts to identify threshold values for the important dosimetric factors will allow the development and validation of more reliable dose/volume guidelines for prevention of late esophagitis after thoracic RT. However, it must be remembered that biological considerations are also important, and research efforts should focus on refining our understanding of the biological mechanisms of esophagitis and associated biomarkers. There is much to be gained from continued research on radioprotective agents. Future investigations will likely involve novel approaches for the biological modulation of the esophageal response to RT as a preventive measure to reduce or eliminate esophagitis. In order to better evaluate RT-induced esophagitis, and to accelerate scientific knowledge in the field, standardized approaches should be adopted broadly. There should be uniformity in how esophageal toxicity is scored. Several options for scoring have been suggested. Just as in the QUANTEC report (Werner-Wasik et al. 2010), we recommend that the latest version of the Common Terminology Criteria for Adverse Events be used to score both acute and late esophageal injury. The use of CTCAE in cooperative group trials has been required by the National Cancer Institute since 2003 (Colevas and Setser 2004). There should be pooling of RT planning, clinical, and outcomes data across institutions contained within a permanent database, as a resource for the evaluation and re-evaluation of dose-volume constraints for esophageal irradiation. Finally, images and other data collected during image-guided radiation therapy should be incorporated into future studies of RT-induced esophageal injury. Future mathematical models based upon these improved streams of dosimetric and clinical data are expected to refine and improve recommendations regarding dose-volume thresholds for esophageal irradiation.

10 History and Literature Landmarks

In a 1931 seminal report of the effects of RT on the gastrointestinal system, Desjardins wrote that the esophagus occupies a protected anatomical location and exhibits low radiosensitivity (Desjardins 1931). The apparent lack of response to RT may be reflected the lack of deep penetration of early therapy beams. The acute and late manifestations of esophageal damage from RT were subsequently characterized during the 1950 and 1960s; a historical timeline of important achievements was provided by Rubin and Casarett in their 1968 publication of *Clinical Radiation Pathology* (Rubin and Casarett 1968) (see Table 9). In 1957, Seaman and Ackerman authored a clinical and pathologic study of the effects of betatron radiation on the esophagus. Among 20 patients treated for lung carcinoma, 5 patients developed severe reactions, and radiographic findings included visualization of stenosis as a late reaction after RT. The authors provided the first clinical estimate of tolerance dose, "6,000 rads at a rate of 1,000 rads/week" (Seaman and Ackerman 1957). Later, Northway et al. used an opossum model to study the effects, both acute and late, after a single dose of esophageal irradiation, and observed focal necrosis of the muscle wall (Northway et al. 1979). In a 1983 report, Lepke and Lipshitz used esophagograms to study RT-induced esophageal injury. They noted different types of responses at different times post-RT: dysmotility within 4–12 weeks after RT, stricture 4–6 months after RT, and fistula formation without a characteristic timeframe (Lepke and Libshitz 1983). Several studies contributed information pertinent to dose-threshold estimates for RT tolerance of the esophagus (Seaman and Ackerman 1957; Dickson 1961; Morichau-Beauchant et al. 1983; Phillips and Margolis 1972; Perez et al. 1988; O'Rourke et al. 1988; Beatty et al. 1979; DeRen 1989; Kramer et al. 1987), including lessons learned from intraluminal brachytherapy for the treatment of esophageal cancer (Hishikawa et al. 1987; Hishikawa et al. 1985, 1991a, b). The first guidelines that included both dose and volume parameters were those published by Emami et al. (1991). A review of the late effects of RT on the esophagus and other gastrointestinal organs was published in 1995, based upon the Late Effects Workshop held in San Francisco in 1992, and provided a solid foundation for understanding this topic (Coia et al. 1995). A recent review of this topic was performed by the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group (Werner-Wasik et al. 2010). The current review is offered to update, enrich, and expand the information included in the prior documents (Table 9).

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Stomach, Small and Large Intestines

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Abstract

- Abdominopelvic radiation therapy plays an important role in the curative and palliative treatment for a large proportion of tumors arising from the abdominopelvic cavity; e.g., from the gynecological, genitourinary, and gastrointestinal systems.
- The maximally tolerated radiation doses for many targets in the abdominopelvic cavity are limited by the tolerance of the stomach, small and large intestines.
- Radiotherapy can be delivered before, after or during chemotherapy and before or after surgery, and the integration of these multiple modalities can impact normal tissue reactions.
- Most treatment approaches involve the use of fractionated external beam radiotherapy, often with the inclusion of brachytherapy for gynecologic malignancies.
- Curative treatment regimens typically utilize total doses in the range of 45–50 Gy delivered at 1.8–2.0 Gy per fraction.
- The risks of injury increase at doses >50 Gy and with fraction sizes $> \approx 2$ Gy.

Abbreviations

CRT	Conformal radiation therapy
ECL	Enterochromaffin-like
G	Gastrin secreting

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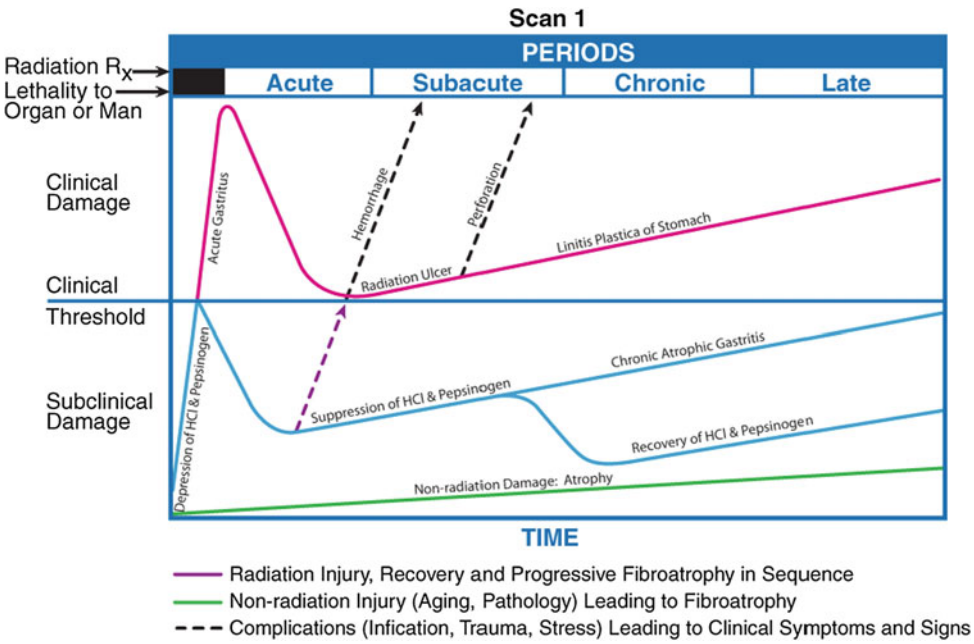


Fig. 1 Biocontinuum of adverse and late effects of the stomach (with permissions from Rubin and Casarett 1968)

IF	Intrinsic factor
IFN-γ	Interferon gamma
IMRT	Intensity-modulated radiation therapy
PPI	Proton pump inhibitors
SIR	Standardized incidence ratio
TGF-β1	Transforming growth factor β1
WAPI	Whole abdominopelvic irradiation

1 Stomach

1.1 Introduction

The major significant late morbidity resulting from gastric irradiation is ulceration, which tends to occur in the pylorus (although that may relate more to the site of delivery of radiation rather than to a specific sensitivity of the cells in this region). The ulceration likely occurs because of destruction of the mucosal cells of the gastric mucosa, with denudation. In most cases this heals adequately with conservative management, but in some cases it can proceed to perforation requiring emergency surgery or, when chronic, to fibrosis and gastric outlet obstruction. The reasons for a variable outcome in individual patients is unclear. Total radiation dose is a critical factor in determining which patients develop ulceration. There have been very few reports of ulceration occurring at doses under 45 Gy, although interpretation of these data is difficult because of the lack of good time-dose parameters in the reports. There is some more recent information, however, which suggests that fractionation is of great importance in ulcer induction. These data from Hodgkin's disease patients strongly suggest that the use of high doses of radiation per fraction predispose to the development of gastric ulceration. It is possible that the apparent decrease in ulcer formation secondary to radiation may be caused by the more common use of low doses of radiation per fraction. *The Biocontinuum of adverse acute and late effects are shown in* Fig. 1.

1.2 Anatomy and Histology

1.2.1 Anatomy

The stomach is a J-shaped, large, distensible portion of the digestive tract between the esophagus and small intestine, usually located in the left upper quadrant, where it occupies parts of the epigastric, umbilical, and left hypochondriac region (Fig. 2). It can expand considerably and can hold 2–3 L of food and/or liquid. The stomach can be divided into five parts: cardia, fundus, body, pyloric part, and pylorus. The cardia is the region around the cardiac orifice, where the esophagus enters the stomach. The fundus is the most superior portion of the stomach, often related to the left dome of the diaphragm and containing a bubble of gas seen on radiographs. The body is the major portion of the stomach between the fundus and the pyloric antrum. The pyloric part of the stomach consists of a wider portion, the pyloric antrum, that leads to a narrow portion, the pyloric canal, that ends at the final portion of the stomach, the pylorus. The pylorus serves as the distal sphincter that controls the discharge of stomach contents into the duodenum.

A Gastric Ulcer occurs most commonly on the Lesser Curvature in the Transitional Area between the Pyloric Antrum and the Body of the Stomach. Ulcers on the Greater Curvature are an ominous sign of a possible Carcinoma.
A Gastric Ulcer is a Disease of the Mucous Membrane in which the Mucosal Defect spreads beyond the Muscularis Mucosae into the Submucosa. If the Muscularis is also Penetrated, an Acute Perforation into the Abdominal Cavity or a Penetration into the Neighboring Organs (e.g., the Pancreas) may result. If the Defect of the Mucous Membrane does Not Penetrate the Muscularis Mucosae, there will be No Associated Perforation of the Stomach at this stage.

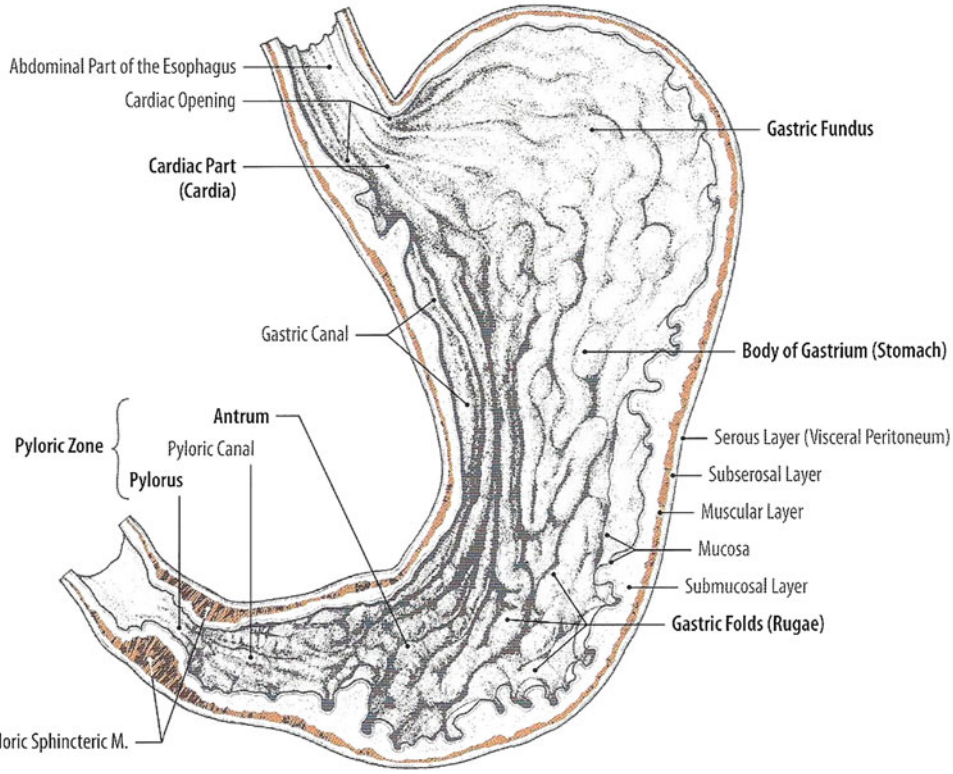


Fig. 2 Anatomy of the stomach (with permission from Tillman and Elbermani 2007)

The stomach is covered entirely by peritoneum except where the blood vessels run along its curvatures and at a small bare area posterior to the cardiac orifice where the fundus of the stomach is in contact with the diaphragm. The stomach "bed" is formed by the posterior wall of the omental bursa and the retroperitoneal structures (pancreas and left kidney) between it and the posterior abdominal wall. Superiorly, the bed is bounded by the diaphragm, the spleen, and the left suprarenal gland. Inferiorly, it is bounded by the body and tail of the pancreas and the transverse colon.

1.2.2 Histology

The general histologic structure of the stomach is maintained throughout its length, with unique components within each substructure accounting for the differences. The basic structure is as follows (in order from outer to innermost layer): mucosa (epithelium, lamina propria, muscularis mucosa), submucosa, muscularis externa, and serosa.

The first layer of mucosa consists of epithelium, the lamina propria underneath, and a layer of smooth muscle, the muscularis mucosa. Underneath the mucosa lies the submucosa, a layer of fibrous connective tissue separating the mucosa from the muscularis externa. The Meissner's plexus is in this layer.

The muscularis externa in the stomach differs from that of other GI organs, as it has three layers of smooth muscle instead of two. The inner oblique layer, a layer not seen in other parts of the digestive system, is responsible for creating the motion that churns and physically breaks down the food. The middle layer is composed of a thick circular muscular wall concentric to the longitudinal axis of the stomach. This is thicker at the pylorus, forming the pyloric sphincter, the portion of the stomach that controls the movement of food into the duodenum. The Auerbach's plexus is found between the outer longitudinal layer and the middle circular layer. Finally, the serosa underneath the muscularis externa is made up of layers of connective tissue continuous with the peritoneum (Fig. 3a, b).

1.3 Physiology and Biology

1.3.1 Physiology

The stomach functions by mixing the food stream with acid and other digestive secretions. These movements are coordinated by both intrinsic and extrinsic neural control, with the intrinsic myenteric plexi being the Meissner plexus (at the base of the submucosa) and Auerbach plexus (between the middle and outer muscle layers of the muscularis mucosa). The acid and digestive secretions are secreted from the mucosa.

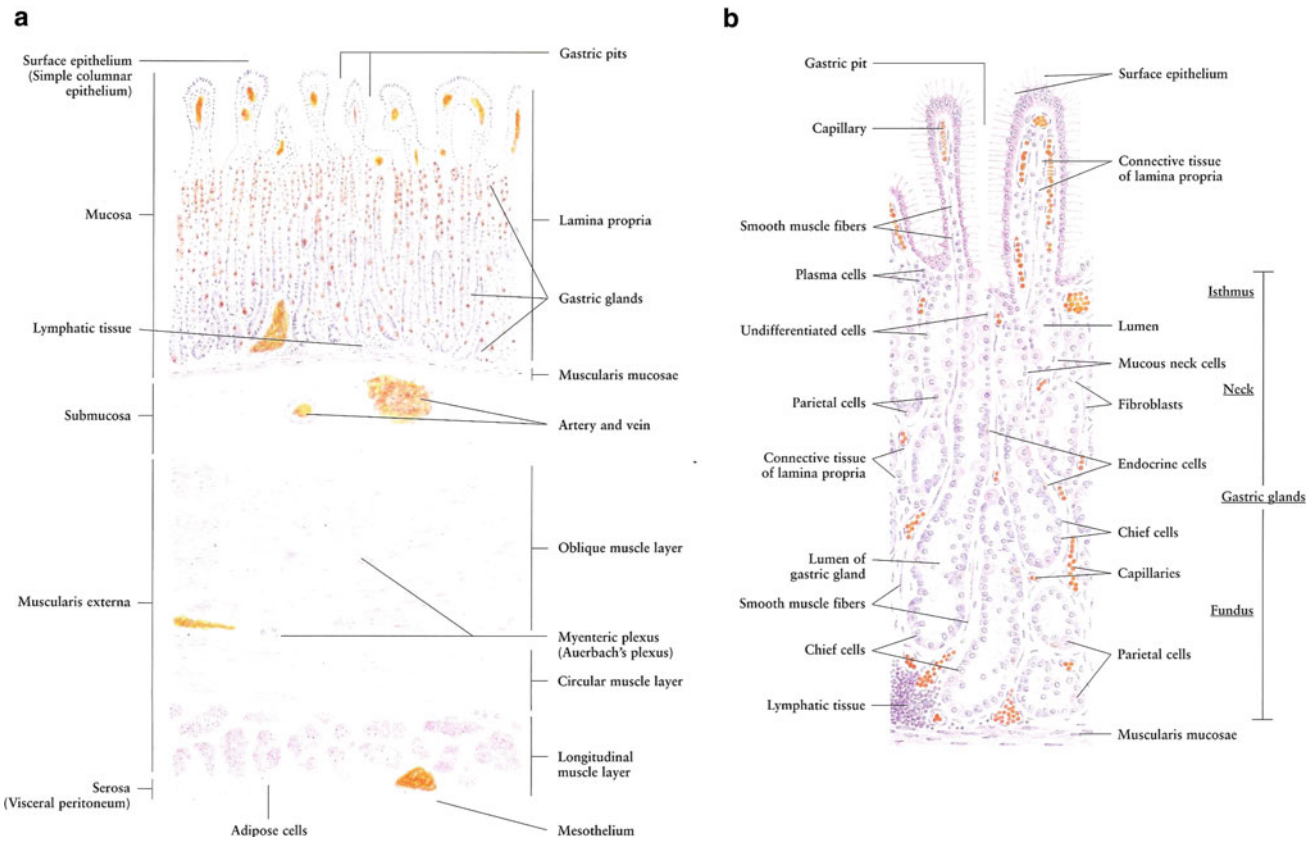


Fig. 3 Histology of **a** Stomach: low magnification. **b** Stomach: gastric glands, high magnification (with permissions from Zhang 1999)

The gastric mucosal surface is primarily composed of a simple layer of columnar epithelial cells 20–40 mm in height that secrete mucus, which provides luminal protection from acid, pepsin, ingested substances, and pathogens. The surface epithelial lining is invaginated by gastric pits, or foveolae, in which the gastric glands reside and which provides the glands access to the gastric lumen. The gastric glands of different anatomic regions of the stomach are lined with different types of specialized epithelial cells. The first region, the cardia, has glands populated by mucous, endocrine, and undifferentiated cells. There is a gradual transition from cardiac glands to the second region (fundus and body), which predominantly has parietal (oxyntic or fundic) glands. Parietal, chief (also known as peptic), endocrine, mucous neck, and undifferentiated cells compose the parietal glands. The antrum and pylorus contains pyloric glands, composed of endocrine cells, including gastrin-producing G cells and mucous cells.

The parietal glands are responsible for the secretion of acid, intrinsic factor (IF), and most gastric enzymes. A typical gland is subdivided into three areas: the isthmus (where surface mucous cells predominate), the neck (where parietal and mucous neck cells predominate), and the base (where chief cells predominate, along with some parietal and mucous neck cells). The principal cell type of the parietal gland is the parietal cell, responsible for the parietal mucosal secretion of 3×10^6 hydrogen ions/second, at a final HCl concentration of around 150 mmol/L. Acid secretion begins within 5–10 min of stimulation. Additionally, parietal cells are the site of intrinsic factor secretion via membrane-associated vesicle transport. Endocrine cells, somatostatin-containing and secreting D cells, and histamine-secreting enterochromaffin-like (ECL) cells are scattered throughout the parietal epithelium.

Closely associated with parietal cells are mucous neck cells, which appear singly, close to parietal cells or in groups of two or three in the parietal gland neck or isthmus. Mucous neck cells differ from their surface counterparts in their synthesis of acidic, sulfated mucus rather than the neutral mucus. Function of the two cell types appears different in that surface mucous cells are cytoprotective, whereas the mucous neck cell functions as a stem cell precursor for surface mucous, parietal, chief, and endocrine cells.

Chief cells, also known as zymogen cells, predominate in deeper layers of the parietal glands. These pyramid-shaped cells play a role in synthesis and secretion of pepsinogens I and II. Once secreted into the gastric lumen, pepsinogens are converted to pepsin and aid in digestion.

Table 1 Physiologic actions of Gastrointestinal hormones (adapted with permission from Ross 2010)

Hormone	Site of Synthesis	Major Action	
		Stimulates	Inhibits
Gastrin	G cells in stomach	Gastric acid secretion	
Ghrelin	Gr cells in stomach	-GH secretion -Appetite and perception of hunger	-Lipid metabolism -Fat utilization in adipose tissue
Cholecystokinin (CCK)	I cells in duodenum and jejunum	-Gallbladder contraction -Pancreatic enzyme secretion -Pancreatic bicarbonate ion secretion -Pancreatic growth	Gastric emptying
Secretion	S cells in duodenum	-Pancreatic enzyme secretion -Pancreatic bicarbonate ion secretion -Pancreatic growth	Gastric acid secretion
Gastric inhibitory peptide (GIP)	K cells in duodenum and jejunum	Insulin release	Gastric acid secretion
Motilin	Mo cells in duodenum and jejunum	-Gastric motility -Intestinal motility	

The final region of the stomach encompasses the antrum and pylorus and contains antral glands composed of endocrine and epithelial cells. The epithelial cells are predominantly mucous cells, and there are small numbers of pepsinogen II-secreting parietal cells. Although small in number, gastrin-secreting (G) cells play a vital physiologic role, as gastrin release is stimulated by gastric distention, vagal stimulation, dietary amino acids, and peptide, with rapid appearance of the hormone into the bloodstream in the postprandial period.

The function of the GI tract is controlled by both neural and hormonal mechanisms. Five major GI hormones have been identified. In addition, there are a number of other hormones, produced by neuroendocrine cells scattered through the mucosa of the stomach and small intestines, which play an important role in regulating and coordinating GI tract function. Once the bolus of food is propelled into the stomach, it is the stimulus to secrete HCl, pepsinogen, and pepsin, to begin the digestive process. In addition to the stimulus of secretions, the vagus nerve stimulates motility and as the food enters the pylorus, gastrin is stimulated and the bolus is further propelled into the duodenum. This stimulates the pancreas, which then secretes enzymes further the digestive process of the food (See Fig. 10 and Table 1).

1.3.2 Biology

1.3.2.1 Mucositis

The molecular biologic mechanisms that induce proinflammatory cytokines, chemokines, and profibrotic cytokines, are illustrated in Fig. 4. Involvement of the intestinal immune system and microvascular endothelium in the regulation of acute radiation mucositis and subsequent adverse tissue remodeling (intestinal fibrosis). When the mucosal barrier becomes disrupted, as after radiation exposure, bacterial products, and other activating agents gain access to subepithelial intestinal tissue where they stimulate a variety of immune cells to produce cytokines and other proinflammatory and anti-inflammatory mediators. Moreover, radiation-induced endothelial dysfunction with loss of thromboresistance, resulting in thrombin formation, neutrophil recruitment and activation, and stimulation of mesenchyme cells is seen.

1.3.2.2 Fibrosis

Recent studies have evaluated molecular mechanisms of radiation-induced fibrosis. Global gene expression profiles have shown induction of genes coding for multiple matrix components, matrix metalloproteinases, and tissue inhibitors of metalloproteinases, suggesting late radiation enteritis may be an active process of fibrogenesis and fibrolysis, with a balance toward fibrogenesis (Strup-Perrot et al. 2004). Ionizing radiation activates the translation of the gene coding for TGF-β (Herskind et al. 1998) and overexpression of transforming growth factor β1 (TGF-β1) has been associated with the development of fibrosis after radiation in the lung, liver, kidney, skin, and intestine. In the intestinal wall, TGF-β promotes fibrosis by stimulating collagen formation and the expression of fibronectin genes and the chemotaxis of fibroblasts and inhibits the degradation of the extracellular matrix. In a study of irradiated rat intestine, the TGF-

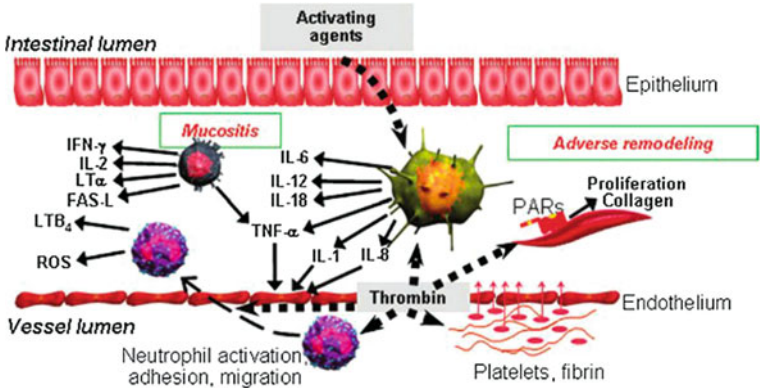


Fig. 4 Molecular biologic mechanisms associated with mucositis

Table 2 Turnover times of epithelial cells of the alimentary tract of the rat (adapted from Rubin and Casarett 1968)

Cell population	Turnover time (days)
Digestive system	
Lip	14.7
Oral cavity	
Buccal mucosa	4.3
Tongue surface	
Superior	4.9
Inferior	7.7
Esophagus	
At thyroid gland level	8.8
At cardiac junction	11.6
Stomach	
Cardia	9.1
Body	
Surface epithelium	2.9
Gland	6.4
Pylorus	
Surface epithelium	1.9
Gland	1.8
Small intestine	
Duodenum	1.6
Jejunum	1.3
Ileum	1.4
Large Intestine	
Colon	10.0
Rectum	6.2
Anus	4.3

From F.D. Bertalanffy and C. Lau: Cell renewal. Int. Rev. Cytol., 13:35–366, 1962. Published by Academic Press Inc.

β1 immunoreactivity score was significantly elevated in segments of bowel with intestinal fibrosis after radiation when compared to sham-irradiated segments (Hauer-Jensen et al. 1998). Interferon gamma (IFN-γ) inhibits the effects of TGF-β1 at the nucleus and has been proposed as a potential treatment for radiation enteritis (Nguyen et al. 2002).

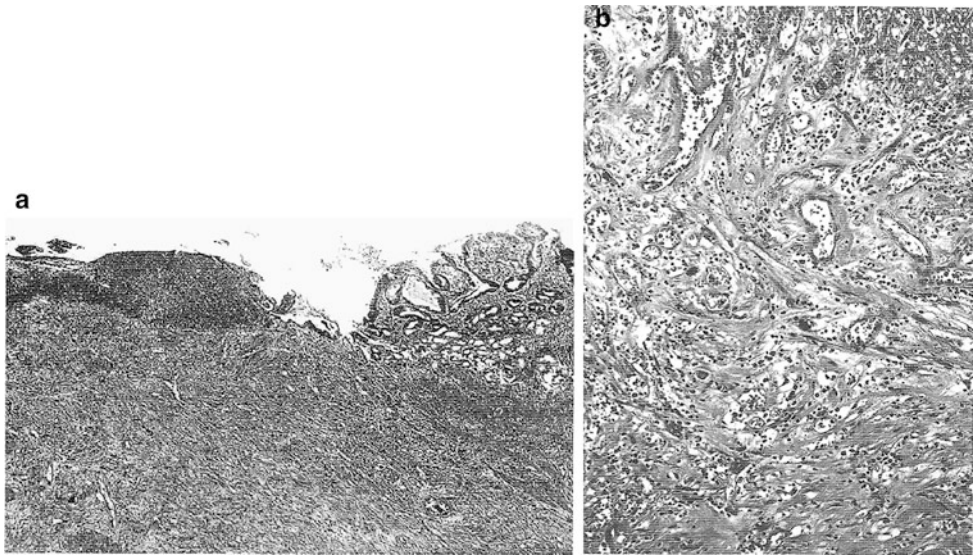


Fig. 5 **a** Chronic postradiation gastric ulcer. Beneath the necrotic ulcer base there is active chronic and atypical granulated tissue with enlarged vascular channels containing prominent and atypical endothelial cells. The gastric mucosa at the ulcer margin shows mild atypia of the glands. **b** This photomicrograph shows exuberant granulation tissue beneath the necrotic base of postradiation ulcer. Note the bizarre vascular channels with large, hyperchromatic endothelial cells (with permission from Fajardo et al. 2001)

1.3.2.3 Cell Kinetics Renewal Time

Cell kinetic turnover times of the gastrointestinal system determine the latent period before the clinical syndromes and manifestations occur. Thus, the acute effects will appear first in the small intestine, and then in the pylorus of the stomach, the body, in the first week of radiation. In the second week, the large intestine, first in the rectum, and then the colon reacts, as well as the cardia of the stomach and esophagus, which occurs simultaneously. It is noteworthy that the oral cavity and anus develop their mucositis in the first week (Table 2).

Cell renewal systems have been accurately estimated by Tritium Thymidine studies based on mitotic indices. On the basis of comparative values, it is apparent that the small intestine has the most rapid cell turnover of the various epithelial cells of the alimentary tract, and manifests the effects of irradiation earlier. From the view of cell kinetics, the time of appearance of the small intestine radiation injury compared to the stomach and to the oral mucosa is explained. The stem cells are in the Cripps of the Lieberkuhn, forming the proliferating or amplifying pool of cells. The differentiating cells lose proliferating capacity and move to the surface where they mature and ultimately, with extrusion, pass into the lumen (Vertalanffy and Lau 1962).

1.4 Pathophysiology of Radiation Damage

The damage to the stomach by radiation is best described in animal models. Breiter et al. (1989) demonstrated after irradiation with single doses, three distinct gastric disorders that occurred at different latency times. Acute death 2–3 weeks after irradiation was caused by an erosive and ulcerative gastritis and occurred in 17 % of the animals given 28.5 Gy with a protective, absorbable liquid diet, in 100 % of animals given 28.5 Gy without the protective liquid diet, and in 13 % of the animals given 23 Gy. Subacute to chronic fatal disorders that occurred 4 weeks to 7 months after irradiation included stomach dilatation and gastroparesis, associated with the replacement of the normal gastric mucosa by a hyperkeratinized multilayered squamous epithelium. These disorders occurred in 40–100 % of the animals after doses between 16 Gy and 28.5 Gy (+diet). Late gastric obstruction occurring at more than 7 months after irradiation resulted from profound changes in the gastric wall in 13–18 % of the animals after doses between 14 and 23 Gy. In animals surviving long term, an atrophic mucosa and intestinal metaplasia developed. It is unclear to what extent these findings in the rat, given in a single high-dose fraction, relate to humans. Friedman (1942) described acute gastric changes due to radiation in animal experiments. Initial early edema takes place shortly after irradiation, followed by degenerative changes (hyperemia, hemorrhage, and leukocytic infiltration) in the epithelial cells of the mucosa and in the stromal cells about 1 week after initiation. These changes can then progress to ulceration, with a peak at 1–2 months. Chen and Withers (1972) evaluated the characteristics of the stem cells of the gastric mucosa in mice after radiation and noted that the cells have a relatively large shoulder on the cell survival curve. Sublethal damage was about two-thirds complete after 1 hour. Regeneration was rapid, with surviving clonogenic cells doubling every 43 h. The relationship of these repair characteristics to that of the cells that produce late stomach injury remains unclear.

Goldgraber et al. (1954) described the results of a study of serial gastric biopsies after irradiation for peptic ulcer and defined the acute response of the mucosa to radiation.

Table 3 Clinical syndromes: gastric endpoints as described by the LENT SOMA system

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Epigastric distress	Occasional and minimal	Intermittent and tolerable	Persistent and Intense	Refractory and excruciating
Emesis	Occasional	Intermittent	Persistent	Refractory
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and Intense	Refractory and excruciating
Objective				
Hematemesis	Occasional	Intermittent	Persistent	Refractory
Weight loss from time of treatment	≥5–10 %	>10–20 %	>20–30 %	>30 %
Melena	Occult/occasional normal hemoglobin	Intermittent <10 % decrease in hemoglobin	Persistent 10–20 % decrease in hemoglobin	Refractory or frank blood >20 % decrease in hemoglobin
Ulceration	Superficial, ≤1 cm^2	Superficial,>1 cm^2	Deep ulcer	Perforation, fistulae
Stricture (antro-pyloric region)	>2/3 normal diameter	1/3–2/3 normal diameter	<1/3 normal diameter	Complete obstruction
Management				
Epigastric distress Emesis	Diet modification antacids	Intermittent prescription medication	Persistent medical management	Surgical intervention
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Embolization, Coagulation or surgical intervention
Ulceration			Medical intervention	Surgical intervention
Stricture			Medical intervention	Surgical intervention
Analytic				
Barium radiography	Assessment of lumen and peristalsis			
Endoscopy	Assessment of lumen and mucosal surface			
CT	Assessment of wall thickness, sinus and fistula formation			
MRI	Assessment of wall thickness, sinus and fistula formation			

Table 4 Representative endpoints for gastric effects: segregated based on their global versus focal nature, and whether they are subclincal versus clinical

Stomach		
	Focal	Global
Subclinical	Atrophy of mucosa Asymptomatic ulceration Localized reduced compliance	Malabsorption Asymptomatic reduced capacity
Clinical	Bleeding, ulceration	Bleeding, anemia Weight loss Early satiety

First, coagulation necrosis of the chief and parietal cells developed, then the tubules sloughed and were replaced by neck cells and a round cell infiltrate. Finally, at the peak of the reaction, there was loss of the glands associated with mucosal thinning, edematous interstitial tissue, and chronic inflammation. A decrease in gastric secretion occur secondary to irradiation. Radiation was used in the past to decrease acid production in patients with peptic ulcer disease (Rubin and Casarett 1968). This suppression persisted for a variable amount of time but is likely related to the total radiation dose. Examples of post-RT gastric ulcers are shown in Fig. 5a, b.

1.5 Clinical Syndromes (Endpoints)

The clinical syndromes are described in LENT SOMA (Table 3) and CTC V4.0. The endpoints can be similarly segregated based on their focal versus global and clinical versus subclinical nature (Tables 4, 5). The nonacute

Table 5 Benign versus malignant gastric ulcers: differential radiologic features

Features	Benign	Malignant
Hampton's line	Yes	No
Carman-Kirklin complex	No	Yes
Crescent sign	Yes	No
Project beyond gastric wall	Yes	
Convergence of folds	To edge of crater	Stop short of crater
Radiating folds thickened, irregular	Smooth	Club-shaped
Ulcer shape	Linear, round, oval	Irregular
Position of ulcer mound	Central	Eccentric
Depth	Considerable depth in relation to size	Shallow in relation to overall size
	at mucosal surface	
Ulcer collar	Smooth, symmetrical	Eccentric
Margin	Smooth	Nodular, irregular
Peristalsis	Preserved	Diminished or absent
Healing	Complete in 8 week	Very rare
Multiplicity	10–30 %	20 %
Associated duodenal ulcer	50–60 %	Uncommon
Location	Rarely in fundus or proximal greater curvature	Anywhere

clinical syndromes resulting from gastric irradiation have been described by Sell and Jensen (1966) consists of four types:

- *Dyspepsia*: arising 6 months to 4 years after irradiation as vague gastric symptoms without clinical or radiographic signs.
- *Gastritis*: arising 1–2 months from the completion of radiation and accompanied by radiological evidence of spasm or stenosis of the antrum. Gastroscopy reveals smoothened mucosal folds and mucosal atrophy, the pathologic basis being fibrosis of the submucosal tissue.
- *Acute ulceration*: occurring shortly after the completion of the radiation, but rarely perforates.
- *Late ulceration*: arising typically at 5 months after irradiation. The ulcer is indistinguishable from an ordinary ulcer. It can heal spontaneously, but can be accompanied by submucosal fibrosis, which can produce antral fibrosis.

1.5.1 Detection: Endoscopy

As is true for esophageal cancer, the late effects endpoint scale is based on symptoms as well as intervention. The major interventional study that is useful for evaluating late effects in the stomach is an upper endoscopy. This allows thorough evaluation of gastritis and ulceration and can give worthwhile information regarding obstruction, although this is usually a secondary effect. Biopsies can also be obtained through endoscopy, which is very useful if there is concern regarding tumor recurrence. Upper GI radiography can also be useful for the same endpoints and is simpler and cheaper for the patient, but the result is often not definitive.

1.5.2 Diagnosis

The radiographic features of benign gastric ulcers (BGU) begin with excluding an associated mass. The characteristics of the BGU are (Fig. 6):

- 'En face' BGU are round or oval craters with surrounding gastric folds that may be enlarged secondary to edema.
- In profile BGU are identified by Hampton's line, an ulcer collar, and an ulcer mound, which separates it from the gastric lumen.
- Benign ulcers tend to be located in the distal half of the greater curvature and respond to complete healing with antacid receptor antagonist.
- Suspicion for malignant ulcer increases if the ulcer is located in the fundus and or proximal half of the greater curvature, especially if there is an associated mass.

1.6 Radiation Tolerance

1.6.1 Dose-Time Fractionation

1.6.1.1 Acute Radiation-Induced Toxicity to the Stomach

Acute nausea due to radiation delivered to the stomach and small bowel are difficult to quantify and separate, as many

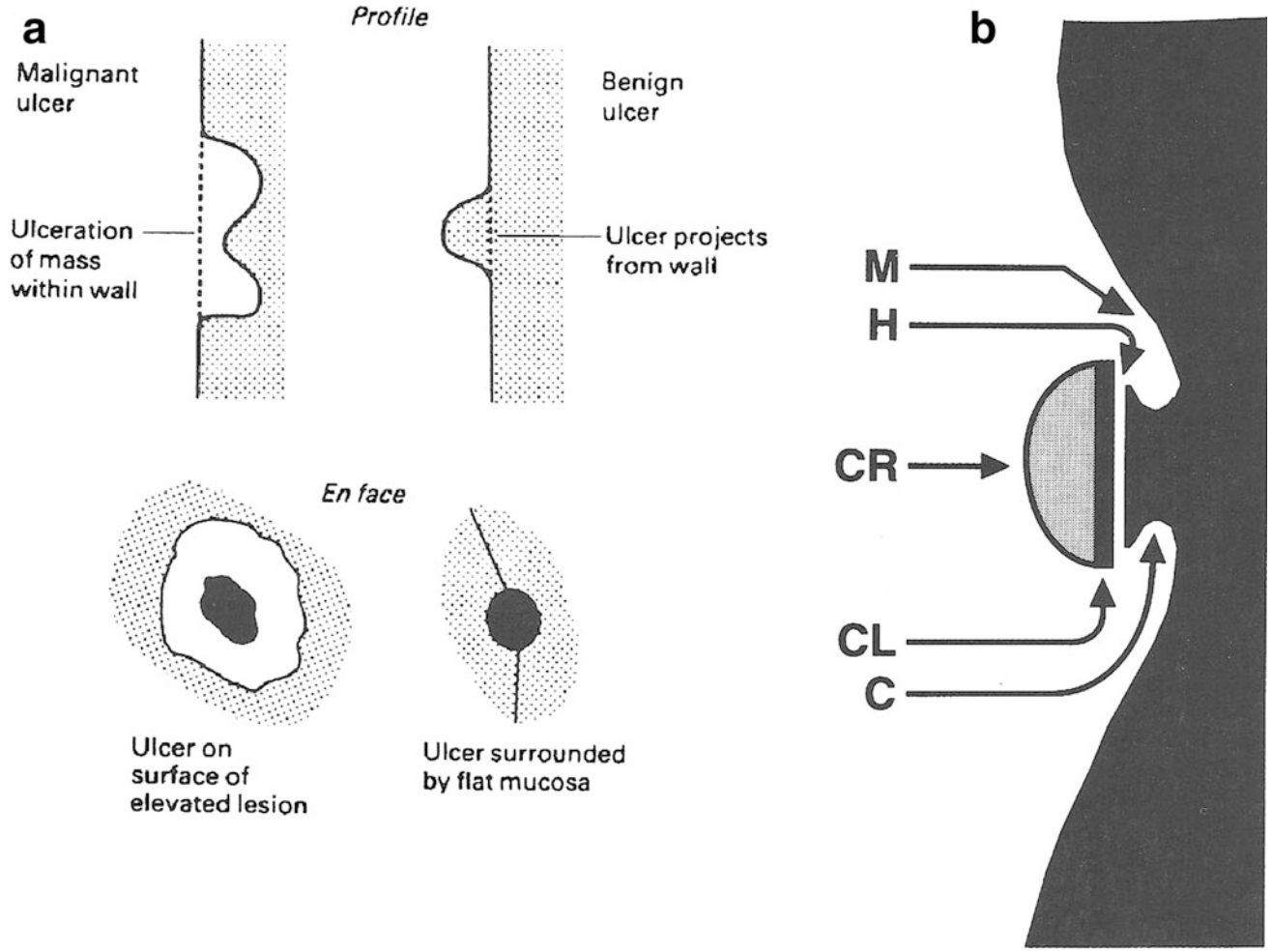


Fig. 6 Diagnosis. **a** Malignant versus benign gastric ulcers. Differentiating radiologic features on double-contrast barium studies (from Bartram et al. 1981). **b** Profiles of a benign gastric ulcer. The crater (CR) is globular, sharp and distinct. The neck is sorrounded by a collar (C) that joins the crater to the lumen. The collar is parallel to the long axis of the stomach and does not project transversely into the lumen. A lucent or Hampton's line (II) intervenes between the collar and crater and marks the mucosa at the entrance to the ulcer. Deep to Hampton's line there may also be a parallel slitlike cleft (CL) that fills with barium. The ulcer is located in the center of a symmetrical mound (M) that projects into the lumen but merges gradually with the adjacent, normally distensible, gastric wall (with permission from Wolf 1973)

studies that involve gastric and small bowel irradiation often are confounded by concurrent chemotherapy. A Japanese study of patients with diffuse large B cell lymphoma of the stomach treated with CHOP chemotherapy followed by 40.5 Gy to the stomach and regional nodes reported a 4 % (2/52 patients) incidence of grade 3 or greater acute nausea (Ishikura et al. 2005). No hemorrhage or perforation of the stomach was seen. In the GITSG study (Moertel et al. 1981) of locally unresectable pancreatic carcinoma treated with AP-PA fields, patients receiving radiation alone to 6,000 rads had a 36 % incidence of nausea (grade not specified). A review of single hemibody irradiation demonstrated a 83 % incidence of nausea and vomiting in patients treated to the upper abdomen (Danjoux et al. 1979). In this study, increased dose per fraction ($\geq$600 rad vs. $\leq$500 rad) resulted in increased nausea and vomiting incidence (87 % vs. 58 %). The Italian Group for Antiemetic Research in Radiotherapy Observational Study (1999) demonstrated a 67 % incidence of nausea, 38 % incidence of vomiting, and a 71 % incidence of both nausea and vomiting in patients treated to the upper abdomen. In general, early effects of radiation (e.g., nausea, vomiting, and diarrhea) are dependent on dose per fraction and are likely to occur in the majority of patients treated with conventional doses of radiation to the stomach.

1.6.1.2 Late Radiation-Induced Toxicity to the Stomach

Cosset et al. (1988) reported late gastric complications (ulcer of stomach/duodenum, severe gastritis, obstruction)

Table 6 A radiation dose-response for major gastric complications following irradiation of testicular cancers

Dose (r)	Number of patients	Gastritis	Ulcer	Perforation
<3,000	82	0	2 (2 %)	0
3,000–3,999	29	0	1 (3 %)	0
4,000–4,999	50	10 (20 %)	3 (6 %)	3 (6 %)
5,000 5,999	48	15 (31 %)	8 (17 %)	5 (10 %)
>6,000	8	0	1 (13 %)	3 (38 %)

Table 7 Details of major complications (resulting in surgical intervention) in six patients following irradiation of testicular cancer

Dose (r)	Days to gastrectomy after irradiation	Reason for surgery	Operative findings
6,456 (32 days)	95	Hemorrhage	Perforated ulcer on postantrum
5,880 (44 days)	169	Hemorrhage	Thickened wall
			Generalized petechiae
5,304 (55 days)	155	Hemorrhage	Pyloric ulcer
			Petechial hemorrhage
6,105 (49 days)	190	Pain	Perforated ulcer on postantrum
5,096 (54 days)	189	Pain	Post pyloric ulcer
4,800 (53 days)	223	Pain	Peritonitis from perforated antral ulcer

Table 8 Chemotherapy: gastrointestinal chemotoxic agents and their late effects

Agent	Late effect
5-Fluorouracil	Enteritis
5-Fluorouracil + mitomycin C (+ RT)	Late benign esophageal stricture
5-Fluorouracil + MeCCNU(+ RT)	Fistulas, perforation
Actinomycin D (+ RT)	Enteritis
Bleomycin (+ RT)	Esophagitis
Cisplatin (+ RT)	Enteritis
Cyclophosphamide (+ RT)	Esophagitis
Doxorubicin (+ RT)	Esophagitis
Methotrexate	Enteritis
Procarbazine	Enteritis

RT = radiation therapy

Modified from Rubin P: The Franz Buschke Lecture: Late effects of chemotherapy and radiation therapy: a new hypothesis Int J Radial Oncol Biol Phys 1984; 10:5–34, with permission from Elsevier Science

in two successive EORTC trials of radiotherapy for Hodgkin's disease. This retrospective review of 516 patients, of whom 25 developed ulcers, two severe gastritis, six small bowel obstruction or perforation, and three with both, suggested complications were related to fractionation schedules and the use of laparotomy. The effect of total dose could not be evaluated because all patients received 40 Gy with only small variations. Patients with higher fraction sizes were significantly more likely to develop complications (4 % in weekly doses of 5 × 2 Gy, 9 % in 4 × 2.5 Gy, and 22 % in 3 × 3.3 Gy).

Goldstein et al. (1975) noted radiological abnormalities of the distal stomach in 8.3 % (10/121) of women who underwent 50 Gy of radiotherapy to the paraaortic nodes for metastatic cervix cancer. Five patients had prepyloric or pyloric ulcers, and the other 5 were located in the antropyloric region. These abnormalities occurred between 1 and 25 months after irradiation. Only two of these ten patients required surgical intervention. One of 52 men who received 40–50 Gy of paraaortic nodal irradiation for testicular tumors developed gastric outlet obstruction secondary to a pyloric ulcer 3 months after completion radiation. These

data are similar to the toxicities observed in the EORTC Hodgkin's trial.

Experience from Walter Reed Army Medical Center from the 1940s and 1950s in over 230 patients with testicular tumors treated primarily with 1 MV X-rays (but one-third were treated with 200 kVp) were reported (Amory and Brick 1951; Brick 1955; Hamilton 1948). There was substantial dose variation, but the majority of patients received between 4,000 and 6,000 r within 50–60 days. Though there were small numbers at the higher doses, there may be a suggestion for increased major complications of ulcer and perforation with increasing dose (see Tables 6 and 7).

The late gastric effects of radiation are summarized by Coia et al. (1995). It appears that for radiotherapy doses in the vicinity of 45 Gy, late effects (primarily ulceration) occur in approximately 5–7 % of patients. Specifically regarding gastric bleeds, Pan et al. (2003) reported on 12 gastric bleeds after radiation to 92 patients with liver tumor. Median time to bleeds was 3.5 months (range: 1.2–7.6 months). Average mean dose to the stomach was 14.06 Gy (range: 0.10–67.55 Gy). The LKB model was fit to the complication data for the stomach for the TD50 (1), "m," and "n" LKB model parameters. For the stomach, the parameters for the stomach were 62, 0.30, and 0.07 Gy, respectively. Multivariate analysis demonstrated that in addition to NTCP, mean dose to stomach was significantly associated with GI bleed. This study confirmed that the stomach and duodenum do not have a large volume effect, and that dose thresholds exist for gastric bleeding risk.

1.6.2 Dose-Volume Factors

The exact volume of stomach irradiation is important to understanding symptoms and for the diagnosis of radiation-induced ulcer. First the location of ulcer within the radiation (PTV) corresponds to high doses delivered in treating neighboring tumor volumes. Second, if the fundus and body are spared or shielded, acid secretion can still occur and contribute to formation of radiation-induced ulcer. The pliability and ability of stomach to alter its volume is a challenge to accurately determine the radiation dose received to a specific region or volume of stomach.

1.7 Chemotherapy Tolerance

Chemotherapy alone does not appear to produce significant late GI complications with any frequency, despite the well-documented acute toxicity caused by a long list of agents (Table 8) (Mitchell 1992). Drugs, such as 5-fluorouracil (5-FU), produce diarrhea and, occasionally, small bowel toxicity (Fata et al. 1999). More severe late effects, such as GI bleeding, generally have been seen only in combined-modality therapy, which has led to severe acute complications, particularly in the small bowel (Minsky et al. 1995; Bosset et al. 1997).

The impact of chemotherapy on late tolerance of the stomach to irradiation has not been studied formally. There has been increasing utilization of combined modality therapy with radiation therapy and 5-FU-based chemotherapy in the treatment of pancreatic tumors where the stomach is of necessity in the radiation field. Although no formal comparisons have been done there is not an obvious increase in late gastric injury after doses in the range of 45–50 Gy to the pancreas in conjunction with concurrent 5-FU compared to similar doses given without chemotherapy. Other agents such as adriamycin and mitomycin C have been used in the treatment of pancreatic cancer without any obvious adverse effects. In many of these studies the chemotherapy was given after the completion of radiation therapy rather than concurrently. The data from Mohioddin et al. (1992) of patients treated to high radiation dose with chemotherapy has already been mentioned. It is not possible to ascribe the GI bleeding in this series to the use of chemotherapy and not to the relatively high radiation dose. All of these studies are difficult to analyze because of the short follow-up inherent in the treatment of patients with pancreatic cancer. However, the data that are available do not suggest a major increase in late gastric toxicity with the combined modality approach of radiation plus 5-FU compared to radiation alone.

1.7.1 Combined Modality

There is little information to support increased toxicity from chemoradiation therapy. In pancreatic cancers, the use of agents such as doxorubicin and mitomycin C in combination with radiation has been well tolerated (Coia et al. 1995). Since most radiation oncology protocols avoid doses higher than 45–50 Gy, gastric late effect toxicity is uncommon.

1.8 Special Topics

1.8.1 Surgery

There was a significant increase in complications in patients who underwent laparotomy prior to radiotherapy (2.7 % without and 11.5 % after laparotomy). The highest complication rate of 39 % was seen in patients given three weekly fractions of 3.3 Gy after laparotomy. There was no documentation on the volume of stomach irradiated.

1.8.2 Peptic Ulcer

Among the numerous benign disease entities treated by irradiation, peptic ulcer was managed prior to the introduction of medical inhibitors of gastric secretion. Relatively modest doses of radiation, i.e., 1,000–2,000 cGy

fractionated in 10 days induced a prolonged suppression of the gastric HCl secretions by inhibiting parietal cells. A 20-year experience was documented by Palmer and Templeton. Approximately 50 % of patients treated with the higher doses of 1,500–2,000 cGy, had prolonged suppression of a year or more, allowing for peptic ulcers to heal. A small percent (15 % of patients) had prolonged depression of HCl secretion for 1–5 years (Palmer and Templeton 1939).

1.9 Prevention and Management

1.9.1 Prevention

Stomach sparing intensity-modulated radiation therapy (IMRT) is helpful in reducing the volume of the stomach being included in the treatment beam when irradiating surrounding structures involved with cancer, i.e., liver, spleen, and pancreas. Efforts at decreasing the risk of stomach complications from abdominal radiotherapy have been aimed at limiting the dose to the stomach while maintaining an adequate dose to the target. IMRT offers the means of limiting the radiation dose to the stomach by creating a more conformal dose distribution. This treatment approach has been introduced into treatment of pancreatic and hepatic malignancies (Cheng et al. 2003; Milano et al. 2004). However, long-term results regarding gastric toxicity is not yet available.

1.9.2 Management

For acute stomach toxicity (nausea and vomiting), decreasing the radiation dose per fraction and eating a light meal prior to radiation therapy can help minimize acute symptoms. Additionally, antacids, H2 blockers, proton pump inhibitors (PPI), and antiemetics are often used. Antiemetic regimens include 5HT3 inhibitors, phenothiazines, metoclopramide, corticosteroids, benzodiazepines, antihistamines, and anticholinergics. Prophylactic 5HT3 inhibitors have been shown in randomized trials to have efficacy compared to placebo in preventing radiation-induced nausea and vomiting (Franzen et al. 1996; Horiot and Aapro 2004). Acute radiation-induced nausea and vomiting typically appear within the first 24 h after treatment.

Patients with bleeding and ulceration require endoscopy. Argon laser coagulation has been used to temporarily control bleeding. Other local therapies include injections of epinephrine and vasoconstrictor agents. At times repeat endoscopy, and blood transfusions or eventually surgery are needed. For patients with intractable bleeding, perforation, fistulae, or obstruction, surgery may be indicated.

For severe complications of perforation, severe bleeding, or gastric outlet obstruction, the appropriate therapy is usually surgical. Generally it is necessary to do a partial gastrectomy to remove the effected area of the stomach. If there is no other significant radiation injury in the abdomen, gastrectomy is usually effective in resolving the morbidity.

1.10 Future Studies

In developing a system by which one can analyze complications to the gastrointestinal tract from therapeutic irradiation, it is important to keep in mind some of the information that is needed for a good analysis and to raise certain issues that it would be helpful to address:

1. The relationship of radiation injury to dose per fraction and whether improved normal tissue sparing by the use of radiation doses of less than 1.8–2 Gy per fraction is a possibility.
2. Find meaningful volume effect relating to radiation injury of the gastrointestinal tract. The development of 3D treatment planning and availability of dose-volume histograms will be important in this regard.
3. Identify variable radiation sensitivity of different anatomical portions of the GI tract.
4. Identify biological manipulations that could be used to decrease the likelihood of radiation-induced gastrointestinal injury.
5. Assess radiation-induced gastrointestinal ulcerations healed satisfactorily with present day medical management. Assess the apparent decrease in incidence of this complication a reflection of more routine aggressive management of early ulcer disease with medical therapy.
6. Identify the impact of the use of combined modality therapy with chemotherapy and radiation therapy on the incidence of gastrointestinal toxicity. This issue is especially important because at present a large number of patients being treated to the esophagus or abdomen for gastrointestinal malignancies receive combined modality therapy with, as a minimum, 5-fluorouracil containing chemotherapy.
7. Evaluate radiation sensitivity of the stomach differ substantially from that of the small bowel, which is typically in the same radiation field. As most of the information on small bowel tolerance has come from pelvic irradiation, decide whether that information applies to the somewhat different anatomy of the upper abdomen. This also is relevant with the increased interest in using high-dose radiation therapy for upper abdominal malignancies.
8. Identify the actual mechanism of the various types of radiation injury to the gastrointestinal tract. Virtually all of the data in this area is very old and most have not approached the issue of the mechanism of the injury, rather just an anatomical description of the injury.

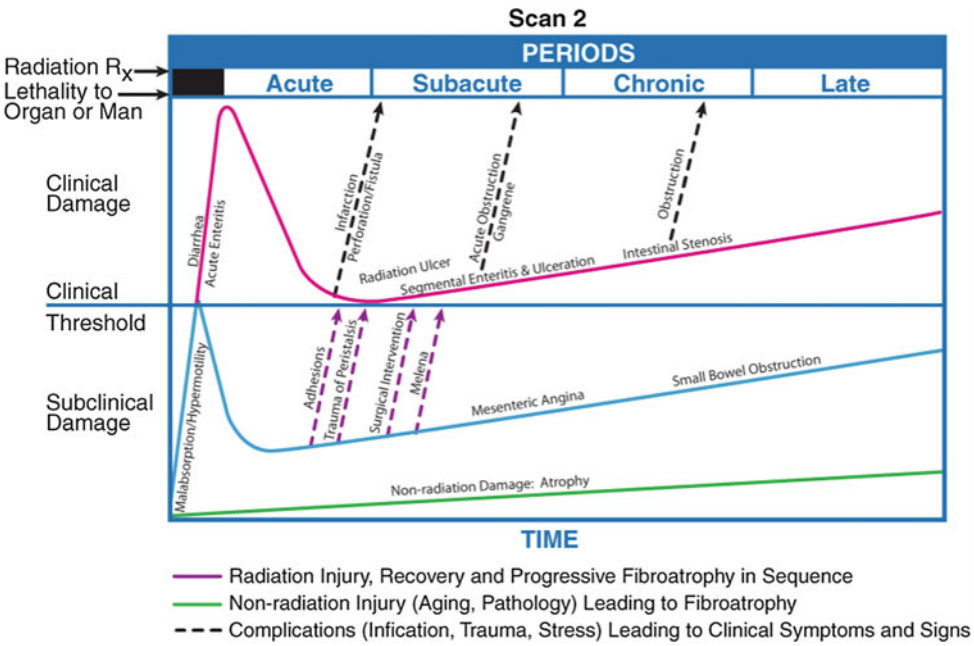


Fig. 7 Biocontinuum of adverse and late effects of the small intestine (with permission from Rubin and Casarett 1968)

9. Choose the scale for early and late complications scoring both useful and reproducible. After establishment of a reliable and self-consistent scale for toxicity, studies can be accomplished that establish dose-volume relationships for complications. The most appropriate disease sites for these ancillary studies should be sites that have a strong track record of protocol accrual where intestinal injury can be a dose-limiting factor and where radiation techniques are fairly well standardized.
10. Identify the most effective method for distinguishing late effects from tumor recurrence. Oftentimes, clinical recurrence cannot be readily distinguished from late effects. Standardized approaches and improved techniques in distinguishing these two competing factors must be developed. It is important additionally to report the time adjusted rate of complications at regular intervals.

It is the goal of the radiotherapist to achieve the highest degree of local regional control with acceptable and defined morbidity. In answering the above questions regarding radiation-related gastrointestinal morbidity, we equip ourselves to design treatment regimens that assist us in maximizing the therapeutic ratio. It is clear from this review that much remains to be determined regarding gastrointestinal morbidity of radiation, but the tools for toxicity measurement and potential means for management have been identified.

1.11 Literature Landmarks

Desjardins (1931): presented a general review of the depressive and injurious effects of irradiation reported up to that time.

Engelstad (1938): conducted careful and complete studies in the rabbit stomach after varying doses of irradiation. A solitary exposure of 1,500 R produced ulcers in 2–4 weeks.

Warren and Friedman (1942): described the pathology of intensive irradiation of stomach and other viscera.

Bowers and Brick (1947): presented the indications and techniques of surgery in radiation gastric ulcer.

Friedman (1952): described four types of stomach injury produced by high-dose radiation.

Goldgraber et al. (1954): Presented beautifully detailed serial studies of histologic changes following irradiation of the stomach.

Jennings and Arden (1960): conducted a serial histopathologic study of radiation changes in the esophagus of rats following single dose exposure to 3,000 R.

Rubin and Cassarett (1968): presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

Rubin (1995): presented the LENT-SOMA toxicity scales for radiation effects to evaluate the grade of severity.

Trotti and Rubin (2003): modified and developed the common toxicity criteria CTC V3.0 which applied similar scales to grade adverse effects of all major modalities—surgery and chemotherapy in addition to irradiation.

2 Small Intestine

2.1 Introduction

Chronic radiation injury of the intestine was first described shortly after the discovery of ionizing radiation. In 1895, Walsh concluded that radiation caused an “inflammation of

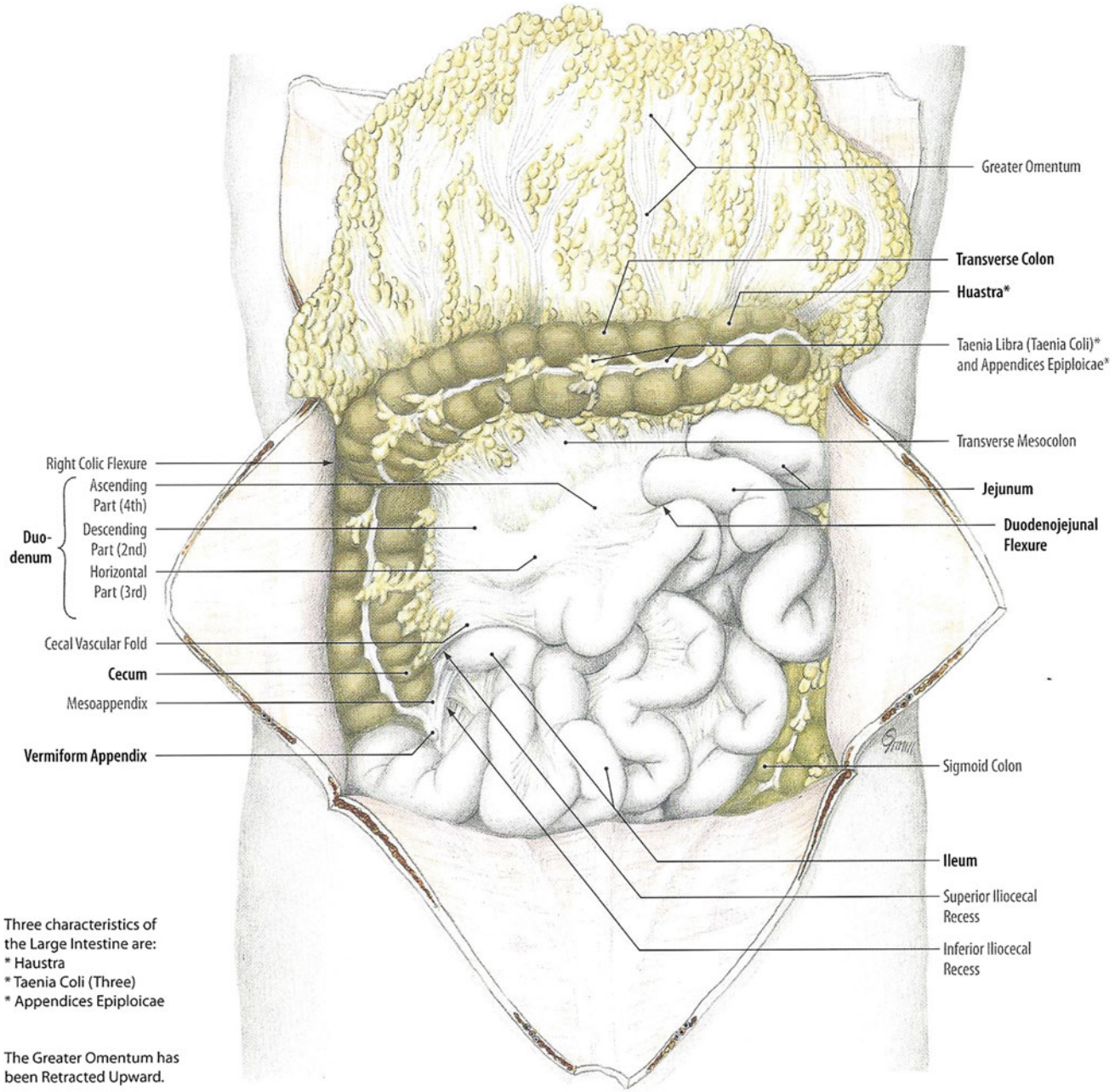


Fig. 8 Anatomy of large and small intestine (with permission from Tillman and Elbermani 2007)

the intestinal mucosa." (Walsh 1897) Further reports in the early twentieth century first described stenosis and fistula development after pelvic radiation (Futh 1915) (Fig. 7).

The genesis of combined-modality treatments have led to increased risk of treatment-related toxicity (Phillips and Fu 1977). Balancing the risks and benefits of treatment has become increasingly difficult for the practicing oncologist. However, with improved survival seen in many malignancies, cognizance and avoidance of late treatment toxicities will become even more important to patients and their physicians. A thorough knowledge of the risk factors associated with late toxicity in a variety of clinical situations is paramount to optimization of the therapeutic ratio. *The Biocontinuum of adverse acute and late effects are shown in* Fig. 1.

2.2 Anatomy and Histology

2.2.1 Anatomy

The small intestine is a hollow tube approximately 2.5 cm in diameter and 6–7 m in length, coiled into tubes and

filling the majority of the abdominal cavity (Fig. 8). It begins at the pyloric sphincter in the stomach and extends to the ileocecal valve where it makes its connection with the large intestine. It is comprised of three anatomically and histologically distinct subunits: the duodenum, jejunum, and ileum. The duodenum is the shortest portion of the small bowel and pursues a C-shaped course around the head of the pancreas. It is partly intraperitoneal and extraperitoneal, but is mostly fixed by peritoneum to structures on the posterior abdominal wall. It is divisible into four separate parts: superior, descending, horizontal, and ascending. The duodenum connects to the jejunum at the duodenojejunal flexure, supported by the ligament of Treitz. The jejunum comprises about two-fifths of the remaining small bowel length and lies primarily in the left upper quadrant of the abdomen. The ileum comprises the remainder of the small

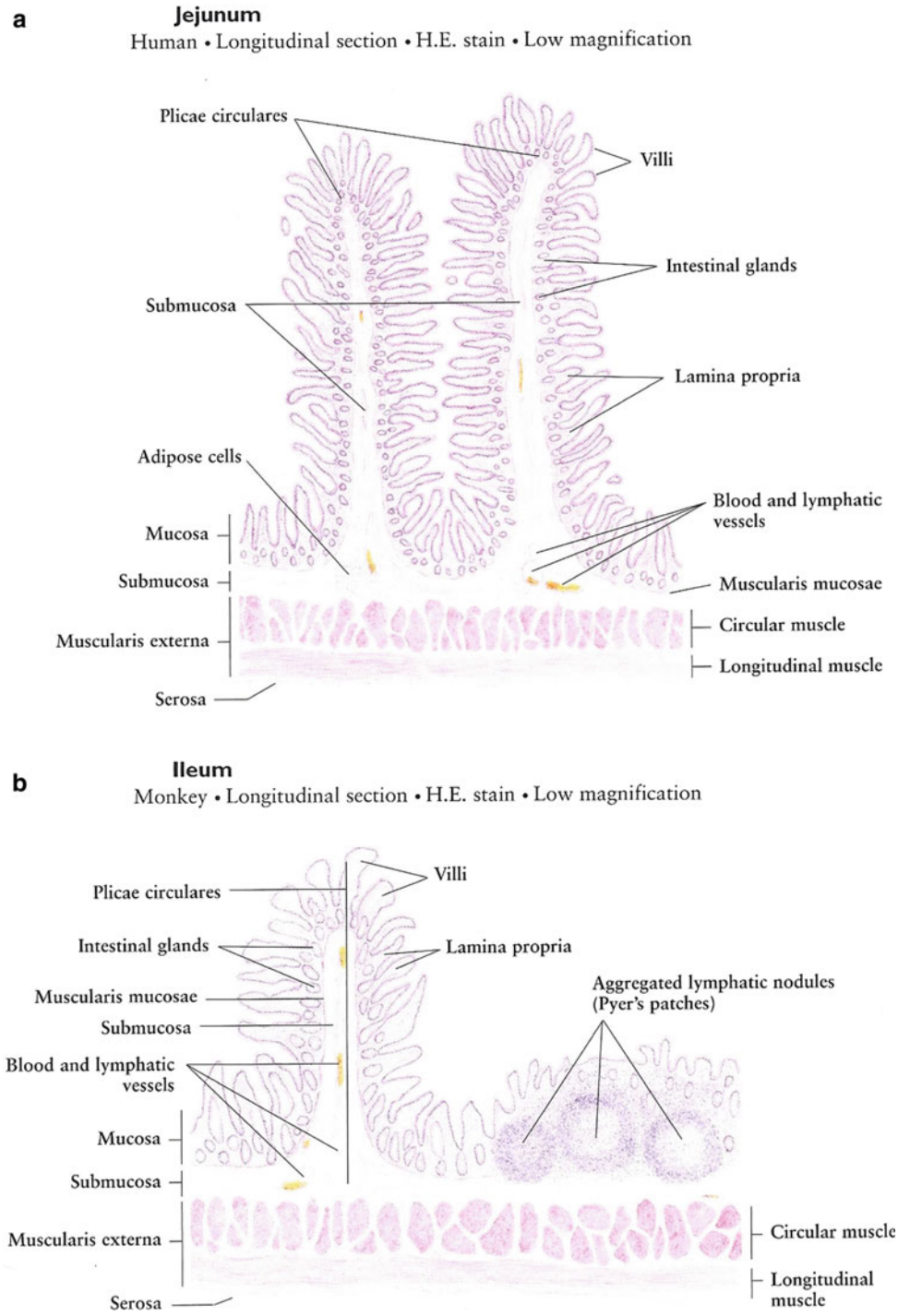
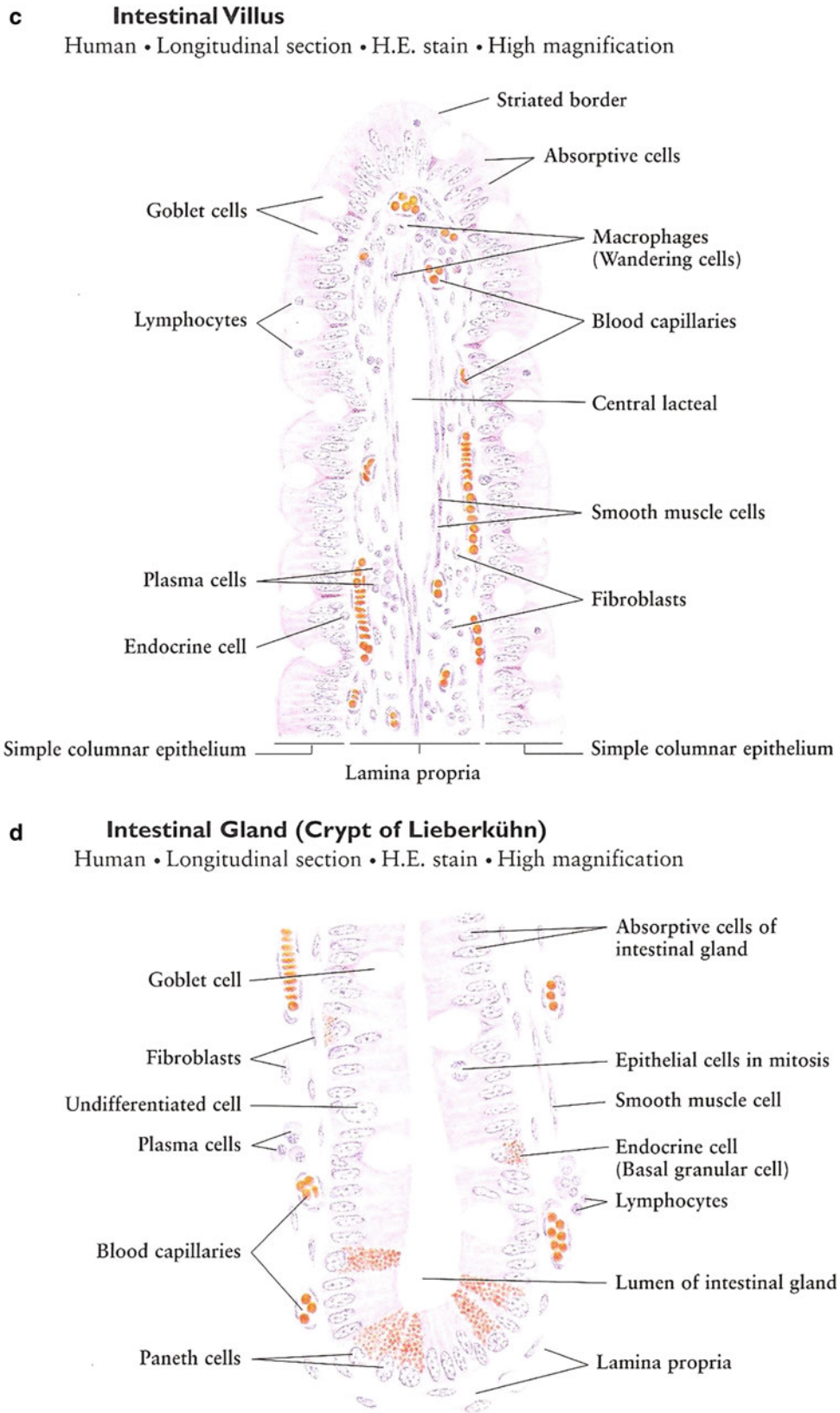


Fig. 9 Histology of the small intestine: **a** Jejunum. **b** Ileum. **c** Intestinal Villus. **d** Intestinal Gland (with permissions from Zhang 1999)

Fig. 9 (continued)



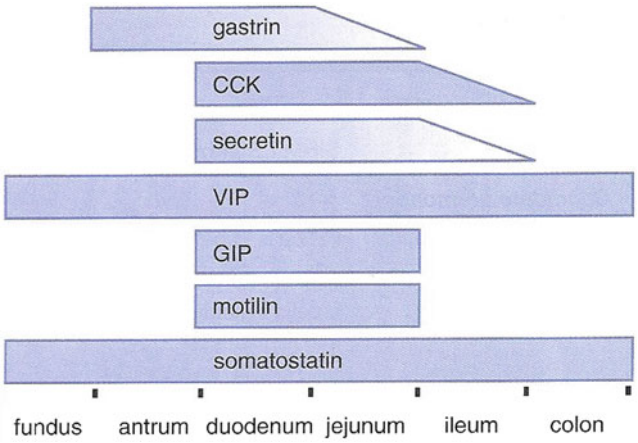


Fig. 10 Physiology. Gastrointestinal hormones. This schematic diagram shows the distribution of gastrointestinal peptide hormones produced by enteroendoorine cells in the alimentary canal.*CCK*,cholecystokinin; *VIP*, vasoactive intestinal peptide; *GIP*, gastric inhibitary peptide. (Modified from Johnson LR 1997)

bowel and lies primarily in the right lower abdominal quadrant, where it terminates at the ileocecal valve. The jejunum and ileum are both intraperitoneal structures.

2.2.2 Histology

The mucosal pattern of the small intestine is basically the same with numerous finger-like villi, which have their core of connective tissue of the lamina propria covered by intestinal epithelium. The intestinal glands (crypts of Lieberkuhn) are housed in the lamina propria. The muscularis mucosae is formed of a layer of smooth muscle fibers. The entire coat of mucosa is thrown into plicae circulares (Fig. 9a).

Intestinal villi are finger-like or leaflike projections of the mucosa, 0.5–1.5 mm in length, found only in the small intestine. They vary in form and length in different regions. Those of the duodenum are broad, spatulate structures, but they become finger-like in the ileum. Each has a core of lamina propria covered with simple columnar epithelium (Fig. 9b).

Intestinal glands (crypts of Leiberkuhn) are tubular structures within the lamina propria, 0.3–0.5 mm in depth, which open between the bases of the intestinal villi. They are lined with simple columnar epithelium composed of absorptive cells, goblet cells, endocrine cells, and undifferentiated cells (Fig. 9c, d).

The general histologic structure of the small intestine is maintained throughout its length: the duodenum, the jejunum, and the ileum, intestinal villi decrease in number; each villus has less villi and intestinal glands. The basic structure is as follows (in order from outer to innermost layer): mucosal epithelium, lamina propria, muscularis mucosa, submucosa, muscularis externa, and serosa. The serosa and muscularis externa are similar throughout the small intestine with the muscularis being characterized by both longitudinal and circular layers, with Auerbach's myenteric plexus in between. The submucosa of the duodenum is distinct from the jejunum and ileum by the presence of Brunner's glands and Meissner's submucosal plexus, which function together to secrete an alkaline solution for combination with the acidic chyme from the stomach. The ileum is histologically distinct due to the presence of Peyer's patches within the lamina propria, which are oval or round aggregations of lymphoid tissue. The mucosal lining throughout the small bowel is simple columnar, with longer villi in the jejunum and progressive villus shortening in the ileum.

2.3 Physiology and Biology

2.3.1 Physiology

The intestinal tract functions grossly through both anterograde and retrograde peristalsis, which serve to mix the food stream and promotes maximal contact of nutrients with the mucosa. These movements are coordinated by both intrinsic and extrinsic neural control, with the intrinsic myenteric plexi being the Meissner plexus (at the base of the submucosa) and Auerbach plexus (between the inner and outer muscle layers of the bowel wall). As the food stream progresses distally through the intestinal tract, nutrients are absorbed and the fecal matter is gradually condensed, with each subunit having a distinct role in the process. Although the shortest portion of the bowel, the duodenum is largely responsible for the breakdown of food in the bowel through mixture of secreted digestive enzymes from the gall bladder and pancreas, as well as coordination of the emptying of the stomach via hormonal pathways. The jejunum and ileum, with their large surface areas, serve primarily to transport nutrients across the epithelial cells. The ileum also plays a role in immune function through Peyer's patches and is also the site where vitamin B12/intrinsic factor complexes are absorbed.

Enteroendocrine cells are specialized cells present in the mucosa of the digestive tract. They account for less than 1 % of all epithelial cells in the gastrointestinal tract, but as a whole, they collectively constitute the largest endocrine "organ" in the body. Most of these cells are not grouped as clusters in any specific part of the gastrointestinal tract. Rather, enteroendocrine cells are distributed singly throughout the gastrointestinal epithelium. For that reason, they are described as constituting part of a diffuse neuroendocrine system (DNES). Enteroendocrine cells secrete their products into either the lamina propria or underlying blood vessels. In general, two types of enteroendocrine cells can be distinguished throughout the GI tract. Enteroendocrine "closed cells" do not reach the lumen, whereas enteroendocrine "open cells" are exposed to the gland lumen (Fig. 10 and Table 1).

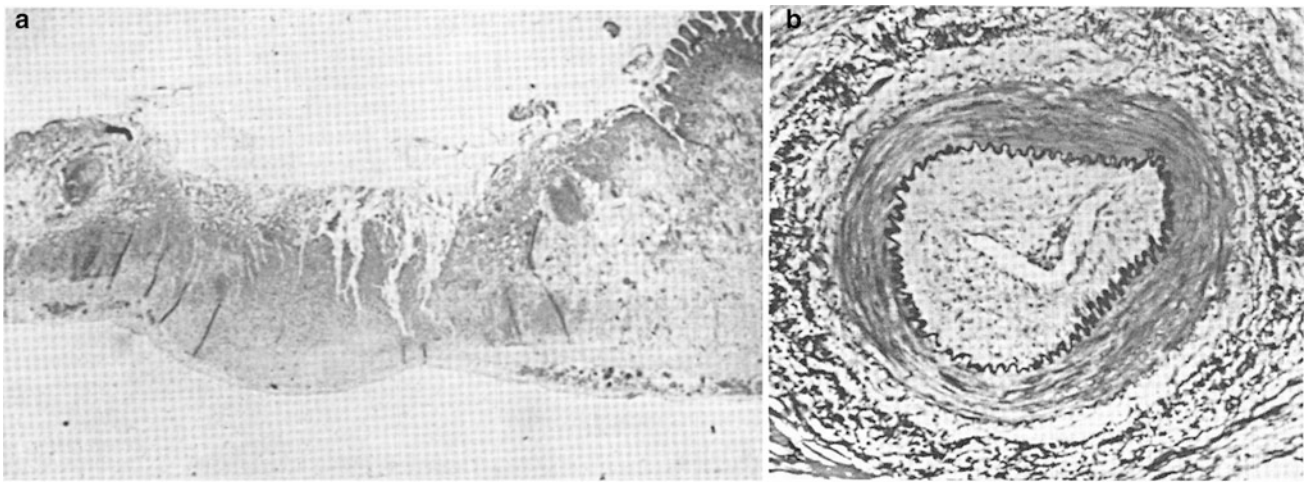


Fig. 11 **a** Pathology of subacute radiation ulcer of the small intestine. 6 months after radiation therapy (about 60 Gy; low mag). **b** Cross section of a small artery underlying the ulcer shown in **a**, showing obstruction of the lumen by marked endothelial proliferation (endarteritis obliterans) and other changes in the arterial wall (high mag) (from Rubin and Casarett 1968, with permission)

Table 9 Clinical syndromes: LENT SOMA system for categorizing and grading toxicities: small intestine/colon

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Stool frequency	2–4 per day	5–8 per day	>8 per day	Refractory diarrhea
Stool consistency	Bulky	Loose	Mucous, dark, watery	
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory/rebound
Constipation	3–4 per week	Only 2 per week	Only 1 per week	No stool in 10 days
Objective				
Melena	Occult /occasional	Intermittent and tolerable, normal hemoglobin	Persistent, 10–20% decrease in hemoglobin	Refractory or frank blood. >20% decrease in hemoglobin
Weight loss from time of treatment	≥5–10%	>10–20%	>20–30%	>30%
Stricture	>2/3 normal diameter with dilatation	1/3–2/3 normal diameter with dilatation	<1/3 normal diameter	Complete obstruction
Ulceration	Superficial ≤1 cm-	Superficial >1 em^2		Perforation, fistulae
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Stool consistency / frequency	Diet modification	Regular use of non-narcotic antidiarrheal	Continuous use of narcotic antidiarrheal	
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Stricture	Occasional diet adaptation	Diet adaptation required	Medical intervention, NG suction	Surgical intervention
Ulceration			Medical intervention	Surgical intervention
Analytic				
CT	Assessment of wall thickness, sinus and fistula formation			
MRI	Assessment of wall thickness, sinus and fistula formation			
Absorption studies	Assessment of protein and fat absorption and metabolic balance			
Barium radiograph	Assessment of lumen and peristalsis			

Table 10 Representative endpoints for intestinal effects: segregated based on their global versus focal nature, and whether they are subclincal versus clinical small/large bowel

	Focal	Global
Subclinical	Atrophy of mucosa Localized reduced mobility Regions of poor absorption	Malabsorption
Clinical	Stricture Bleeding, ulceration	Obstruction Bleeding, anemia Weight loss Diarrhea

2.3.2 Biology

2.3.2.1 Molecular Mechanisms

For the molecular mechanisms of the acute inflammatory mucositis and the late fibrosis stage, the proinflammatory cytokines and chemokines for the inflammatory mucositis and the profibrotic cytokines for the later fibrosis stage are described in Sect. 1.3.2 (Fig. 4).

2.3.2.2 Cell Kinetics Renewal Times

Cell kinetic turnover times of the gastrointestinal system determine the latent period before the clinical syndromes and manifestations occur. Thus, the acute effects will appear first in the small intestine, and then in the pylorus of the stomach, the body, in the first week of radiation. In the second week, the large intestine, first in the rectum, and then the colon reacts, as well as the cardia of the stomach and esophagus, which occurs simultaneously. It is noteworthy that the oral cavity and anus develop their mucositis in the first week (Table 2).

2.4 Pathophysiology

The majority of clinical symptoms, including abdominal pain, diarrhea, steatorrhea, and obstruction are related to decreased intestinal motility and malabsorption. Decreased motility is a direct result of functional impairment from collagen proliferation within the bowel wall. Malabsorption is a multifactorial process resulting from mucosal atrophy, vascular insufficiency, and decreased motility resulting in bacterial overgrowth. Increased fibrosis within the bowel wall and the surrounding connective tissues can lead to focal narrowing with resultant bowel obstruction.

The subacute to chronic radiation toxicity can be rapid in onset due to obstruction of small intestinal arteriole(s) resulting in bowel wall ulceration and necrosis. If progressive, it will result in perforation of the bowel wall and peritonitis (Fig. 11a, b).

Late radiation toxicities are typically classified as those occurring more than 60–90 days after the completion of treatment. Late radiation toxicity of the small bowel can occur after a variable latency period, with the majority of symptoms occurring 6 months to 3 years after completion of treatment. However, patients are at risk of complication many years and even decades after treatment, and patients who recover from a first complication are at increased risk of further complications (Galland and Spencer 1985).

Gross examination of affected bowel reveals gray, roughened peritoneal surfaces with telangiectasias, fibrinous deposits and adhesions. The bowel wall and mesentery appear thickened and indurated and mucosal ulceration and luminal stenosis are common (Berthong and Fajardo 1981; Berthong 1986). Typical microscopic findings include mucosal atrophy, wall fibrosis, obliterative vascular sclerosis and lymphatic dilation. The majority of chronic radiation damage is seen in the submucosa, which is in contrast to acute injury which is most prominent in the mucosa. Stromal tissue within the bowel wall contains an abundance of atypical fibroblasts with collagen proliferation. These fibroblasts are characterized by large, irregular nuclei and cytoplasmic projections. Arterioles are characterized by a chronic vasculitis with hyalinized thickening of the vessel wall. Thickening of the vessel wall can lead to occlusion or necrosis within the wall with resultant rupture.

2.5 Clinical Syndromes (Endpoints)

The clinical syndromes are described in LENT SOMA (Table 9) and CTC V4.0. The endpoints can be similarly segregated into Global versus Focal and acute versus subacute (Table 10).

2.5.1 Acute Phase

2.5.1.1 Diarrhea

Diarrhea is, perhaps, the most common acute-radiation bowel toxicity. It can be daily, but more often it is intermittent and, in some instances, can alternate with constipation. Tenesmus can also occur with or without associated diarrhea.

Short-bowel or short-gut syndrome is a malabsorption disorder due to functional loss of a large portion of the small intestine, usually at least two-thirds. It is characterized by diarrhea, steatorrhea, abdominal pain, fatigue, weight loss, and malnutrition.

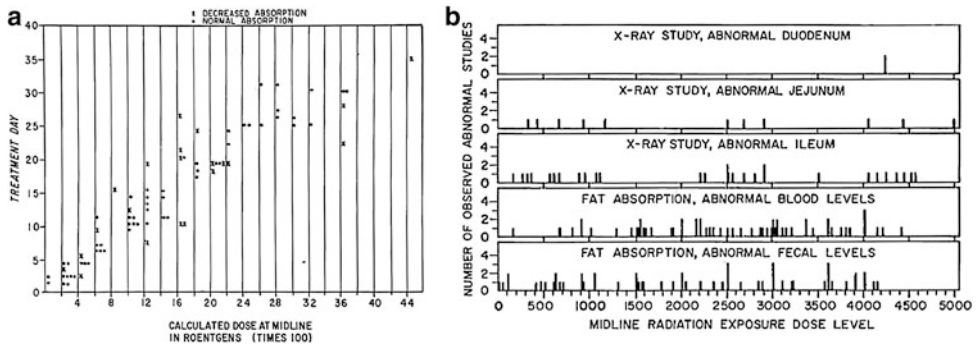


Fig. 12 **a** Clinical syndromes detection: Alterations in fat absorption correlated with time-dose during deep X-ray therapy of the abdomen in 29 patients. Given I^{131} labeled glycerol trioleate and/or oleic acid, 13 of 29 patients exhibited a transient decrease in fat or fatty acid absorption at various times starting at the fifth day and as late as the thirty-fifth day of treatment. (From Rubin and Casarett 1968; Reeves et al. 1959). **b** Clinical syndromes detected after abdominal RT. Correlation between abnormal findings and midline exposure dose level (with permission from Rubin and Casarett 1968)

2.5.2 Late Phase

Clinically, late radiation injury may take years to develop. However, most series report a median of about 8–12 months before the injury became apparent (Anseline et al. 1981; Coia and Hanks 1988; Cox et al. 1986; Kottmeier 1964; Perez et al. 1991; Potish et al. 1979). The clinical signs and symptoms of chronic radiation intestinal injury may be multifactorial in etiology. The most common symptom is frequent and urgent stools (Pilepich et al. 1987a, b). This need not take the form of frank watery diarrhea. This can be a consequence on injury anywhere in the intestine. It has been suggested that diarrhea without tenesmus, frank blood, or mucus discharge may be a manifestation of injury from more proximal segments, and therefore should be distinguished from other presentations of frequent loose stools (Pilepich et al. 1987a, b). However, this is often a difficult distinction to make clinically. Certainly a patient may have injury both in the rectum and more proximally. Blood, fecal urgency, and lower abdominal cramping can be present with more distal bowel segments (Cox et al. 1986; Pilepich et al. 1987a, b; Roswit 1974; Rubin and Casarett 1968; Yeoh and Horowitz 1987). Rectal pain can be present with chronic proctitis, particularly if there is ulceration extending into the anal canal. The chief problems that may require major medical or surgical intervention are intestinal obstruction (because of the luminal size this is rare in the large bowel), severe bleeding, fistula formation, and intractable diarrhea (Anseline et al. 1981; Cox et al. 1986; Lillemoe et al. 1983; Lucarotti et al. 1991; Marks and Mohiuddin 1983; Schmitt and Symmonds 1981). Clinically apparent malabsorption is unlikely except in cases where surgical management of other problems requires the removal of extensive small bowel (Fajardo 1982; Newman et al. 1973). Fortunately, as indicated above, the likelihood of severe complications is low (about 5 % or less) with modern treatment approaches.

2.5.2.1 Detection

Patients with chronic small bowel injury can show an increase in the intraluminal bile salt contents, as manifested by a radiolabeled cholylglycine-ethanol breath test (Newman et al. 1973). This is because of a combination of impaired reabsorption and bacterial overgrowth. For this reason the use of cholestyramine for patients with severe radiation-associated diarrhea has been suggested (Chary and Thomson 1984; Newman et al. 1973).

2.5.2.2 Absorption Studies

Absorption studies are of value for early detection of abnormal effects of intestinal malfunction. Alterations in fat absorption using I^{131} labeled glycerol trioleate and/or oleic acid become evident in the second week and rapidly deteriorate as treatment continues during the next 2–8 weeks. Figure 12a illustrates the correlation between abnormal findings and midline exposure dose level (in R). The relationship between the abnormal results and the midline radiation dosage is shown for both the small bowel x-ray and the fat absorption studies. The majority of the abnormal

findings in this series occurred at a midline exposure dose of 2,000–3,000 R between the second and third weeks of therapy. There appears to be absolutely no correlation between the findings of abnormal small bowel X-ray patterns and abnormal small bowel X-ray patterns and abnormal fat absorption studies (Fig. 12b). (Reeves et al. 1965).

2.5.3 Severe Presentations/Occurrences

2.5.3.1 Obstruction

Bowel obstruction is a potentially life-threatening late complication of radiation to the intestine. Although a fairly rare occurrence in most recent clinical series with reported incidences less than 5 %, small bowel obstruction is a complication that often requires hospital admission and surgical intervention. Patients typically present with symptoms such as nausea, vomiting, abdominal distention, constipation, and anorexia.

2.5.3.2 Bleeding

Reported incidences of chronic enteric bleeding related to radiation toxicity are very low. However, when present and substantial, surgical management is usually inevitable. Symptoms can include melena and anemia-related fatigue from chronic bleeding, or, hematochezia from acute bleeding.

2.5.3.3 Perforation

As aforementioned, in the pathophysiology section, arteriolar thrombosis can lead to a sudden dramatic bowel necrosis and perforation with spillage of intestinal contents, resulting in peritonitis and subphrenic abscess formation. If air is expelled, this can result in percutaneous crepitation.

2.5.3.4 Fistula

Fistula formation is one of the more common late gastrointestinal toxicities, especially patients treated with brachytherapy or a combination of radiation and prolonged chemotherapy. Fistula formation between the vagina and adjacent rectum, bladder or small bowel is all possible. Fistulae not involving the vagina are less common, but ileosigmoidal, ileorectal, ileovesical, and ileoureteral fistulae have all been reported (Watanabe et al. 2002). Symptoms associated with fistula formation are dependent upon the organs involved. Vaginal fistulae usually present with vaginal discharge or bleeding, whereas bowel fistulae typically present with abdominal pain, diarrhea, bleeding, and malnutrition.

2.5.3.5 Diagnosis

The radiologic picture of late radiation injury is of fibrosis and ischemia (Cox 1986; Fajardo 1982; Roswit 1974; Rubin and Casarett 1968, Yeoh and Horowitz 1987). Contrast studies may show spasm with either increased or decreased transit times. Thickened folds, ulceration, and smoothly narrowed segments of intestine may be present. Patients with chronic small bowel injury can show an increase in the intraluminal bile salt contents, as manifested by a radiolabeled cholylglycine-ethanol breath test (Newman et al. 1973). This is because of a combination of impaired reabsorption and bacterial overgrowth. For this reason the use of cholestyramine for patients with severe radiation-associated diarrhea has been suggested (Chary 1984; Newman et al. 1973).

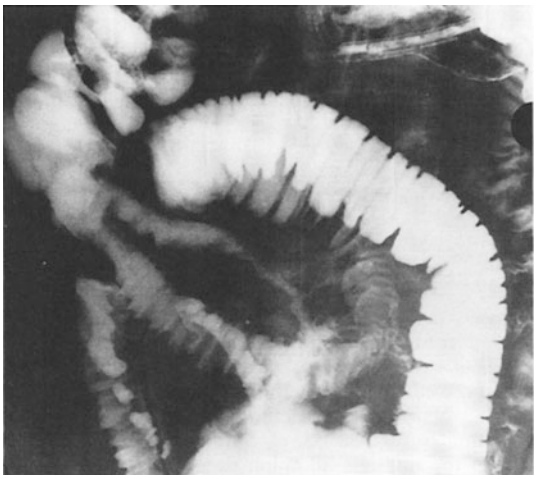


Fig. 13 Clinical syndromes diagnosis: postradiation changes in the small bowel: strictures. This barium image of the small bowel reveals severe late effects of radiation in the small intestine. Long irregular strictures, fixation, and separation of the loops are seen (with permission from Rubin 2001)

The small intestine is very sensitive to radiation, and changes confined to irradiated areas, despite movement of loops, can be seen on both barium enema and CT studies. On barium studies, radiologic signs are thickening of folds and bowel wall, impaired peristalsis, tapered strictures, thumbprinting, and adhesions. Small bowel loops and, especially, the terminal ileum should be examined carefully, because early signs of radiation injury such as fixation of loops are easily overlooked (Fig. 13).

Fistulas to adjacent organs (vagina and bladder) are not uncommon. CT scans of irradiated small bowel demonstrate changes in wall thickness, ascites, abnormal angulations, and an increased density and fibrosis of the mesentery as well as fixation of bowel loops, mostly within the pelvis (Husband and Reznek 1998; Decosse et al. 1969; Mason et al. 1970; Lepke and Libshitz 1983).

The differential diagnosis of radiation-induced stricturing versus recurrent carcinoma has been suggested to be made based on the following criteria:

- radiation-induced stricturing is longer than expected with recurrent carcinoma

- radiation-induced stricturing margins are not abrupt or as sharp as in recurrent carcinoma
- radiation-induced stricturing has multiple bowel loops involved with strictures, fixation, and separation of loops.

2.6 Radiation Tolerance

2.6.1 Dose, Time, Fractionation

Historical data are informative on the risk of late gastrointestinal toxicity comes from the treatments of gynecologic malignancies as well as Hodgkin's lymphoma and testicular tumors. Treatments were designed without the aid of three-dimensional (3D) planning and typically delivered using orthovoltage or cobalt teletherapy units. The use of concurrent chemotherapy was rare and many patients had extensive surgical treatment prior to radiotherapy. Nevertheless, the lessons learned about the volumes treated and doses used have helped to shape our current understanding of normal tissue tolerances of the abdomen and pelvis.

Some of the largest and most informative series of patients treated with pelvic radiation have been in cervix cancer. Perez et al. (1991) reviewed the experience of treating 1,211 patients with carcinoma of the uterine cervix with primary radiation therapy alone. They noted an incidence of severe small bowel sequelae of 1 % with doses <50 Gy, 2.5 % for 50–60 Gy, and 3.6 % for doses above 60 Gy. Similarly, Eifel et al. (1995) reviewed records from 1,784 patients with stage IB cervix cancer treated with initial radiation therapy. The vast majority of patients were treated with opposed anterior and posterior pelvic fields using 18–25 MV photons at 2 Gy per fraction to a dose of 40 Gy with an external boost to involved lymph nodes to 60 Gy and intracavitary boost using a Fletcher-Suit after loading applicator. They reported an overall incidence of small bowel obstruction of 5.3 % and fistula formation of 3.1 %. There was an increased risk in patients weighing under 120 pounds or who underwent staging laparotomy, but not in patients who underwent adjuvant hysterectomy. Additionally, there was a decreased risk of gastrointestinal complications in Hispanic women, independent of the patient's body weight and anterior-posterior separation.

Gallez-Marchal et al. (1984) reported on gastrointestinal complications in patients treated on EORTC trials H2 and H5 for Hodgkin's lymphoma. Patients were treated with 25 MV photons using opposed anterior and posterior fields, with one field being treated per day in one of two fractionation schemes: 3.3 Gy 3 days/week or 2.5 Gy 4 days/week. Treatment volumes were either the paraaortics only, paraaortics with the spleen, or a traditional "inverted Y." In a series of 134 patients, they identified 24 radiation complications in 19 patients: gastritis (5), gastric ulcer (5), duodenal ulcer (7), small bowel obstruction (5), and bowel perforation (2). They identified staging laparotomy and increased dose per fraction as important parameters in increasing the risk of complication. Patients who underwent staging laparotomy and were treated with 3.3 Gy per fraction had a 42 % complication rate, whereas patients without laparotomy treated with 2.5 Gy per fraction had only a 5 % complication rate. Morris et al. (1985) reviewed patients treated with staging laparotomy with or without abdominopelvic radiation for Hodgkin's lymphoma. Patients were treated with 4,000 rad at 200 rad per day. They found an increased risk of small bowel obstruction in patients treated with paraaortic and iliac radiotherapy compared with paraaortic only and no radiation (13.9 % vs. 2.4 % and 2.2 %, respectively). Also see the discussion in Sect. 3 on large bowel (particularly Sects. 3.6 and 3.7, and Table 11) as some studies combine large and small bowel injury reporting.

2.6.2 Dose Volume

The impact of radiation dose and volume on the risk of small bowel injury can be estimated only by comparing multiple retrospective studies. The overall sense of the literature is that the incidence of major small bowel complications increases rapidly with doses above 50–55 Gy when substantial small bowel, but less than whole abdominal, radiation is administered. Several studies for cancer of the cervix suggest that the incidence of severe small intestinal injury is increased to 15–25 % if paraaortic radiation to doses of 50–55 Gy is combined with pelvic radiation (Lepanto et al. 1975; Potish et al. 1979; Tewfik et al. 1982) On the other hand, more recent studies using doses in the 45–50 Gy range do not show an increased incidence of small bowel injury with the addition of a paraaortic portal (Pilepich et al. 1987a, b). At the low dose levels used for Seminoma and Hodgkin's disease, the patterns of care study found that the incidence of grade ≥3 small bowel toxicity was dose dependent; however, this was independent of volume for treatment to paraaortics alone or to paraaortics plus iliac nodes). For patients treated to a more limited volume, the sharp increase in likelihood of small bowel toxicity occurs at higher doses. Perez found that patients with carcinoma of the cervix had a 1 % incidence of severe small bowel toxicity when the pelvic sidewall dose was <50 Gy and a 5 % incidence at >70 Gy (Perez et al. 1991). Dose per fraction is also critical with a 15 % increase in severe late complications noted with >2 Gy/fx versus 1.8 Gy/fx (Hanks et al. 1983). Some data related to small bowel are also included in the section on colon, as some reports address small and large bowel toxicity together (see Sects. 3.6 and 3.7, and Tables 11, 12, 13, 14). A proposed summary of the available dose/volume/risk information for conventionally fractionated external beam RT is shown in Fig. 14. The recent Quantec review concluded, "The

Table 11 Late gastrointestinal toxicity of preoperative pelvic radiotherapy

Study	Publication year	Patients (*n*)	Median follow-up	Treatment arms	≥Grade 3 late GI toxicity (%)	Small bowel obstruction[a] (%)
Uppsala	1993	217	Minimum 5 years	Pre-op 5.1 Gy x 5; resection	11	5
		215		Resection; post-op split course 60 Gy	15	11
Polish rectal cancer	2006	155	48 mos	Pre-op 5 Gy x 5; TME	5.1	–
		157		Pre-op 50.4 Gy + 5-FU/LV; TME	1.4	–
Swedish rectal cancer	2008	454	14 years	Pre-op 5 Gy x 5; surgery	–	13.9
		454		Surgery alone	–	5.5
Dutch rectal cancer	2005	306	5.1 years	Pre-op 5 Gy x 5; TME	–	11
		291		TME alone	–	11

[a] Requiring surgical intervention or leading to death
5-FU/LV = 5-fluorouracil with leucovorin
TME = total mesorectal excision

Table 12 Late gastrointestinal toxicity of postoperative pelvic radiotherapy

Study	Publication year	Patients	Median follow-up	Treatment arms	≥Grade 3 late GI toxicity (%)	Small bowel obstruction[a] (%)
GOG 92	2006	137	10 years	Rad Hyst + PLND; pelvic RT 46-50.4 Gy	2.2	1
				Rad Hyst + PLND	0	0
GOG 109	2000	243	42 mos	Rad Hyst + PLND; pelvic RT 49.3 Gy	1	0
				Rad Hyst + PLND; pelvic RT 49.3 Gy + cis/5-FU	1.6	1.6
PORTEC	2001	691	5 years	TAH/BSO; 46 Gy pelvis	3	<1
				TAH/BSO alone	0	0
GOG 99	2004	392	69 mos	TAH/BSO + PLND; 50.4 Gy pelvis	8	2.6
				TAH/BSO + PLND alone	1	0
RTOG 97-08	2006	46	4.3 years	TAH/BSO + PLND; 45 Gy pelvis + cisplatin + ICBT + cis/paclitaxel x4 cycles	11	2

[a] Requiring surgical intervention or leading to death
Rad Hyst = radical hysterectomy
PLND = pelvic lymph node dissection
cis/5-FU = concurrent cisplatin and 5-fluorouracil chemotherapy
cis/paclitaxel = concurrent cisplatin and paclitaxel chemotherapy
TAH/BSO = total abdominal hysterectomy and bilateral salpingo oophorectomy
ICBT = intracavitary brachytherapy

absolute volume of small bowel receiving ≥15 Gy should be held to <120 cc when possible to minimize severe acute toxicity, if delineating the contours of bowel loops themselves. Alternatively, if the entire volume of peritoneal space in which the small bowel can move is delineated, the volume receiving >45 Gy should be <195 cc when possible. Such a limit likely also reduces late toxicity risk, although this correlation is not established. The volume of small bowel receiving higher doses should also be minimized."

Knocke et al. (1997) published a large experience of intracavitary high-dose rate brachytherapy for 280 medically inoperable patients with endometrial cancer. Brachytherapy was performed once weekly with the majority of patients receiving six total applications with 8.5 Gy prescribed to the uterine canal and 7 Gy prescribed to the vaginal mucosa for

Table 13 Late gastrointestinal toxicity of pelvic radiotherapy, with or without chemotherapy

Study	Publication year	Patients (n)	Median follow-up	Treatment arms	≥3 Grade 3 late GI toxicity (%)	Small bowel obstruction[a] (%)
German Rectal Trial	2004	823	46 mos	Pre- or postoperative 50.4 Gy with 5-FU	3.8	1.5
EORTC 22911	2006	1011	5.4 years	Pre- or postoperative 45 Gy with or without 5-FU/LV	–	1.4
RTOG 90-01	2004	194	6.6 years	45 Gy Pelvic RT + ICBT + weekly cisplatin	3.7	–
		195		45 Gy Pelvic + PAN RT + ICBT	4.6	–
NCIC	2002	126	82 mos	45 Gy pelvis + ICBT	13.0	1
		127		45 Gy pelvis + ICBT + weekly cisplatin	7.0	0
GOG 120	2007	518	106 mos	Pelvic RT 40–51 Gy + ICBT + weekly chemotherapy	0.7	0
GOG 125	1998	86	34 mos	45 Gy PAN + 40–48 Gy pelvis + ICBT + cisplatin/5-FU weeks 1 and 5	14	0
Vienna	1997	280	49 mos	50–60 Gy in 6–7 fractions HDR ICBT	2	2

[a] Requiring surgical intervention or leading to death
[b] Primarily rectal complications
5-FU = 5-fluorouracil
LV = leucovorin
ICBT = intracavitary brachytherapy
PAN = paraaortic lymph node regions
HDR = high-dose rate

Table 14 Late gastrointestinal toxicity of whole abdominal and pelvic irradiation

Study	Years	Patients	Median follow-up	Treatment arms	≥Grade 3 late GI toxicity (%)	Small bowel obstruction[a] (%)
Swedish–Norwegian	2003	172	n/a	Surgery; cis/adria; surgery; WAPI 20 Gy abdomen, 40 Gy pelvis	10.1	5.8
				Surgery; cis/adria; surgery; cis/adria	4.2	–
Dembo	1992	1098	n/a	Post-op WAI ≤ 22.5 Gy	–	1.4
				Post-op WAI ≥ 30 Gy	–	14.3
Beaumont	2002	119	5.8 years	Post-op WAPI 30 Gy abdomen, 51 Gy pelvis	12	10

[a] Requiring surgical intervention or leading to death
cis/adria = concurrent cisplatin and adriamycin chemotherapy
WAPI = whole abdominal and pelvic radiation
WAI = whole abdominal irradiation

each fraction. Twenty-four patients received additional external beam pelvic radiotherapy. At a median follow-up of 49 months the rate of late gastrointestinal toxicity was 2 % with a small bowel obstruction rate of 2 %.

2.7 Chemotherapy Tolerance

Chemotherapy alone does not appear to produce significant late GI complications with any frequency, despite the well-documented acute toxicity caused by a long list of agents (Table 8). Drugs, such as 5-fluorouracil (5-FU), produce diarrhea and, occasionally, small bowel toxicity. More severe late effects, such as GI bleeding, generally have been seen only in combined-modality therapy, which has led to severe acute complications, particularly in the small bowel.

Most of the evidence suggests that 5-FU infusion as a bolus, with radiation doses ranging from 45 to 50 Gy, is well tolerated with few reports of late toxicity. However, administering the chemotherapy concurrently frequently enhances the risk for intestinal complications (Varveris et al. 1997).

2.7.1 Combined Modality

The use of concurrent radiation therapy and chemotherapy has come to play an increasingly important role in the management of pelvic and abdominal malignancies. The

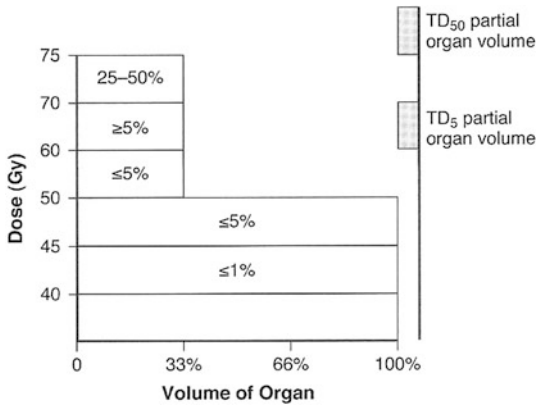


Fig. 14 Dose-volume histogram parameters and associated risks of late effects seen in the gastroinyestinal tract. The right Y-axis indicates the tolerance dose ranges for the TD_5 and TD_{50} for partial organ volume (POV) irradiation. (Modified from Rubin 2001)

addition of chemotherapy to radiation therapy is often for purposes of improving local control as well as treating systemic disease. Because of late effects, the dose of radiation therapy can be limited and the additional cytotoxic effects of chemotherapy can improve the results locally. In this regard, it is very important to establish that adding the chemotherapy does not significantly enhance late effects. It has been shown that the use of concurrent adriamycin or actinomycin D can, in fact, enhance the risk of late intestinal complications (Phillips and Fu 1975, 1976, 1977). Most treatment regimens for gastrointestinal malignancies are based on 5-FU. Recently, a series of national studies have investigated the use of 5-FU-based chemotherapy and radiation therapy for rectal carcinoma. The chemotherapy in these studies is centered around the bolus administration of 5-FU (400–500 mg/m^2 per injection with or without additional agents such as leucovorin or levamisol). Most of the national studies, while displaying positive disease-free survival benefits to combined modality, do not report in great detail on late effects. However, the Mayo North Central Study (Krook 1991) comparing radiation therapy alone (45 Gy pelvis plus a boost up to 9 Gy to the tumor bed) with radiation therapy plus bolus 5-FU for postoperative rectal cancer patients, documented that the addition of bolus 5-FU did not add to the risk of late intestinal complications. This is in contrast to mild to moderate acute complications, which are increased by the addition of chemotherapy. It is possible that chemotherapy regimens that include high-dose infusional 5-FU (on the order of 1 gm/m^2/day for a total of 96 h) can enhance the risks of late intestinal complications. When infusional 5-FU-based chemotherapy is administered with low-dose radiation therapy (pelvic doses $\leq$30 Gy) for carcinoma of the anus, the intestinal complication rate is quite acceptable with severe late small or large bowel injury <5 % (Cummings et al. 1991). There is, however, a suggestion that higher doses of radiation therapy in conjunction with infusional 5-FU-based chemotherapy is less well tolerated. Cummings et al. (1991) found that when they administered 50 Gy in 20 fractions with infusional 5-FU and mitomycin C, that the incidence of grade 3 or higher late gastrointestinal toxicity was 25 % (4 out of 16). Similarly, Grigsby et al. (Grigsby and Perez 1991) reported a series of patients treated with full dose radiation therapy and concurrent infusional 5-FU plus cisplatinum chemotherapy for carcinoma of the cervix. The incidence of severe small or large bowel complications was 18 % (7 out of 40).

2.8 Special Topics

2.8.1 Predisposing Host Factors

There are a variety of factors associated with the degree of risk for late intestinal injury. Risk as a function of radiation dose and volume were discussed earlier in this section. Some studies have suggested that a history of hypertension or diabetes mellitus may be associated with a greater risk of late intestinal injury (Potish et al. 1983, .). Probably the most significant nonradiation-related risk factor is a history of prior abdominal surgery or pelvic inflammatory disease. This has been particularly well documented for small bowel injury (Hanks et al. 1983, Potish et al. 1983, 1987). Some series for gynecologic malignancy show an increase of 10–15 % in the incidence of grade 3 or 4 chronic intestinal injury (Hanks et al. 1983, Potish et al. 1983, 1987). To some extent this may reflect evolving radiation therapy practices as a number of patients in these series were treated with techniques that would not be used today: AP/PA with one field per day treated and/or 60 C treatment. More recent series for cancer of the cervix do not show this marked association with prior surgery (Perez et al. 1991). Patients treated to lower doses of radiation have a lesser association between surgery and intestinal complication. The patterns of care survey reviewed patients with seminoma and Hodgkin's disease (doses generally below 45 Gy) and found that when the radiation was preceded by laparotomy, the incidence of grade 3 or 4 intestinal complications was only 3 % (Coia and Hanks 1988).

2.8.2 Whole Abdominal Irradiation

Data on the use of whole abdominal irradiation (WAI) in adult patients comes primarily from the treatments of ovarian and uterine cancers. Data are informative because, unlike treatment with pelvic radiotherapy, WAI treats the entirety of the small bowel. The majority of reports on WAI are old, but there are some fairly recent institutional reviews (Beaumont Hospital) and phase III trials in ovarian cancer

(Swedish-Norwegian Ovarian Cancer Study Group) and endometrial cancer (GOG 122) that employed WAI on a randomized treatment arm. Unfortunately, late toxicity data have not been reported for GOG 122 (Randall et al. 2006).

The Swedish–Norwegian Ovarian Cancer Study Group conducted a phase III trial in FIGO stage III epithelial ovarian cancer (Sorbe 2003). All patients underwent cytoreductive surgery followed by consolidative chemotherapy and a second look surgery. Patients were then classified by response to treatment and randomized to WAI or further chemotherapy, with a no further therapy subgroup in patients with complete pathologic response. WAI was 20 Gy in 20 treatment days using open anterior-posterior fields with no blocking, followed by a boost to the pelvis of another 20.4 Gy at 1.7 Gy per fraction. The incidence of grade 3 or greater intestinal toxicity was 10.1 % in the WAI group, with 5.8 % requiring surgical intervention. This is in comparison to 4.2 % incidence of late grade 3 or greater gastrointestinal toxicity in the chemotherapy group. Toxicity data are not reported for the group receiving no further therapy.

Stewart et al. (2002) reported on 119 patients treated with adjuvant WAI for stage I to III endometrial cancer. Patients were treated to the whole abdomen and pelvis to 30 Gy in 1.5 Gy fractions followed by boosts to the paraaortic region to 42 Gy, to the pelvis to 51 Gy and vagina to 58.2 Gy. At a median follow-up of 5.8 years, the grade 3 or 4 late gastrointestinal toxicity rate was 12 %, with 10 % of patients requiring surgical intervention. Dembo (1992) summarized the bowel complications after postoperative WAI for ovarian cancer in 1,098 patients in ten separate reports. The rate of bowel surgery for gastrointestinal complications was 5.6 %, with a 0.4 % mortality rate. Complication rates appeared related to dose and dose per fraction, with a 1.4 % risk in patients receiving 2,250 cGy in 22 fractions and 14.3 % for 3,000 cGy in eight fractions. In addition, the risk of complication was higher in patients with previous surgery, particularly lymph node sampling.

2.8.3 Second Malignant Neoplasms

The risk of a second, radiation-induced malignancy after abdominopelvic irradiation in the adult is small and difficult to define, but one that radiation oncologists are fully aware of. Data on second malignancies are most abundant in pediatric populations but less commonly reported in adults. Ionizing radiation increases the frequency of malignant transformation of intestinal epithelium both in humans and in experimental animals (Denman et al. 1978; Osborne et al. 1963). The relative risk of second malignancy from abdominopelvic radiotherapy appears to be on the order of 1.5–2.0 compared to similar patients treated without radiation, with radiation-induced cancers appearing within or adjacent to the previously irradiated volume (Baxter et al. 2005; Birgisson et al. 2005). In a large international review of over 100,000 women surviving more than 1 year after treatment for uterine cervix cancer, Chaturvedi et al. (2007) showed an increased risk of second malignancy for all patients with an overall standardized incidence ratio (SIR) of 1.3. Women treated with radiotherapy to fields including the intestine, colon, and rectum/anus had SIRs of 1.94, 1.22, and 1.90, respectively. In comparison, there was no increased incidence of second cancer at these sites in women treated without radiotherapy.

2.9 Prevention and Management

2.9.1 Prevention

2.9.1.1 Bowel Sparing IMRT

Efforts at decreasing the risk of bowel complication from pelvic radiotherapy has been aimed at limiting the integral dose to a volume of the peritoneal cavity while maintaining an adequate dose to the target. Increasing the therapeutic benefit of pelvic radiotherapy in this manner is not a new idea (Green et al. 1975), but the technology necessary to implement it is now available. IMRT offers the means of limiting the radiation dose to the bowel by using multiple treatment segments to create a more conformal dose distribution. Clinically, this treatment approach has been used commonly in the postoperative radiation of gynecologic malignancies, where surgical absence of the uterus leads to an increased volume of small bowel in the pelvis.

Roeske et al. (2000) described treatment planning for whole pelvic radiation for ten patients, five with endometrial cancer in the postoperative setting and five with cervix cancer. All patients were planned to 45 Gy with a traditional 4-field pelvic technique as well as with IMRT. The CTV was defined as the proximal vagina, parametrial tissues, uterus (if present), and regional lymph nodes. The PTV was defined using a uniform 1 cm expansion on the CTV. The bladder, rectum, and small bowel were created as avoidance structures. The average volume of bowel receiving the prescription dose was decreased by a factor of two (33.8 % vs. 17.4 %, $p = 0.0005$) for all ten patients in the study.

Portelance et al. (2001) published a series of ten patients with cervix cancer planned for treatment of an extended field using a conventional 4-field technique and multiple IMRT plans. The target volumes were the uterus, cervix, and pelvic and paraaortic lymph nodes with a prescription dose of 45 Gy to all target volumes. The average volume of small bowel receiving 45 Gy was decreased using IMRT compared to traditional planning (11 % vs. 34.2 %).

Mundt et al. (2002) published the dosimetric results and acute toxicities of 40 patients treated with pelvic IMRT for

gynecologic malignancies. Their toxicity profiles were compared to a group of 35 similar patients treated using conventional whole-pelvic RT. Patients treated with IMRT had significantly less acute grade 2 gastrointestinal toxicity (60 % vs. 91 %, $p = 0.002$) with no grade 3 toxicities reported in either group. IMRT patients were also more likely to require no or infrequent antidiarrheal medication during treatment (75 % vs. 34 %, $p = 0.001$). The same authors published a preliminary analysis on a separate group of patients comparing late gastrointestinal toxicity with IMRT and conventional whole pelvic RT (Mundt et al. 2003). Patients treated with IMRT had a lower overall rate of all late GI toxicity (11.1 % vs. 50 %, $p = 0.001$) as well as fewer grade 3 toxicities (0 % vs. 3.3 %), despite having a higher proportion of patients with a history of surgery (75 % vs. 54 %, $p = 0.02$).

IMRT has also been used in the treatment of the pelvic lymph nodes in prostate cancer. Ashman et al. (2005) reviewed 13 patients treated with whole pelvic IMRT as part of the whole pelvic phase of treatment for prostate cancer. They generated treatment plans using conventional 2D and 3D treatment planning for comparison and found that IMRT decreased the volume of small bowel receiving 45 Gy by 60 % relative to 3D-CRT. At a median follow-up of 30 months they had observed no cases of late radiation enteritis. Similarly, Liu et al. (2007) compared the dosimetry of whole pelvic IMRT with 2D treatment plans and found decreased dose to the small bowel for IMRT plans prescribed to 78 Gy compared with 2D plans prescribed to 72 Gy.

The popularity and clinical implementation of IMRT for treatment of the pelvis has rapidly increased. Currently, a guideline exists for postoperative pelvic IMRT in cervix and endometrial cancers. It is a consensus effort from the RTOG, GOG, ACRIN, ESTRO, and NCIC (Small et al. 2008). Also, there is a CT-based treatment volume atlas from the same group of authors available on the RTOG website (www.rtog.org).

2.9.1.2 Surgical/Gravitational/Physiological Displacement

Green noted that 65 % of patients referred for postoperative radiation had fixed loops of small bowel within the pelvis, in contrast to 18 % of patients with no prior surgery (Green 1983; Green et al. 1975). He recommended surgical displacement of the bowel prior to radiation. Gallagher has shown that the use of lateral portals and prone position with bladder compression can reduce the volume of small bowel in the pelvis from 600–1,010 cc to 145–385 cc (Gallagher et al. 1986). A follow-up study showed that the most important factors in reducing the incidence of small bowel complications in patients with prior surgery were smaller radiation fields and the use of small bowel contrast at the time of simulation (Herbert et al. 1991).

Similarly, the volume of incidentally exposed small bowel during pelvic irradiation can sometimes be reduced by treating the patient with a full bladder, and/or in the prone position. Small bowel displacement with prone positioning can often be further enhanced by a false tabletop to provide a "place for the anterior abdominal contents to go"—a maneuver most helpful in heavier patients. For central/lateral abdominal targets, the use of decubital positioning can also sometimes be very helpful in displacing small bowel away from the targeted area (e.g., having the patient lying on their left side [right side up] when targeting the right flank). These non-standard positions need to be used with care since the patient's set-up reproducibility can be more challenging. In many instances, the geometric advantages afforded by alternative positioning exceed the "dose-steering" ability of IMRT to reduce small bowel exposure.

2.9.2 Management

Mild cases of chronic radiation toxicity of the small and large intestine can be managed conservatively with stool softeners and a low residue diet. Antidiarrheals such as loperimide can be added for better control of bowel frequency and for episodic diarrhea. More severe cases can lead to malabsorption with resultant malnutrition. Successful use of total parenteral nutrition to counteract malabsorption from radiation enteritis has been described in multiple reports. Scolapio et al. (2002) recently reviewed their experience of 54 patients over a 25-year period treated with home parenteral nutrition. The most common indications for treatment were mechanical obstruction and short bowel syndrome. They reported a 5-year survival for patients managed with home parenteral nutrition of 64 % with only one death from catheter-related sepsis (Table 2a).

More severe cases of radiation enteritis often require aggressive medical management with consideration of surgical intervention. Indications for surgery include stricture, perforation, fistula, and bleeding. The recommended surgical procedure is not clearly defined and has been debated in the literature. Studies from the 1980s reported a high rate of suture failure at anastomotic sites and, therefore, recommended that surgical approaches should be limited to bypass and colostomy (Smith and Decosse 1986). However, more recent surgical series for the treatment of radiation enteritis have shown good success with minimal postoperative morbidity using bowel resection with reanastomosis (Onodera et al. 2005; Regimbeau et al. 2001).

In one of the largest reported series in the literature, Regimbeau et al. described the treatment and outcomes of

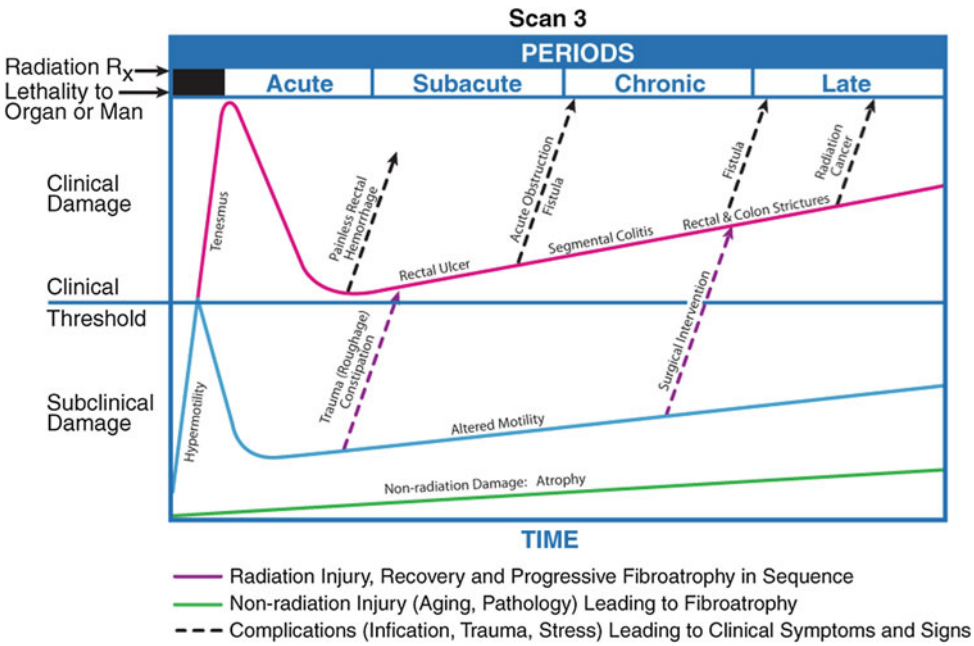


Fig. 15 Biocontinuum of adverse and late effects of the colon/rectum (with permission from Rubin and Casarett 1968)

109 patients who underwent surgery for radiation enteritis during the time period 1984–1994 (Regimbeau et al. 2001). Sixty-five patients had resection and 42 were treated with conservative surgical management with a 30 % postoperative complication rate and 5 % mortality. The authors found improved overall survival and a lower rate of re-operation in the resection group without an increased rate of postoperative complications when compared to the conservative treatment group. Five- year overall survival for all patients without cancer recurrence was 69 %.

In summary, functional resection with re-anastomosis appears to have superior outcome compared to enteric bypass with colostomy. When possible, the entirety of the affected segment of bowel should be resected and at least one of the anastomotic ends should be from an unaffected portion of bowel. For chronic dysmotility and malabsorption, parenteral nutrition appears to be a reasonable alternative to surgical therapy in appropriately selected patient groups. Improvements in enteral nutrition, surgical techniques, and postoperative care have improved long-term survival and quality of life in patients with severe radiation enteritis, with recent series reporting long-term survivals of 60–70 % in the absence of cancer recurrence.

2.10 Future Directions

Investigations into radioprotectors for the bowel have been inconsistent and disappointing, with no current clinically accepted protector available. Further advances in surgical care as well awareness of the complex nutritional needs of these patients will hopefully continue to improve outcomes. See Sect. 1.10.

2.11 Literature Landmarks

See Sect. 3.11.

3 Colon and Large Intestine

3.1 Introduction

The tolerance of the small and large bowel is a major dose-limiting factor in the treatment of many cancers of the abdomen and pelvis. Although the acute effects of radiation therapy to the abdomen and pelvis can usually be managed conservatively, the risk of life-threatening subacute and chronic injury must be kept to an acceptable minimum (approximately 5 %). Thus, for example, dose limitations make the role of radiation therapy in the management of primary cancers of the gastrointestinal tract one of adjunctive treatment to surgery in most cases. Even in this setting the radiation dosage is limited. For example, in administering postoperative radiation therapy for carcinoma of the rectum most radiation therapists would give approximately 45 Gy to the pelvis followed by a boost to the tumor bed of an additional 5–9 Gy. This is in contrast to postoperative treatment at other sites, such as the head and neck, where postoperative doses of 60 Gy or higher are frequently administered. Moreover, tolerance of the rectum and small

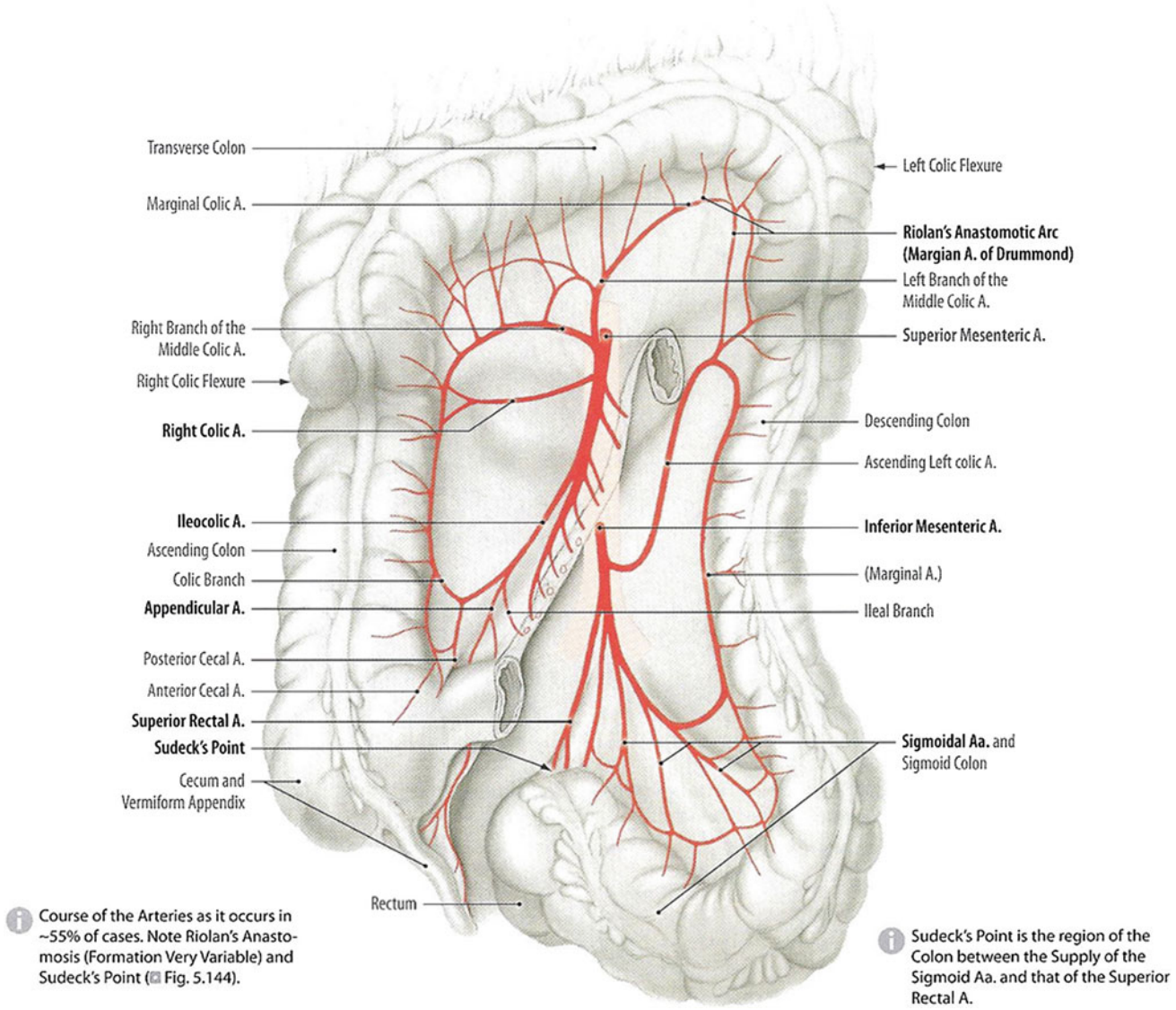


Fig. 16 Anatomy large intestine (with permission from Tillman and Elbermani 2007)

intestine can limit the dosage administered for definitive radiation treatment, for example of GU and GYN malignancies. *The Biocontinuum of adverse acute and late effects are shown in* Fig. 15.

3.2 Anatomy and Histology

3.2.1 Anatomy

The large intestine lies partially in mesentery i.e., cecum, appendix, transverse, and sigmoid colon which continues the vascular and lymphatic vessels, lymph nodes and nerves (Fig. 16). The ascending and descending colon are attached directly to the posterior abdominal wall and are retroperitoneal. The large intestine originates at the ileocecal valve and courses distally to the anal canal. The most striking difference between the small and large bowel is the presence of taenia coli, which are three separate longitudinal bands of smooth muscle on the outside of the bowel just below the serosa, analogous to the muscularis externa. The large bowel is comprised of eight distinct anatomical subunits: the cecum, the appendix; the ascending, transverse, and descending colon; the sigmoid, the rectum, and the anal canal. The cecum and appendix both lie in the right lower quadrant within the iliac fossa and are contiguous with the ascending colon. The ascending colon is retroperitoneal and passes superiorly on the right side of the abdomen toward the liver where it turns into the transverse colon at the hepatic flexure. The transverse colon is intraperitoneal and courses laterally in

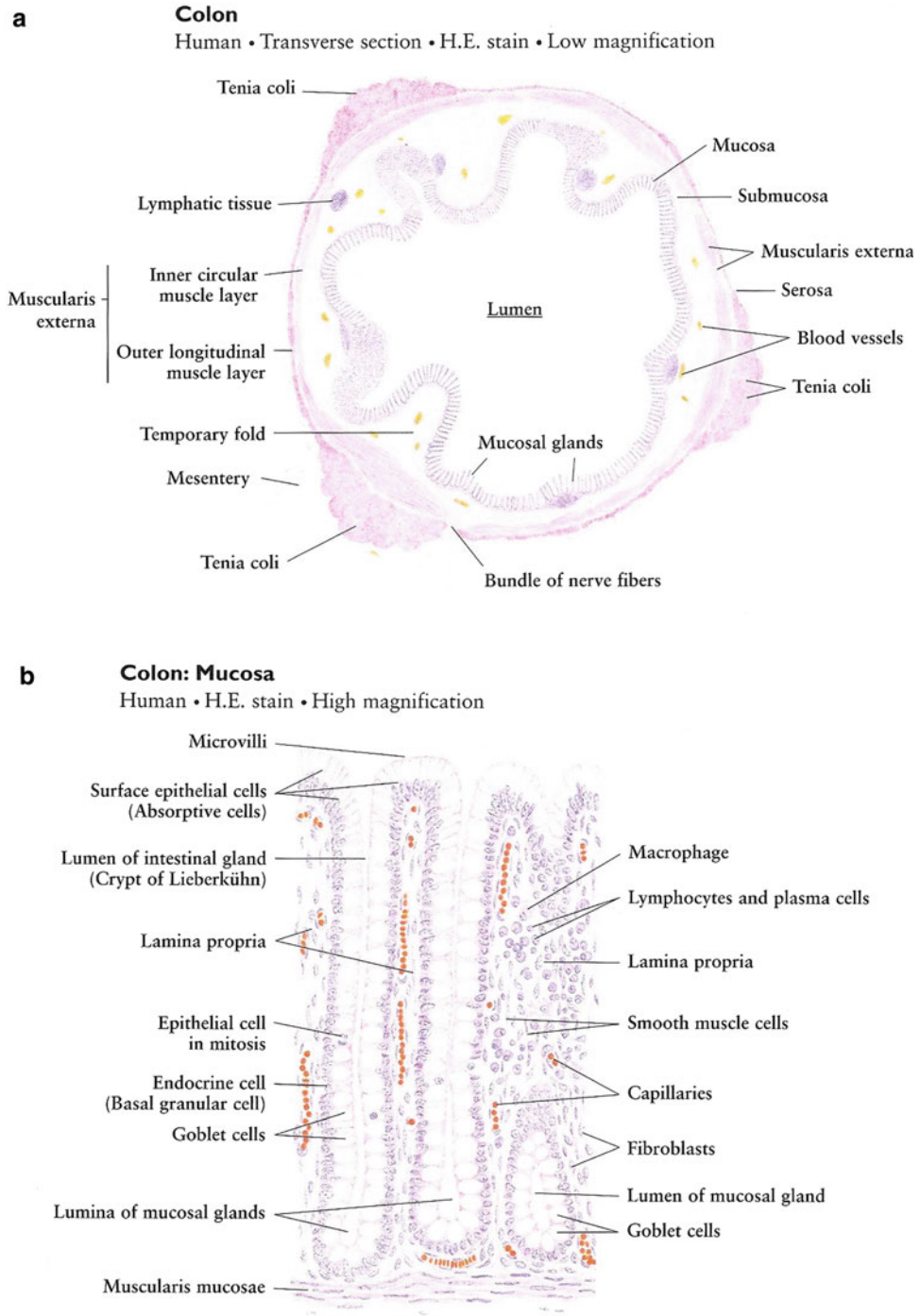


Fig. 17 Histology of **a** Colon, **b** Colon Mucosa (with permission from Zhang 1999)

the upper abdomen toward the spleen where it turns into the descending colon at the splenic flexure. The descending colon passes retroperitoneally to the left iliac fossa and its junction with the sigmoid colon. As its name implies, the sigmoid colon is an S-shaped loop of intestine that links the descending colon and rectum at the rectosigmoid junction.

3.2.2 Histology

The histologic structure of the large intestine is organized in a manner similar to the small intestine with the presence of the same structural subcomponents. Notable differences include the presence of taenia coli in place of the muscularis externa as well as a markedly different mucosal lining. The colonic mucosa is flat and has no villi and is punctuated by

Table 15 Colorectal radiation-induced lesions of the early period

Mucosa	Blood vessels
Necrosis	Endothelial cell atypia
Erosions	Vascular dilatation
Crypt abscesses (eosinophilic)	Fibrin-platelet thrombi
Crypt shortening	Necrotizing vasculitis
Kpithelial atypia	Leukocyte infiltrations Petechia in lamina propria Hemorrhages in mucosa Edema of submucosa and muscularis propria

Note These abnormalities may begin after administration of 10–20 Cy and may persist actively for 2–3 weeks after completion of therapy of 50–60 Gy. Lesions usually heal by 2–3 months. Infrequently, they develop into delayed lesions

Table 16 Colorectal radiation-induced lesions of the delayed period

Mucosa	Blood vessels	Stroma
Erosions	Petechiae	Strictures
Ulcers	Hemorrhages	Obstruction
Perforations	Hyalin arterioles	Submucosal fibrosis
Fistulas	Healed necrosis	Interstitial of muscular fibrosis
Neoplasms	Fibrous intimal plaques	Serosal fibrosis Loss of sphincter control

Note These lesions develop after 6 months of radiotherapy and worsen progressively thereafter. They may not become clinically evident for many yearsafter radiation exposure, but they cause most of the pathologic and clinical problems of radiation injury

numerous straight tubular crypts that extend down to the muscularis mucosa. This architectural difference is related to the primary functional purpose of the large intestine which is to reclaim luminal water and electrolytes. The wall of the colon has the typical four layers of the gastrointestinal tract: mucosa, submucosa, muscularis externa, and serosa (Fig. 17a). The lamina propria of the mucosa is occupied by the intestinal glands, which are deep and closely packed (Fig. 17b).

3.3 Physiology and Biology

3.3.1 Physiology

The small and large intestines are long muscular tubes in linear continuity from the gastric pylorus to the anus. The wall is composed of mucosa, submucosa, smooth muscle wall, and serosa (except at points of attachment). The small intestine is about 7 m long and gradually diminishes in diameter. The large intestine is about 1.5 m long, is largest in caliber at the cecum, and gradually diminishes as far as the rectum where it again enlarges.

The large intestine possesses specialized digestion and absorption functions, regulate fluid and electrolyte movement, and absorb vitamins and minerals. Movement of contents through the small and large intestines is controlled by the intrinsic activity of the smooth muscle together with the influence of the autonomic nervous system and gastrointestinal hormones.

The colon, through a variety of colonic motility actions results in the gradual and maximal absorption of fluids from fecal content prior to its expulsion. In the right colon, peristalsis can be reversed, prolonging content to be in contact with mucosa for the fluid to be gradually absorbed. In the transverse colon, haustration results in a pendular motion, prolonging content mucosal contact, and more time for fluid absorption. The left colon tends to have mass propulsion into the sigmoid and rectum, where adaptive relaxation allows for the final fluid phase of reabsorption prior to fecal evacuation.

3.3.2 Biology

3.3.2.1 Molecular Mechanisms

For the molecular mechanisms of the acute inflammatory mucositis and the late fibrosis stage, the proinflammatory cytokines and chemokines for the inflammatory mucositis and the profibrotic cytokines for the later fibrosis stage are described in Sect. 1.3.2 (Fig. 4).

3.3.2.2 Cell Kinetics Renewal Times

Cell kinetic turnover times of the gastrointestinal system determine the latent period before the clinical syndromes and manifestations occur. Thus, the acute effects will appear first in the small intestine, and then in the pylorus of the

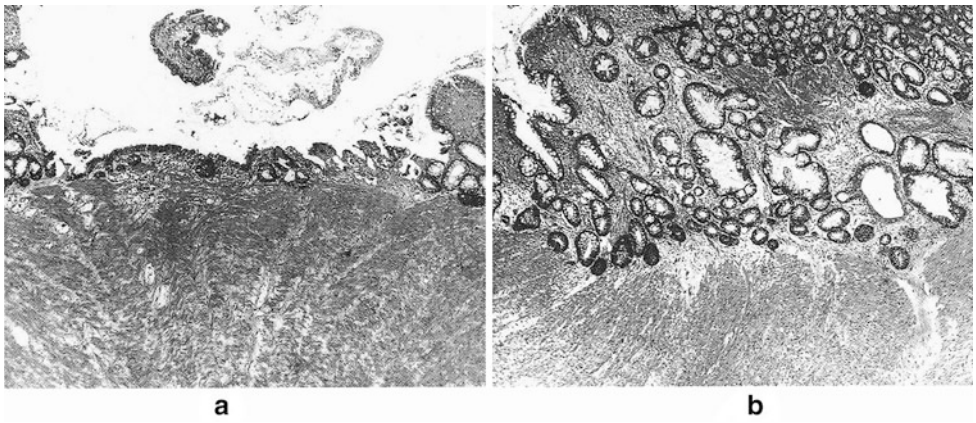


Fig. 18 Histology of late radiation-associated colonic injury: **a** A healing postradiation ulcer. Colonic mucinous epithelium is growing over the ulcer base of chronic granulation tissue composed of blood vessels and fibrous tissue. **b** A group of dilated colonic glands lie beneath the lamina propria and even lie upon the muscularis propria, an arrangement characteristic of colitis cystica profunda. (with permission from Fajardo et al. 2001)

stomach, the body, in the first week of radiation. In the second week, the large intestine, first in the rectum, and then the colon reacts, as well as the cardia of the stomach and esophagus, which occurs simultaneously. It is noteworthy that the oral cavity and anus develop their mucositis in the first week (Table 2).

3.4 Pathophysiology

3.4.1 Acute Phase

The majority of the bowel tract is supported by mesentery, which refers to the double-layer of visceral peritoneum responsible for connecting the bowel to the back wall of the abdomen. Within the mesentery lie blood vessels, lymphatics, and nerves. The jejunum, ileum, appendix, transverse, and sigmoid colons are all considered to be intraperitoneal organs, meaning they have a formal mesentery. The presence, structure and function of the mesentery are very relevant to the physician as it forms the conduit between the bowel and the body as a whole and, hence, are often involved in pathologic conditions. Acute changes are summarized in Table 15.

3.4.2 Late Phase

The principal findings of chronic radiation injury to the intestine are attributable to fibrosis and vascular insufficiency (chronic ischemia). Grossly, the intestine with chronic radiation injury has been described as fibrotic with adhesions and a mottled appearance. There may be focal areas of stenosis and/or ulceration. The mucosa can appear pale and telangiectatic. Ulceration and/or fistula formation may be present. In some cases, the area of radiation injury can be highly localized with fairly normal-appearing segments of bowel immediately adjacent, presumably reflecting a localized precipitating factor such as adhesion or a superimposed vascular event. The most common portions of the intestinal tract involved reflect the practice of radiation therapy. Most series report the preponderance of injury in the pelvis: involving the cecum, terminal ileum, rectum, and distal sigmoid. In the treatment of gynecologic cancer and prostate cancer, portions of the rectum will receive doses close to the full tumor dose, and therefore it is not surprising that rectal injury is more common than small bowel injury in series where gynecologic or urologic radiation therapy is the predominant modality.

Microscopically the most marked changes are noted in the submucosa. This is in contradistinction to acute radiation injury, which is most prominent in the mucosa. When chronic radiation injury is present, the submucosa is characterized by atypical fibroblasts and collagen proliferation. The fibroblasts are described as having multiple cytoplasmic projections and large hyperchromatic and irregular nuclei. Atypical vascular changes may be present. Small arteries may show hyalinized thickening of the wall with intimal foam cell proliferation and recanalized fibrin thrombi within the lumen. Telangiectatic vessels may be present.

The mucosal layer may show little abnormality, or ulceration or thickening of the villi with fibrosis. Again, vascular changes may be noted within the lamina propria, fibrotic changes, and vascular changes in the muscularis propria may also be present. Examples and description are provided in Table 16 and Fig. 18.

3.5 Clinical Syndromes

The clinical syndromes are described and graded in LENT SOMA (Table 9) and CTC V4.0. The endpoints can be similarly categorized as shown in Table (10).

3.5.1 Acute Phase

In the first month of pelvic or abdominal irradiation, the onset of watery and frequent bowel movements associated with intermittent cramps is a common complaint. As the end of the course of fractionated therapy is reached, this may prove to be a distressing symptom. On physical

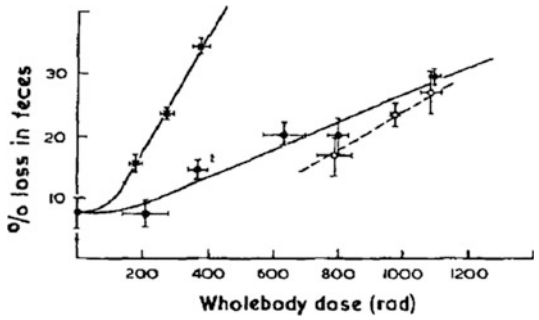


Fig. 19 Radiation-associated colonic injury measured as percent loss of protein in the feces. *Symbols*: *x* animals given single whole-body neutron irradiation, ● animals given single whole-body 250 kv x-irrradiation, ○ animals given split doses of 250 kv x-irrradiation. The S.E. on the means of the measured activity and the mean doses is shown (with permissions from Vatistas and Hornsey 1966)

examination, gurgling and borborygmi are prominent, but rarely is the abdomen tender to deep palpation. Subacute clinical period symptoms: usually the onset of symptoms is sudden and may be quite violent, presenting a picture of acute abdomen (Rubin and Casarett 1968).

3.5.2 Chronic Late Phase

As early as one year and as late as 11 years after a course of RT, intermittent abdominal pains and gradual obstruction may occur. The pain may be severe and colicky and be accompanied by nausea and vomiting. The patient may be aware of rumbling and gurgling at the peak of pain. Limited bleeding has been reported but *is* rare. On the other hand, weight loss *is common*. Examination of the abdomen shows *some* distention but no acute tenderness.

3.5.2.1 Detection

When the entire abdomen is treated, the loss of I^{131} labeled PVP through the small intestine is measured by activity in the feces. As anticipated, the biologic effects of irradiation increase as a function of quality and dose of irradiation (Fig. 19):

- *Neutron irradiation* 2.0–6.0 Gy (R) *dramatically escalates* the loss of the I^{131} PVP since this is HIGH LET beam.
- *Kilovoltage x-irradiation* (lowLET) results in a more *gradual loss* of I^{131} PVP 2.0 to 12 Gy
- *Split course x-irradiation* further attenuates the loss of I^{131} PVP from 6.0 to 12.0 Gy.

Few laboratory studies have been done, but alterations in absorption patterns may he detected when large enough segments of small and large bowel have been exposed to irradiation. The finding of anemia and hypoproteinemia is not uncommon (Rubin and Casarett 1968).

3.5.2.2 Diagnosis

Physiologic studies for patients with chronic proctitis indicate reduced rectal compliance and volume (capacitance) (105, 106). Anal manometry in patients with proctitis can show a reduced maximum resting pressure, an abnormal rectoanal reflex, and a decrease in the functional sphincter length (105, 106). However, a longitudinal study of patients undergoing a moderate (45–50 Gy) dose of radiation to the anus and rectum disclosed no significant anal manometry changes in most patients (7).

In a radiologic-pathologic correlative study of nine patients with radiation injury to the small bowel, Perkins and Spjut (1962) noted that on barium studies the involved segment usually appeared to be longer than the pathologic specimen. The stenosed segment as seen on roentgenograms measured from 3 to 8 cm in length, whereas corresponding surgical specimens ranged from 0.5 to 5 cm. This is explained by the lack of distensibility of the edematous segment surrounding the original injured segments. The strictures are believed to be larger segments of bowel that have undergone contracture. This is based on the experimental studies of Spratt et al. (1962), in which 5 cm segments of dog ileum were exposed to 4,000 R in air as a single dose. Eight months later marked scarring occurred, and in one instance a 2 mm band remained from the original 5 cm exposed loops. Similar findings might apply to the large bowel. Points to be considered in regard to the radiologic differential diagnosis of recurrent carcinoma invading the bowel as opposed to stricturing radiation lesions are similar to those for the small bowel, including:

1. The radiation-induced strictured segment is longer than would be expected in recurrent carcinoma.
2. A sharp margin between normal and abnormal bowel segments is seen in carcinoma but is lacking in radiation strictures.
3. A "saw-toothed" appearance of the edematous mucosa or lack of distensibility persists in radiation enteritis or colitis.

Colon changes induced by chemotherapy are nonspecific and therefore can be difficult to demonstrate radiologically. Radiation, with or without chemotherapy can lead to a delayed stricture and/or fistula (Fig. 20a, b).

3.6 Radiation Tolerance

For the colorectum, the tolerance dose TD_5 is given as 50 Gy and TD_{50} as 55 Gy, which also applies to the entire gastrointestinal system. The colon may be less radiosensitive than the small intestine, but the same tolerance doses apply.

Kummermehr and Trott (1994) have studied changes in the rat rectum following single doses of radiation and found that doses higher than 20 Gy caused severe proctitis in

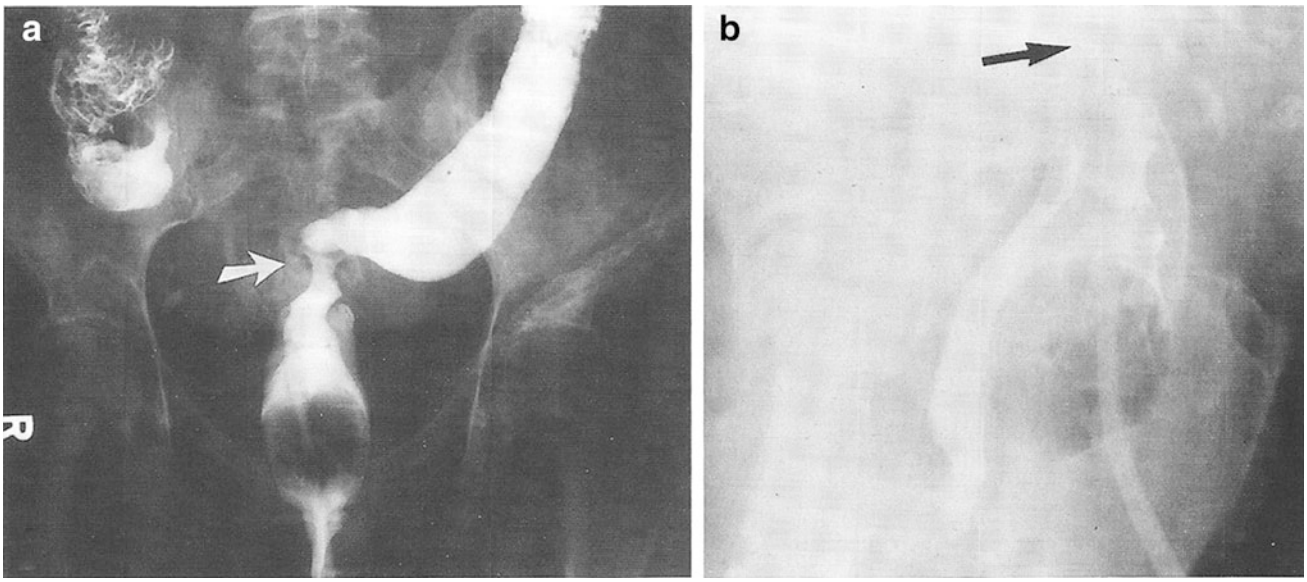


Fig. 20 Postradiation changes in the colon: Rectovaginal fistula. Frontal projection of the barium-filled rectum (R) and sigmoid in a woman after pelvic radiation shows a stricture in the rectosigmoid region (**a** *arrow*). The vagina (V) fills with contrast medium, which leads to the diagnosis of a rectovaginal fistula after radiation. The oblique view (**b**) demonstrates the vagina and the fistula located at the rectosigmoid stricture (*arrow*) (with permission from Rubin 2001)

50 % of animals within 40–200 days; 24.5 Gy in two fractions caused similar changes. However, although these changes were volume dependent, the degree of dependency and the threshold values varied according to the criteria studied (Trott et al. 1995).

Clinically, tolerance in the colorectal region is considered to be higher than in the small intestine and, again, is highly volume dependent (Frykholm et al. 1996). Two excellent sources of data exist: patients with cervical cancer receiving external radiation and brachytherapy, and patients with cancer of the prostate also exposed to both external and internal sources. The incidence of severe proctitis in cancer of the cervix is dose dependent: less than 4 % with doses of 80 Gy or lower, 7–8 % for 80–95 Gy of higher (Perez et al. 1991). In prostate cancer, the incidence is 5 % for 60–70 Gy, and with dose escalation to 75 Gy, severe rectal bleeding occurs in 15–20 % of patients with proton and photon beam (Shipley et al. 1995; Teshima et al. 1997). Rectal shielding has become more critical because improved techniques (e.g., three-dimensional dynamic conformal therapy) have allowed for dose escalation up to 80 Gy for patients with prostate cancer (Horowitz et al. 1998; Hanks et al. 1998). Limiting the volume of bowel irradiated is likely critical (Fig. 14). The longitudinal and circumferential character of the dose may also be important. For example, limiting the percent circumference of the bowel irradiated probably reduces the risk for stricture.

3.6.1 Dose Time Fractionation

Many clinical trials performed by national and international cooperative groups in the treatment of colorectal cancers or gynecologic cancers provide information regarding the incidence of colon/rectal complications(sometimes combined with small bowel toxicity rates). Several of these are summarized in Tables 11, 12, 13, and 14.

The Uppsala Swedish rectal cancer study compared preoperative pelvic radiotherapy 5.1 Gy times 5 fractions with postoperative radiotherapy using a split-course radiotherapy to 60 Gy, with a cone down for the last 10 Gy for patients with Dukes B or C cancers (Frykholm et al. 1993). At a minimum follow-up of 5 years, the rates of small bowel obstruction for the preoperative, postoperative and surgery alone groups were 5, 11, and 6 %, respectively ($p < 0.01$). Of note, any late toxicity with symptoms that may be attributable to radiotherapy was reported in 20 % of preoperative patients, 41 % of postoperative, and 23 % in the surgery alone group, suggesting increased late toxicity only with postoperative irradiation. However, this is confounded by the drastically different radiation treatment regimens used in the pre- and postoperative patients.

The Dutch Rectal Cancer Study Group trial (Table 11) and the Swedish Rectal Cancer trial were both large phase III studies comparing short-course preoperative radiotherapy for rectal cancer with surgery alone (Folkesson et al. 2004; Peeters et al. 2007). Both studies used a similar

technique of 25 Gy delivered in 5 Gy fractions in the course of 1 week, followed by surgical resection the following week. The Swedish trial used a larger treatment field (superior border at the fourth lumbar vertebrae) with more small bowel in the field compared to the upper border in the Dutch trial (sacral promontory). In a questionnaire study of 597 patients without recurrent disease at a median follow-up of 5.1 years, patients treated with preoperative radiotherapy in the Dutch study reported increased rates of fecal incontinence, pad wearing, blood loss, and mucus loss and overall satisfaction with bowel function was significantly worse when compared to unirradiated patients (Peeters et al. 2005).

Investigators in the Swedish Rectal Cancer trial performed a detailed toxicity analysis of patients admitted for gastrointestinal complaints treated on their trial and a similar tandem prospective trial, Stockholm II (Birgisson et al. 2008). In all, there were 908 patients available for review at a median follow-up of 14 years, with half receiving preoperative short-course radiotherapy and the other half surgery alone. They found an increased risk of small bowel obstruction (relative risk 2.47) in the radiation group compared to unirradiated patients with absolute incidences of 13.9 and 5.5 %, respectively ($p < 0.001$). Patients in the irradiated group were also more likely to have abdominal pain and to require multiple admissions for gastrointestinal complaints. A detailed review of radiation treatment records was performed and found an increased risk of obstruction when photon energies greater than 12 MV were used, but no differences between 2-, 3-, and 4-field techniques. However, a previous report did show increased postoperative mortality in patients treated with an anterior-posterior technique (Holm et al. 1996).

Bujko et al. (2006) published the results of a randomized trial comparing short course preoperative radiotherapy with concurrent preoperative radiochemotherapy for rectal cancer. Radiotherapy-alone patients were treated wtih 25 Gy in 5 fractions over the course of 1 week followed by surgery within 7 days of completion. Radiochemotherapy patients received 50.4 Gy in 1.8 Gy fractions with concurrent 5-FU and leucovorin for five consecutive days during weeks 1 and 5 of radiation, followed by surgery 4–6 weeks later. At a median follow-up of 48 months the incidence of grade 3 or greater late gastrointestinal toxicity was 5.1 % in the radiotherapy group and 1.4 % in the radiochemotherapy group.

The German Rectal Cancer Study Group (Table 13) conducted a large phase III trial comparing preoperative versus postoperative radiochemotherapy for locally advanced rectal cancer (Sauer et al. 2004). Preoperative radiotherapy was given to 50.4 Gy with concurrent 5-FU during weeks one and five. Postoperative therapy was similar with the addition of a 5.4 Gy boost to the anastomotic site. Long-term gastrointestinal toxicity rates appeared to favor preoperative radiochemotherapy (9 % vs. 15 %, $p = 0.07$) with significantly increased stricture formation at the anastomotic in the postoperative group (12 % vs. 4 %, $p = 0.003$). At a median follow-up of 46 months the rate of small bowel obstruction requiring re-operation was small and not statistically different between the preoperative and postoperative treatment groups (2 % vs. 1 %, respectively, $p = 0.70$). It is difficult to determine the effect of the boost dose on late toxicity in the postoperative treatment group. A summary of trials reporting the late toxicity of preoperative pelvic radiotherapy is presented in Table 11.

Gynecologic Oncology Group trial GOG 99 was a large phase III trial evaluating the role of postoperative pelvic radiotherapy for early stage endometrial cancer. Patients underwent total abdominal hysterectomy and bilateral salpingooophorectomy with pelvic and paraaortic lymph node dissection and then were randomized to postoperative pelvic radiotherapy to 50.4 Gy or no further treatment. At a median follow-up of 69 months, the incidence of late grade 3 or greater gastrointestinal toxicity was 8 % with postoperative radiotherapy and 1 % with surgery alone. In the radiotherapy group 2.6 % of patients developed small bowel obstruction requiring surgical intervention with none in the surgical arm (Keys et al. 2004). PORTEC was a phase III trial similar to GOG 99 except for less extensive surgical therapy. Again, patients were randomized to postoperative pelvic radiotherapy (46 Gy in 2 Gy fractions) or observation. At a median follow-up of 60 months, the late grade 3 or greater gastrointestinal toxicity rate was 3 % with postoperative radiotherapy and 0 % after surgery alone. There was a less than 1 % incidence of small bowel obstruction after surgery and radiotherapy (Creutzberg et al. 2001).

GOG 92 was a trial evaluating the role of postoperative pelvic radiotherapy for cervix cancers with high risk histologic features. Patients underwent a radical hysterectomy with pelvic lymphadenectomy and were randomized to pelvic radiotherapy or observation. Patients in the radiotherapy arm received 46–50.4 Gy in 1.8 or 2 Gy fractions using a 4-field technique. At a median follow-up of 10 years the rate of chronic grade 3 or greater late gastrointestinal toxicity was 2.2 % with 1 % of patients developing an enteric fistula (Rotman et al. 2006). GOG 109 was another postoperative study in cervix cancer comparing pelvic radiotherapy with or without concurrent weekly cisplatin chemotherapy for patients with positive surgical margins or lymph node involvement. All patients underwent radical hysterectomy with pelvic lymphadenectomy followed by pelvic radiotherapy to 49.3 Gy at 1.7 Gy per fraction via a 4-field box technique. Patients were randomized to radiotherapy with or without concurrent cisplatin and 5-FU chemotherapy given during weeks 1 and 4 with an additional two cycles after the completion of radiotherapy. At a median follow-up of 42 months, there were no differences

in late gastrointestinal toxicity rates (1.6 % vs. 1 % for with and without chemotherapy, respectively). Two patients in the group receiving radiochemotherapy developed small bowel obstruction compared to none in the radiation group alone (Peters et al. 2000). The GOG trials are included in Tables 12 and 13.

Radiation Therapy Oncology Group RTOG 97-08 (Table 12) was a phase II study evaluating postoperative concurrent pelvic radiochemotherapy and vaginal brachytherapy for high risk endometrial cancer. Forty-six patients underwent total abdominal hysterectomy with bilateral salpingo oophorectomy followed by radiochemotherapy, vaginal brachytherapy, and additional chemotherapy. Radiochemotherapy was 45 Gy to the pelvis with two cycles of cisplatin 50 mg/m^2 on days 1 and 28 followed by intracavitary brachytherapy to the vaginal surface. This was followed by four additional 28-day cycles of cisplatin and paclitaxel. At a median follow-up of 4.3 years there was a 11 % rate of grade 3 or greater late gastrointestinal toxicity with a 2 % incidence of small bowel obstruction (Greven et al. 2006). A summary of trials reporting the late toxicity of postoperative pelvic radiation is given in Tables 12 and 13.

In concert, these data suggest that bowel injury following conventional therapy for abdominal/pelvic tumors occurs in roughly 1–14 % of patients, with a significant component of this being small bowel obstruction.

3.6.2 Dose Volume

The volume of irradiated colon depends on the location of the cancer, lymphoma, or neuroendocrine tumor, which is being treated in a juxtaposed position to a segment of the colon. The tolerance dose for each segment of the colon is considered to be of the same order of magnitude. The radiation tolerance dose, as noted above, is 50 Gy for each segment. The total colon is considered to be less radiosensitive than the small intestine, which will be included in whole abdominal radiation fields. The dose for treating the entire small and large bowel is usually limited to 20 Gy, given in small fractional doses of 1–1.5 Gy.

3.7 Chemotherapy Tolerance

3.7.1 Chemotherapy Tolerance

See discussion in Sect. 2.7.1.

3.7.2 Combined Modalities

The absence of predictive parameters for late intestinal events was demonstrated in the catastrophic complications that occurred in a carefully piloted Eastern Cooperative Oncology Group (ECOG) study using split-course irradiation. The radiation protocol was 60 Gy in 10 weeks (20 Gy for three 2-week courses with 2-week rest intervals). It was followed by maintenance chemotherapy with 5-FU and semustine for 1 year (Danjoux et al. 1979). Although no undue acute toxicity occurred with the administration of either radiotherapy or chemotherapy, late fistulization, and necrosis occurred in 29 % of patients 6 months to 2 years after all therapy ceased. Generally, 5-FU alone can be added to treatment with 45–50 Gy and is well tolerated. The addition of mitomycin C raises the incidence of grade III toxicity to 25 % (Cummings et al. 1991), and similarly the addition of cisplatin in patients with cancer of the cervix leads to an $\approx$18 % large bowel complication rate (Grigsby and Perez 1991).

The bulk of contemporary clinical data treating the abdomen and pelvis comes from the treatment of gynecologic and gastrointestinal malignancies. Concurrent radiochemotherapy with either platinum- or fluorouracil-based chemotherapy and 3D-conformal radiation therapy (CRT) or intensity-modulated radiation therapy (IMRT) is the accepted standard of care in the majority of the common abdominopelvic tumors. Furthermore, data are available on abdominopelvic radiation in multiple clinical settings including with and without concurrent systemic therapy as well as pre- and postoperatively. Outcomes and toxicity data for definitive radiochemotherapy are available from a multitude of phase III clinical trials in cervix and anal canal cancers. Data for postoperative radiotherapy or radiochemotherapy are available in studies in the treatment of rectal, cervix, and endometrial cancers and for preoperative radiochemotherapy in rectal cancer. In addition, data are available on the toxicity of whole abdominopelvic irradiation (WAPI) for the treatment of ovarian and endometrial cancers. The details from several specific studies are provided below (also see Tables 11, 12, 13 and 14).

GOG 120 was a large phase III trial comparing three different concurrent weekly cisplatin- or hydroxyurea-based chemotherapy regimens given concurrent with pelvic radiotherapy to a dose of 40–51 Gy with a brachytherapy boost (Rose et al. 2007). At a median follow-up of 106 months the grade 3 or greater late gastrointestinal toxicity rate for all patients was 0.7 % with only two late gastrointestinal complications and no bowel obstructions. The majority of grade 4 toxicities were rectovaginal or vesicovaginal fistula formations or ureteral obstruction, thought to be related to vaginal brachytherapy. The NCIC published a trial comparing pelvic radiotherapy with brachytherapy boost with or without weekly concurrent cisplatin-based chemotherapy (Pearcey et al. 2002). After a median follow-up of 82 months the grade 3 or greater late gastrointestinal toxicities were 13 % for the radiation arm versus 7 % for the combined-modality arm. One patient in the radiation-alone treatment arm died from a small bowel obstruction 9 months after the completion of therapy.

RTOG 90-01 was a phase III trial comparing pelvic radiochemotherapy to extended-field radiotherapy without concurrent chemotherapy for locally advanced cervical cancer (Eifel et al. 2004). At a median follow-up of 6.6 years for surviving patients, the grade 3 or greater late gastrointestinal toxicity was 3.7 % in the pelvic radiochemotherapy group and 4.6 % in the extended-field radiotherapy group. There were three cases of fistula formation between the small bowel and vagina with no cases of small bowel obstruction. GOG 125 was a phase II trial evaluating extended-field pelvic and paraaortic radiotherapy with concurrent weekly cisplatin and 5-FU chemotherapy (Varia et al. 1998). At a median follow-up of 34 months, the 4-year grade 3 or greater late GI toxicity rate was 14 %, with the majority of toxicities involving the rectum and no bowel obstructions.

In concert, these studies and others suggest that grade ≥ 3 colorectal toxicity occurs up to ≈ 14 % of patients, with higher toxicity rates in patients undergoing more extensive surgery and radiation treatment.

3.8 Special Topics

3.8.1 Pediatrics

Donaldson et al. (1975) evaluated 44 children who received abdominal irradiation for lymphoma, Wilms tumor, or other malignancies. Eleven percent of the entire population and 36 % of the long-term survivors developed late radiation injury to the digestive tract attributable to vascular injury. Contributing factors included prior abdominal surgery, the use of concurrent actinomycin D, and very young age. In a report of 42 survivors of the Wilms tumor treated from 1968 to 1994 with megavoltage RT, actinomycin D, and vincristine with or without doxorubicin, the actuarial incidence of bowel obstruction at 5, 10, and 15 years was 9.5, 13, and 17 %. Of 23 patients, five irradiated within 10 days of surgery and one of 19 irradiated after 10 days developed bowel obstruction (Paulino et al. 2000). In a report from the Intergroup Rhabdomyosarcoma Study Committee, extended follow-up of 86 children and adolescents who were treated for paratesticular rhabdomyosarcoma on the Intergroup Rhabdomyosarcoma Studies I and II (IRS I-II) revealed that 4 patients who underwent abdominal RT had chronic diarrhea (Heyn et al. 1992).

3.8.2 Total Body Irradiation: Acute Gastrointestinal Syndrome

The chief cause of the signs and symptoms of the G.I. syndrome after total body irradiation is the depletion of the epithelial lining of the intestine, with denudation of the mucosa, particularly in the small intestine. However, damage to the bone marrow, particularly to the granulocytopoietic system, with the resulting neutropenia, is also strongly implicated in the symptomatology and cause of the G.I. syndrome after total-body irradiation. The chief consequence of the intestinal denudation and granulocytopenia in this syndrome is loss of fluid and electrolytes, nutritional impairment and infection. The water loss and electrolyte loss are marked in the G.I. syndrome, leading to death. They result from failure of absorption, failure of resorption from bile in the lumen, leakage through the denuded mucosa and loss from the bowel through marked diarrhea. The infection and bacteremia which occur in the gastrointestinal syndrome after total-body irradiation are the consequences of the neutropenia and also the loss of the epithelial lining of the intestine. The neutropenia has also been suspected of being involved in the enhancement of intestinal cell death and mucosal denudation by infecting microorganisms and possibly also commensal intestinal bacteria. The loss of body weight during this syndrome seems to be largely the result of reduced intake, malabsorption, and fluid loss.

When the G.I. syndrome is caused by irradiation of only a part of the body, including the entire gastrointestinal tract, as in lower body irradiation or abdominal irradiation, a lesser degree of neutropenia develops, infection tends to be less prominent, the denudation of the intestinal mucosa takes somewhat longer to develop and survival times tend to be longer, than in the case of whole-body irradiation. These differences are even greater when only the intestine or part of the intestine is irradiated. The shielding of bone marrow from irradiation, resulting in lesser degrees of neutropenia, seems to be associated with delayed intestinal denudation and increased survival time, possibly through reduction of infection after irradiation, and the shielding of parts of the intestine reduces the degree of fluid and electrolyte loss after irradiation. The LD_{50} for germ-free animals or for animals treated with antibiotics after irradiation in the lethal range for the G.I. syndrome has been increased 40 and 60 % respectively, and the mean survival time has also been increased as compared with ordinary untreated irradiated animals.

3.9 Prevention and Management

3.9.1 Prevention

The prevention and management of radiation digestive tract injury relies primarily on the exclusion of normal tissues from the treatment beam whenever possible. For the esophagus, stomach, and large bowel, this usually relies on beam direction planning and patient positioning. For the mobile portions of the small bowel, the clinician also evaluates the prone versus supine position; the use of compression, tilt tables, and false table tops; surgical placement of omental slings and absorbable mesh; and other

techniques. The patient with acute radiation enteropathy may be helped by symptomatic interventions. Medical therapy for late-onset radiation enteritis is unsatisfactory and has relied on intermittent steroids, sulfasalazine, parenteral nutrition, and other supportive care. Surgical resection of damaged or obstructed bowel may be used, but there is a high incidence of anastomotic dehiscence, operative mortality, and reobstruction (Sher et al. 1990).

Refer to Sect. 2.9.1.

3.9.2 Management

Mild cases of chronic radiation toxicity of the small and large intestine can be managed conservatively with stool softeners and a low residue diet. Antidiarrheals such as loperimide can be added for better control of bowel frequency and for episodic diarrhea. More severe cases can lead to malabsorption with resultant malnutrition. Successful use of total parenteral nutrition to counteract malabsorption from radiation enteritis has been described in multiple reports. Scolapio et al. (2002) recently reviewed their experience of 54 patients over a 25-year period treated with home parenteral nutrition. The most common indications for treatment were mechanical obstruction and short bowel syndrome. They reported a 5-year survival for patients managed with home parenteral nutrition of 64 % with only one death from catheter-related sepsis.

3.10 Future Directions

Investigations into radioprotectors for the bowel have been inconsistent and disappointing, with no current clinically accepted protector available. Further advances in surgical care as well awareness of the complex nutritional needs of these patients will hopefully continue to improve outcomes. Refer to Sect. 1.10.

3.11 Literature Landmarks

Ingelman-Sundberg (1947): presented a thorough review of the pathogenesis of rectal radiation injury at Radiumhemmet. Direct measurement of dosage suggested 3,300 R as the threshold dose.

Kottmeier (1953): found serious rectal lesions in 1 % of 2,756 patients treated for cervical cancer. Extrinsic lesions were rare and fistulas occurred in 0.3 % of cases.

Tison (1934): divided chronic rectal lesions into intrinsic and extrinsic lesions

Todd (1938): conducted a detailed study of rectal ulceration in the treatment of cancer of the cervix and developed further concepts of intrinsic and extrinsic lesions.

Warren and Friedman (1942): presented a good review of the radiopathology of the intestinal tract.

Gray and Kottmeier (1957): demonstrated a correlation between radium dosage and total radiation received by the rectum and the incidence of rectal injuries in that a total dose of 5,000 gamma or 6,000 R is at the tolerance level.

Fletcher et al. (1958): gave an excellent presentation of direct rectal and bladder measurements of dosage and their limitations in planning therapy.

Black and Ackerman (1965): noted a case of carcinoma of the rectosigmoid arising in an area of radiation stricture due to previous pelvic irradiation.

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Liver

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Abstract

- The hepatic toxicity related to radiation therapy is classic radiation-induced liver disease (RILD) which presents within 3 months following radiation therapy with anicteric ascites and hepatosplenomegaly, characterized with central and sublobular hepatic vein occlusive lesions, with sparing of the periportal areas, larger hepatic veins, and hepatic arterial vasculature.
- No established standard exists.
- In 2 Gy per fraction, the mean liver doses estimated to be associated with a 5 % risk of classic RILD for primary and metastatic liver cancer are 28 and 32 Gy.
- Other non-classic RILD radiation hepatic toxicities include hepatitis and a general decline in liver function that may be precipitated by radiation therapy.
- TGF-β has been implicated in playing a role in the fibrogenesis leading up to RILD.
- Irradiation of rat liver in vivo induces upregulation of proinflammatory cytokines IL-1-beta, IL-6, and tumor necrosis factor alpha (Christiansen et al. in Radiology 242:189–197, 2007).

P. Rubin et al. (eds.), *ALERT – Adverse Late Effects of Cancer Treatment*, Medical Radiology. Radiation Oncology,
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- Changes in CT and MRI contrast enhancement have been seen within regions of the liver (Herfarth et al. in Int J Radiat Oncol Biol Phys 57:444–451, 2003).
- Veno-occlusive disease (VOD) is a frequent, serious, and often life threatening complication of hematopoietic stem cell or bone marrow transplantation.
- Patterns of chemotherapy liver toxicity include: hepatitis, cholestasis, steatosis, fibrosis, and vascular lesions.
- Hepatic toxicity related to chemotherapy is usually idiosyncratic, unpredictable, and not dose-related.
- Direct hepatocellular injury from chemotherapy is less common and predictable.
- Baseline liver function tests and imaging, with serial re-evaluation, can aid in determining the cause of deteriorating liver function which may be related to underlying liver dysfunction, reactivation of a dormant virus, drug, or the cancer itself.

Abbreviations

APR	Acute phase reactant
AST	Aspartate transaminase
ALT	Alanine transaminase
ASGPR	Asialoglycoprotein receptor
BUdR	Bromodeoxyuridine
BMT	Bone marrow transplantation
CTCAE	Common terminology criteria for adverse events
CLIP	Cancer of the liver Italian program
CT	Computed tomographic
DVHs	Dose–volume histograms
RBCs	Erythrocytes
FUdR	Fluorodeoxyuridine
GIT	Gastrointestinal tract
GSH	Glutathione
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HSC	Hepatic stellate cell
ICG	Indocyanine Green
IVC	Inferior vena cava
IMRT	Intensity modulated radiation therapy
IORT	Intraoperative radiation therapy
NTCP	Normal tissue complication probability
RILD	Radiation-induced liver disease
RTOG	Radiation Therapy Oncology Group
RHV	Right hepatic vein
SECs	Sinusoidal endothelial cells
SOS	Sinusoidal obstructive syndrome
SMA	Smooth muscle actin
SPECT	Single-photon emission computerized tomography
SBRT	Stereotactic body radiotherapy
TACE	Transarterial chemo-embolization
TBI	Total body irradiation
TGF-β	Transforming growth factor-β
VOD	Veno-occlusive disease

1 Introduction

Irradiation of the liver is required in the treatment of many cancers, including those of the upper abdomen (e.g. hepatocellular carcinoma, cholangiocarcinoma, pancreatic carcinoma, gastric carcinoma), cancers near the upper abdomen (lower thoracic cancers, mesothelioma, retroperitoneal sarcoma) and following hematopoietic stem cell transplant and total body irradiation. The liver is a critically important organ that plays many vital roles. It aids in the digestive process with the production of bile, facilitating the metabolism of ingested nutrients, and the elimination of many waste products; it is involved in glycogen storage, decomposition of red blood cells, plasma protein synthesis, and detoxification. Injury to the liver can range from transient, clinically unimportant parenchymal damage that is only detected via serum measurements of enzymes leaked from damaged hepatocytes, or subclinical transient changes on imaging, to fatal hepatic insufficiency characterized by decreased production of proteins such as albumin and blood clotting factors, ascites, bleeding predilection, and encephalopathy.

The first type of radiation-associated liver toxicity described, termed classic radiation-induced liver disease (RILD) (Lawrence et al. 1995), presented as anicteric ascites, hepatomegaly, and elevated alkaline phosphatase following whole abdominal radiation therapy. Other liver toxicities seen following liver irradiation (termed 'non-classic RILD') include a general decline in liver function, elevation of liver enzymes, and reactivation of viral hepatitis. These toxicities are more common following irradiation of patients with an impaired liver functional reserve (for example, with cirrhosis). Veno-occlusive disease (VOD) can occur following stem cell transplant with or without total body irradiation. This differs in its presentation from classic RILD, in that elevated bilirubin is part of the diagnostic criteria (vs. little change in bilirubin in classic RILD). Both classic and nonclassic RILD can lead to liver failure and death, and avoidance of any liver toxicity following irradiation is always desirable.

The whole liver tolerance to irradiation is low. The partial volume tolerance of the liver is better understood for classic RILD than nonclassic RILD. For classic RILD, mean dose to the liver is correlated with RILD risk. A variety of dose/volume parameters can be used to provide clinical guidelines (Sect. 5). The toxicity models are highly

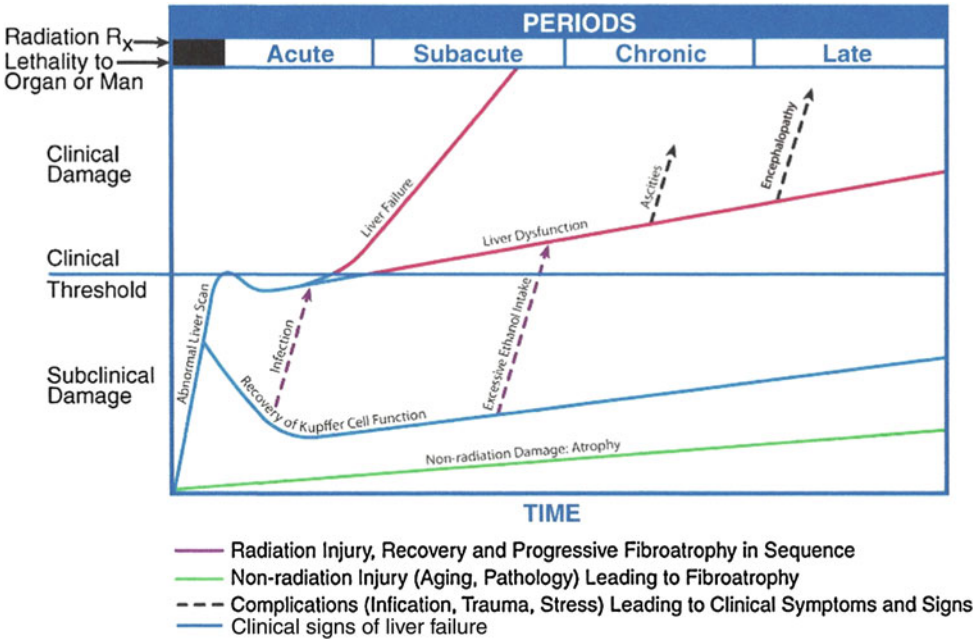

Fig. 1 The time course of liver symptoms in patients treated with radiation therapy (with permission from Rubin and Casarett 1968)

dependent on the patient population, presence of underlying liver disease (hepatitis B or C infection, or cirrhosis), radiation dose fractionation, and the toxicity endpoint investigated.

The pathophysiology of classic and non-classic RILD is becoming better understood (Sect. 3), but there is still much to learn in order to develop interventions that may mitigate the development of liver toxicity (Sect. 8). In this chapter, we will review radiation liver toxicity and provide dose/volume recommendations for the clinician.

Figure 1 summarizes timeline of our understanding of radiation liver toxicity.

2 Anatomy and Histology

2.1 Anatomy

2.1.1 Gross Anatomy

The liver is the largest internal organ in the human body, representing slightly less than 3 % of body weight, weighing 1,200–1,500 g, but receiving 25–30 % of the cardiac output. It is located in the right upper abdominal quadrant within the peritoneal cavity.

During weeks two to three of development, the gastrointestinal tract (GIT) arises from the endoderm of the trilaminar embryo. The three distinct portions, an anterior foregut, a central midgut, and a posterior hindgut ultimately contribute different components of the GIT. The foregut includes hepatic cells and bile ductules, gall bladder and common bile duct, pancreatic acinar and island cells, and duodenum. The liver and biliary tree appear late in the third week or early in the fourth week as the hepatic diverticulum, an outgrowth of the ventral wall of the distal foregut. The hepatic diverticulum subsequently divides into a small ventral part, the future gall bladder, and a larger cranial part, the liver primordium; the latter portion grows and differentiates into the parenchyma of the liver (hepatocytes) and the lining of the biliary ducts. The hepatocytes arrange into a series of branching and anastomosing plates in the mesenchyme of the transverse septum. These plates subsequently intermingle with vitelline and umbilical veins to form hepatic sinusoids. Besides contributing to the sinusoids, the splanchnic mesenchyme in the transverse septum also forms the stroma, the fibrous and serous coverings (liver capsule), the falciform ligament, and the blood forming, or hematopoietic tissue (Kupffer cells), of the liver. The connective tissue and smooth muscle of the biliary tract also develop from this mesenchyme. By the sixth week, the liver performs hematopoiesis (the formation of blood cells) and represents 10 % of the total weight of the fetus by the ninth week.

The liver is divided into two lobes: the right and the left, separated by the middle hepatic vein, which defines the imaginary line, the so-called Cantlie's line, from the middle of the gallbladder fossa and corresponding to the plane of the inferior vena cava (IVC), which runs posteriorly to the liver. The right and left lobes are each drained by a major vein (the right and left hepatic veins, respectively). The middle hepatic vein and these two veins drain into the IVC on the superior-posterior aspect of the liver. There is variation to the overall vascular drainage, and in some people, the left and middle hepatic veins become confluent prior to emptying into the IVC.

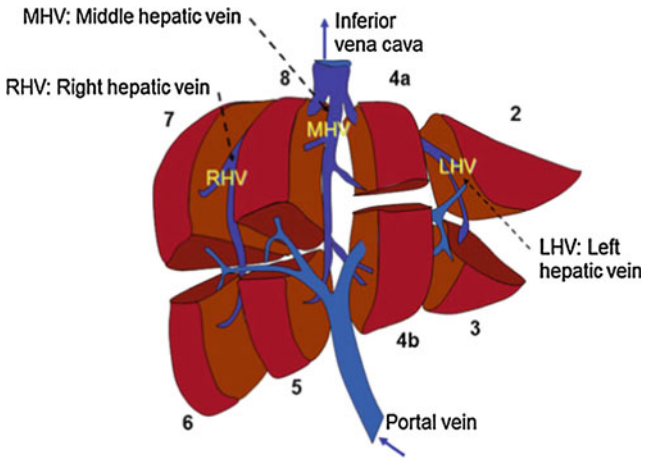

Fig. 2 The natural anatomy of portal vein flow and the right hepatic vein (RHV), middle hepatic vein (MHV), and left hepatic vein (LHV) drainage is utilized in the definition of hepatic segments; the caudate lobe (not shown here) represents segment 1

Using the anatomic location of the three hepatic veins, the liver has been divided into seven segments, based on the Couinaud classification system. Each lobe is divided into four segments, I through IV on the left and V through VIII on the right with segment I representing the caudate lobe (Couinaud 1992). Each segment has its own vascular inflow, vascular outflow, and biliary drainage (Fig. 2).

2.1.2 Vasculature

The liver receives dual blood supply from the portal vein (70 %) and hepatic artery (30 %). The hepatic artery is rich in oxygen, while the portal vein provides the liver with metabolite-rich but relatively poorly oxygenized blood. The portal vein takes its origin from the confluence of superior mesenteric vein and splenic vein, between the posterior surface of pancreatic neck and anterior surface of the IVC. The portal venous and hepatic arterial blood supplies parallel each other as they enter the portal triad and sequentially divide among the segments and subsegments of the liver.

The relationship of the liver to the portal vein is important in the understanding of portal hypertensive changes. Although the larger part of blood supply to hepatocytes is from the portal vein, the biliary system obtains all its supply from the hepatic artery. An injury to the hepatic artery therefore tends to have more severe effect on the biliary system than the hepatocytes. The portal vein is autoregulated, but the extent of arterial flow is partly dependent on the portal flow, such that situations reducing portal flow reflexively increase arterial flow. The mean pressure in the portal vein is 10 mm Hg compared to 90 mm Hg in the artery. However, the intrahepatic regulation ensures the arterial pressure does not extend into the sinusoids, which have a mean pressure of 5 mm Hg. Any pathologic process interfering with sinusoidal flow could have a far-reaching effect on this arterial pressure regulation and hepatic hemodynamics. This has relevance, as described in Sect. 3.3.2, in the pathogenesis of sinusoidal obstruction syndrome.

In summary, the liver receives dual arterial and venous blood supply, which flow through a system of sinusoids within the hepatic parenchyma in well-regulated pattern, to empty through small hepatic veins, that in turn drain into one of three major hepatic veins, and ultimately into the IVC. Details of the intrahepatic flow through the sinusoids are discussed in the next section—microanatomy.

2.2 Histology (Microanatomy)

The flow from the portal vein and hepatic artery enter the hepatic hilum soon after each divides into the right and left branches. Subsequent intrahepatic divisions create up to 1,000,000 interlobular branches of the portal vein and hepatic artery. The biliary system drains in the opposite direction but follows similar architecture, such that interlobular bile ducts (that drain bile canaliculi) progressively confluent to form the right and left hepatic ducts, which exit at the hilum, and fuse to become the common hepatic duct. The point where the cystic duct draining the gallbladder joins the common hepatic duct represents the beginning of the common bile duct, which eventually empties into the duodenum at the ampulla of Vater. Lymph flows in the same direction as bile. Thus, each interlobular portal tract consists of (at least) an arteriole, a venule, a bile duct, and lymphatic vessels enmeshed within a fibrous connective tissue, hence the term portal triad. Figure 3a shows the low magnification hepatic lobules and Fig. 3b shows the high magnification intralobular structure.

Surrounding the connective tissue is a single layer of hepatocytes running concentric to the triad and termed the limiting plate. The next layers of hepatocytes are arranged perpendicular to this plate running from the portal tract to the central vein (strictly a venule from its size). Separating the hepatocyte cords from each other is a system of sinusoids, lined by hepatocyte-specific fenestrated endothelial cells with a different immunophenotype from endothelial cells elsewhere in the body (see below). They function to regulate the passage of material between the sinusoids and subendothelial space that is in direct contact with hepatocytes. This perisinusoidal space (space of Disse) houses hepatic stellate cells (Ito cells) and native liver macrophages (the Kupffer cells). The stellate cells are storage site for vitamin A, and can become activated to assume myofibroblastic phenotype and function, playing significant role in fibrosis formation in most chronic liver injuries. After traversing the sinusoids, the vascular outflow proceeds to the

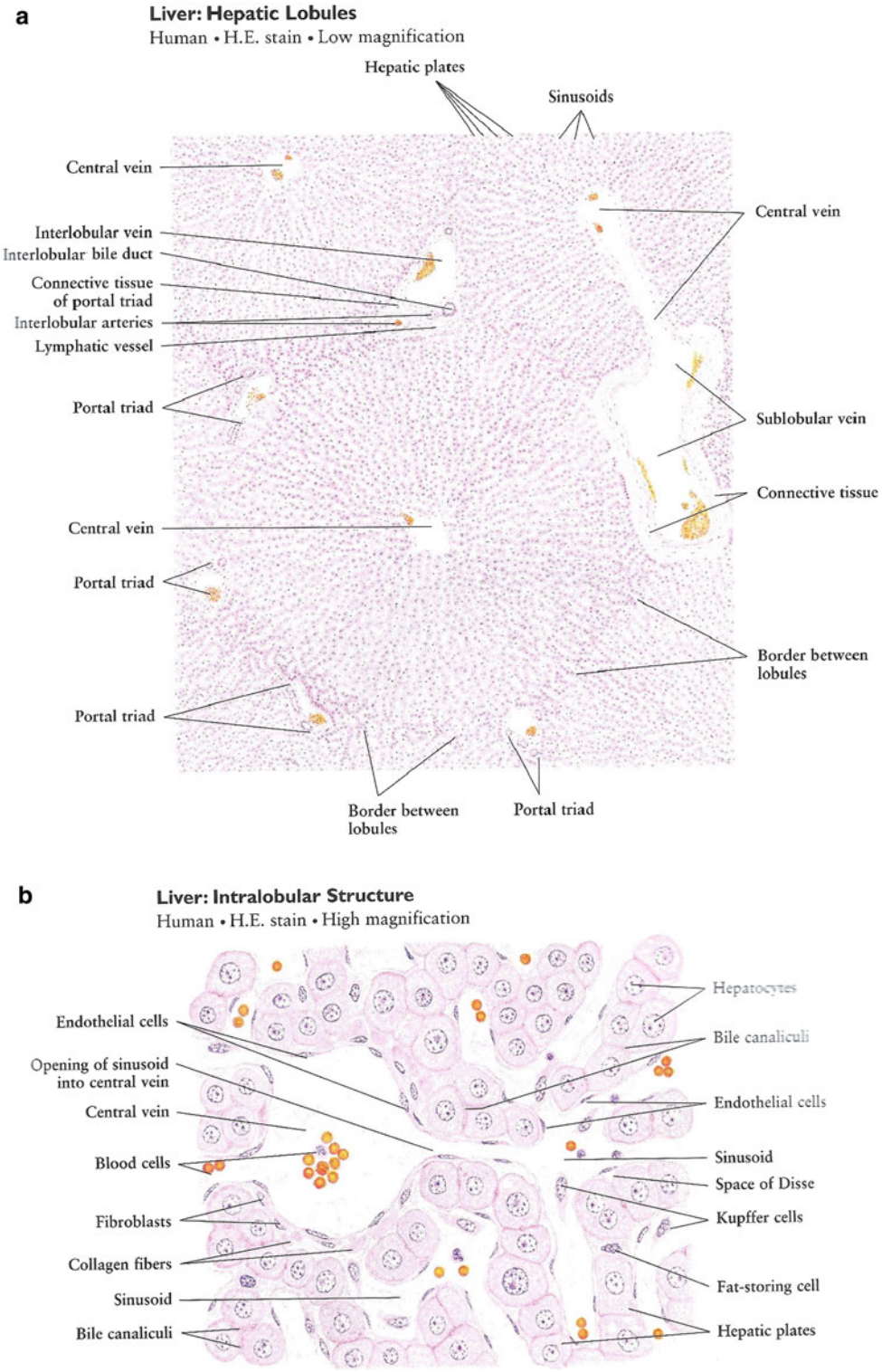

Fig. 3 Liver histology. **a** Low magnification. **b** High magnification (with permission from Zhang 1999)

central veins, the sublobular veins, and then to the supra-hepatic vein that ultimately drains into the IVC.

Endothelial cells, with two types of phenotypes, line the entire vascular system of the liver. The endothelial cells lining the portal veins, hepatic artery, hepatic venules, and hepatic veins exhibit systemic phenotype in that they are continuous and express among others, CD34 and factor VIII-related antigens, as would be expected elsewhere in the body. In contrast, the endothelial cells lining the sinusoids are fenestrated and do not express these antigens. In pathologic states such as neoplasms and cirrhosis, sinusoidal endothelium can revert to systemic phenotype (Couvelard et al. 1996).

3 Biology, Physiology, and Pathophysiology

3.1 Physiology (Functional Unit)

Traditionally, two structural systems have been considered as representing the functional unit of the liver, i.e., the smallest unit that represents the complete structure, function, and hemodynamics of the entire system: the acinar and the lobular systems. The lobule has a hepatic venule at its center with 3–6 vascular inflow portal triads arranged at the periphery of a polygonal unit (Fig. 3). Blood flows from the portal triad toward the central vein, and the oxygen concentration accordingly decreases toward the perivenous sinusoids. This does not truly represent the entire complex, as blood flows in the opposite direction to the lobular concept. For this reason, Rappaport defined the acinar concept as being more representative of the true function and hemodynamics of the liver (Rappaport 1976). The hepatic acinus includes the portal tract at its center, where blood and nutrients enter the unit and the central vein at the periphery or distal end, where the liver is drained. The hepatocytes closest to the portal tracts are functionally and metabolically different from the ones further away, around the hepatic venule (Jungermann 1988). Among these differences is their relative susceptibility to various forms of injury; for example the distal (peri-venular) hepatocytes are more susceptible to hypoxic/ischemic injuries than the more proximal hepatocytes. The proximal or periportal hepatocytes, also known as the zone 1 hepatocytes, are better oxygenized, but more susceptible to injury from some toxins that enter the liver via portal flow and are more concentrated at this zone. The distal hepatocytes in the unit are termed zone 3 hepatocytes, and those between zones 1 and 3, termed zone 2. Zones 1, 2, and 3 therefore correspond, respectively, to periportal, mid-zonal, and centrilobular (or perivenular) divisions of the lobular unit, as shown in Fig. 4. For most practical and descriptive purposes, the acinar unit is often utilized to describe the functional unit of the liver.

Within the liver, there are many functional subunits, with substantial redundancy.

3.2 Pathophysiology

3.2.1 Tissue, Cellular Mechanisms

The numerous redundant functional subunits within the liver allows the liver to endure substantial injury prior to development of any clinical sequelae. In noncirrhotics, surgical resection of a majority of the liver that leaves only a 20–25 % liver remnant has been shown to be well tolerated. Because of this redundancy, partial liver irradiation to high doses is possible using conformal radiation therapy if adequate normal liver parenchyma can be spared.

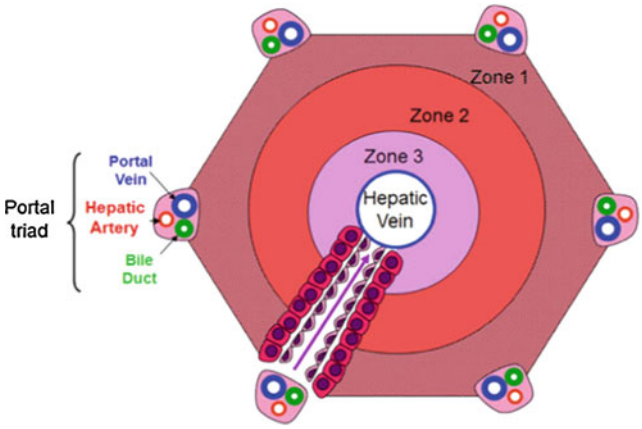

Fig. 4 Illustration of normal hepatic acinus illustration showing zones 1–3 as they relate to the portal tracts and hepatic vein. The arrow depicts direction of blood flow through the sinusoids

Due to the surplus of functional subunits in one liver, the architecture of the liver can be considered predominantly arranged "in parallel". Seriality in vascular and biliary function exists, as the vascular structures and the biliary system have many bifurcations throughout the liver that ultimately drain to main vessels or the common bile duct. Injury to the main vessels or common bile duct will have more adverse clinical consequence that injury to a distal branch. Furthermore, large vascular or biliary injury may alter the function of the liver associated with these structures. Thus the liver function itself may be considered mainly "in parallel", with potential for some "serial" function.

Regarding classic RILD, the underlying pathophysiology is poorly understood. However, injury to endothelial cells rather than hepatocytes has been postulated to be initiating, due partially to the timing of pathological changes observed in classic RILD (described in Sect. 3.2).

3.2.2 Morphological Appearance of RILD

The morphological appearance of classic RILD in humans is one of VOD, predominantly of the central and sublobular hepatic veins, with sparing of the periportal areas, larger hepatic veins, and hepatic arterial vasculature (Fajardo and Colby 1980; Reed and Cox 1966; Ogata et al. 1963) (Fig. 5c). While the lesion may affect anywhere from a portion of a lobule to the entire liver, it occurs strictly within the irradiated region and is sharply demarcated from adjacent unaffected areas of liver (Fig. 5a, b). Grossly, the involved liver appears markedly congested, and may contain areas of necrosis and parenchymal collapse in the center of larger involved regions.

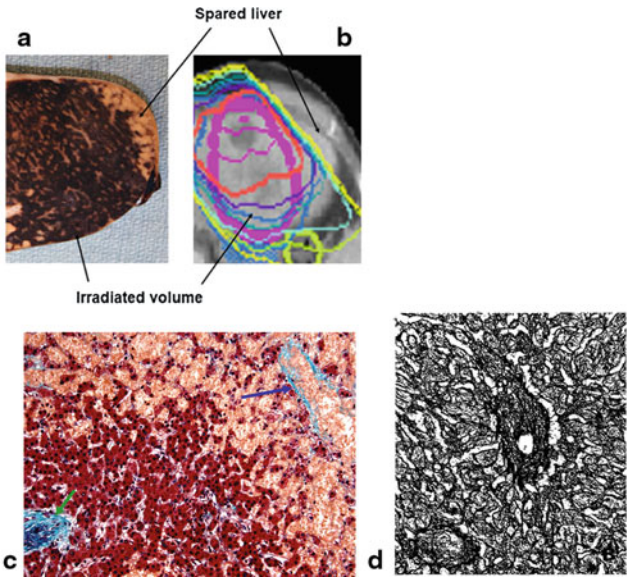

Fig. 5 **a** Gross photograph showing acute sinusoidal obstruction in resected left liver lobe following previous radiation therapy to a neoplasm (neoplasm not shown here), delivered 3 months previously. The sharp delineation of the change in the gross specimen is consistent with the radiation dose falloff, rather than anatomic regions. **b** Radiation plan: 30 Gy in 6 fractions (*yellow*), with sparing of the lateral left lobe. **c** Microscopy of acute sinusoidal obstruction in resected left liver lobe following radiation therapy; hepatic vein—*blue arrow*; portal tract—*green arrow*. The sinusoids and later the hepatic vein become prominent due to severe congestion (Trichrome stain, original magnification: 100x). (PDF Fig. 4). **d** Late fibrosis: typical centrilobular areas in moderately severe radiation-induced liver disease (RILD), fibrillary material (collagen) (with permission from Fajardo and Colby 1980[14])

In their classic description that established the features of RILD, Reed and Cox described in detail the progression of morphological changes that occur over the course of RILD (Reed and Cox 1966). In the early subacute period, typically the first month after RT, affected liver portions are markedly hyperemic, but display few venous lesions and only minimal evidence of outflow obstruction and hepatic cell loss. During the ensuing months, which correlate with the clinical presentation of RILD, veno-occlusive lesions become frequent and prominent, with severe vascular congestion and atrophy of centrilobular liver plates. The pathological hallmark of RILD, veno-occlusive lesions, are characterized by complete obliteration of central vein lumina by erythrocytes trapped in a dense network of reticulin and collagen fibers that crisscross the lumen of the central veins, sublobular veins, and centrilobular sinusoids. Fibrin appears to be deposited peripherally along the intimal walls of these vessels, rather than in center of the lumens as are collagen and reticulin. Collagen is present not only in the centrilobular veins, but appears to proliferate along the hepatic sinusoids and produce mild congestion in periportal areas as well. Centrilobular hepatocytes (zone 3) are largely absent, presumably due to hypoxic cell death secondary to vascular congestion. After approximately 4 months, vascular congestion resolves as the liver begins to gradually heal. Although asymptomatic, the hepatic architecture remains largely distorted, with persistent fibrosis of central veins, fibrous tracts bridging portal and central veins, and unrepaired lobular collapse prominent throughout the affected region (Fig. 5d).

A characteristic feature of RILD, which is not yet well studied in the other forms of VOD, is the deposition of fibrin strands with entrapment of platelets within the central veins as demonstrated by electron microscopy. The elevation of alkaline phosphatase more than the transaminases in classic RILD suggests that bile ducts or hepatic canaliculi may also be injured in irradiated livers.

Of note, thrombosis of larger hepatic veins, such as seen in Budd-Chiari syndrome, has been uncommonly seen following liver irradiation (Rahmouni et al. 1992). However, radiation-induced thrombosis is typically not associated with centrilobular coagulative necrosis and clinically does not usually induce jaundice, which is often seen in patients with Budd-Chiari syndrome.

3.2.3 Animal Models

The pathogenesis of RILD is difficult to investigate because of the lack of a suitable animal model. Rat (DeLeve et al. 2002), mice (Tabbara et al. 2002), dog (Reiss et al. 2002; Bearman 2001), and rhesus monkey (Shulman et al. 1980) models studied to date do not develop a similar pathology or clinical syndrome to that seen in humans (the VOD of classic RILD). However, the murine and rodent microvascular endothelial cells are sensitive to radiation injury (Shulman et al. 1987). Furthermore, perivenous atrophy of hepatocytes has been noted in rodent models of RILD, despite a lack of central vein occlusion by platelet thrombi (Shulman et al. 1994).

Geraci and colleagues first reported that rats receiving whole liver irradiation in excess of 25 Gy developed liver dysfunction after a latent period of 35–40 days (Geraci et al. 1991). In their study, hepatocellular injury was evident by elevations in AST, ALT, alkaline phosphatase, and ^{131}I rose bengal retention, an indicator of hepatobiliary clearance. Morphologically, these rats appeared to develop a pathology that somewhat resembled the VOD described in humans, with venous outflow obstruction by collagen deposition, sinusoidal vascular congestion, interstitial fibrosis, and focal necrosis of centrilobular hepatocyte (Geraci et al. 1991). However, no studies to date of hepatic irradiation in rodents by other investigators have successfully reproduced these pathological findings. This may be due to the fact that unless the entire liver is irradiated, even a small spared portion can rapidly regenerate and prevent

the clinical syndrome of RILD (Geraci et al. 1991). Thus, despite the promise of Geraci's reports, a reproducible rodent model that mirrors human RILD remains elusive.

3.2.4 Viral Hepatitis

Another mechanism thought to contribute to the pathogenesis of nonclassic RILD is the subclinical or ongoing cirrhosis of the liver associated with hepatitis B virus (HBV). Most patients undergoing irradiation of the liver in East Asia are HBV carriers. Cheng et al. found that chronic infection with HBV was associated with a higher risk of developing nonclassic RILD (which presented as elevated serum transaminases) in a univariate analysis of patients treated with radiation (Cheng et al. 2002, 2004a). After stratifying their patients, they noted that the HBV carrier group had a shifted normal tissue complication probability curve, with a reduced tolerance compared to the noncarrier group. These arguments suggested the possibility of a unique mechanism (e.g. HBV reactivation) in the development of non-classic RILD (and reduction in liver dose tolerance) in carriers of HBV.

In general, the reactivation of viral hepatitis in HBV carriers can occur without a causative factor as a sporadic event (Tsai et al. 1992). Hepatic venulitis can be seen as part of the picture in viral hepatitis, and other causes of severe hepatitis, leading to significant injury and subsequent loss of affected venules. This could subsequently produce sinusoidal congestion. Because the injury is often patchy, the sinusoidal congestion usually is minimal, as the liver is capable of diverting flow toward adjacent veins with no or milder injury. Chemotherapeutic agents have been associated with HBV reactivation (Yeo et al. 2000). The reactivation of HBV is implicated as the mechanism why HBV patients may have a reduced tolerance to irradiation, though only recently has data been collected to confirm viral reactivation after liver irradiation. In the 2004 Cheng et al. report, 2 of the 17 patients who developed RILD were examined for reactivation of HBV, and both patients demonstrated serologic evidence of viral reactivation (Cheng et al. 2004b). In a separate report by Cheng et al., it was shown that 6 of 8 patients with gastric cancer who developed nonclassic RILD were chronic HBV carriers, and 4 of the 6 carriers had serologic evidence of viral reactivation following adjuvant chemotherapy and radiation therapy (Cheng et al. 2004a).

Kim et al. compared liver irradiation in a group of patients with chronic hepatitis B requiring antiviral treatment at the time of irradiation versus a group of HBV carrier patients without active disease. They found that reactivation of HBV and nonclassic RILD, though not necessarily together, occurred more commonly in the latter group (Kim et al. 2007).

Although it has become established that reactivation of HBV may occurs after liver irradiation, the mechanism is not yet known. Radiation could directly reactivate HBV residing in a hepatocyte, or it may be due to the effect of radiation on nearby nonparenchymal cells (Chou et al. 2007). The direct effect and the so-called bystander effect were tested by Chou et al. by transferring various conditioned media in vitro. They found that the direct effect of radiation on hepatocytes, normal or cancerous, did not show reactivation of HBV. However, transferring conditioned medium of irradiated noncancerous hepatocytes or irradiated endothelial cells resulted in HBV DNA replication (Chou et al. 2007). They went on to show that IL-6 that is released from endothelial cells after irradiation, suggesting that radiation-induced reactivation of viral hepatitis B probably occurs due to a bystander effect of IL-6.

3.3 Biology (Molecular Mechanisms of RILD)

3.3.1 Sinusoidal Endothelial Injury

It has been traditionally postulated that the initiating lesion of VOD in RILD occurs at the level of the sinusoidal endothelium. Electron microscopy studies of affected liver in classic RILD have revealed fibrin deposits throughout the central veins and adjacent sinusoids. These findings led to the supposition that damage to sinusoidal endothelial cells (SECs) and central vein endothelium initiates activation of the coagulation cascade, leading to accumulation of fibrin in the central veins and hepatic sinusoids (Lawrence et al. 1995). It is thought that deposited fibrin serves as a foundation for the proliferation of reticulin and collagen, which eventually occludes the vessel lumen. The trapping of erythrocytes in this collagen meshwork produces vascular congestion and decreased oxygen delivery to the central zone, which is inherently sensitive to hypoxia due to the physiological oxygen gradient within the hepatic lobule. This hypoxic milieu presumably results in death of centrilobular hepatocytes and atrophy of the inner hepatic plate, producing the hepatic dysfunction observed clinically in RILD (Lawrence et al. 1995).

3.3.2 Sinusoidal Obstructive Syndrome

A similar pathological entity to the VOD of classic RILD, named sinusoidal obstructive syndrome (SOS) to distinguish it from other forms of VOD, has been observed in several clinical scenarios. Classic causes of SOS include ingestion of herbal teas or foods containing pyrrolizidine alkaloids, prolonged immunosuppression with azathioprine, and a wide range of chemotherapeutic agents, including dacarbazine, and cyclophosphamide. The most common cause of SOS is myeloablative chemotherapy or

combination chemoradiotherapy for bone marrow transplantation (BMT).

Studies of monocrotaline-induced SOS models have delineated a clear sequence of events by which sinusoidal and venous obstruction occurs in rats (DeLeve et al. 1999). In this model, the earliest observed changes appear to be loss of SEC fenestrations and appearance of gaps in SEC endothelium (DeLeve et al. 1999). Digestion of extracellular matrix on the abluminal side of SECs membrane causes SECs to "round up" and facilitates penetration of red blood cells into the underlying space of Disse, leading to dissection of the endothelial lining and narrowing of the sinusoidal lumen (DeLeve et al. 1999, 2003). The dissected sinusoidal endothelium embolizes and obstructs downstream sinusoids and central veins, producing hepatic vascular congestion. Clinical signs of SOS can occur in the absence of central vein occlusion, implying that sinusoidal injury is sufficient to cause clinically significant microcirculatory hepatic dysfunction, as confirmed in this animal model of SOS. By comparison, central vein obstruction is considered a prominent and defining pathological feature of classic RILD, presumably occurring secondary to luminal deposition of fibrin, reticulin, and collagen that traps of erythrocytes and produces vascular congestion and hepatic hypoperfusion.

The earliest morphological change observed in human studies of SOS is edematous widening of the subendothelial space of central and sublobular veins by fragments of erythrocytes (RBCs) and cellular debris (Shulman et al. 1980, 1987, 1994). This is accompanied by sinusoidal dilation and engorgement, erythrocyte penetration into the space of Disse, and necrosis of perivenular hepatocytes (DeLeve et al. 2002). Similar to the animal models, the sinusoidal pathology in SOS is typically more prominent than the central vein changes, an important difference from classic RILD. Sinusoidal injury is thought to be the responsible for the hepatocellular damage and clinical signs of SOS. This hypothesis is supported by findings that clinical signs of SOS correlate with perivenular lesions in the absence of venous occlusion, and that, in one series, 45 % of patients with mild-to-moderate SOS and 25 % of patients with severe disease lacked central vein obstruction on autopsy (Shulman et al. 1994). However, central vein involvement has been shown to correlate with both ascites and disease severity, suggesting that while not requisite to disease development, central vein obstruction significantly exacerbates circulatory impairment and hepatic dysfunction in SOS (Shulman et al. 1994; Rollins 1986).

As in classic RILD, deposition of fibrin and collagen has been observed in SOS, although reports of this finding vary. The fibrosis occurs in the zone-3 sinusoids and can range from mild-to-severe (cirrhotic) depending on the severity and extent of sinusoidal injury. Shulman et al. compared autopsy samples of liver tissue from BMT patients with VOD and without VOD by immunohistochemical analysis (Shulman et al. 1987). Of 11 patients 9 with early VOD demonstrated dense factor VIII staining of central veins, compared to only 2 out of 12 patients without VOD, suggesting activation of the coagulation cascade in the development central vein obstruction in SOS. The observation in this study that positive staining for fibrinogen was present in 4 out of 4 patients with early VOD, compared to 0 out of 4 patients without VOD, supports a role for clotting in the development of early SOS. Furthermore, extensive luminous obliteration by collagen in late VOD was identified in central veins (2/4 pts) and centrilobular sinusoids (3/4 pts), as compared to the localization of collagen in early VOD to only sinusoids (2/3 pts) and not central veins (0/3 pts) (Shulman et al. 1987). Although derived from a small patient population, the temporal differences in these findings between early and late VOD support the theory that sinusoidal endothelial injury initiates the pathogenic cascade in SOS, and that consequent deposition of fibrin serves as a scaffolding upon which collagen accumulates and obstructs sinusoids and downstream central veins.

Other studies of patients undergoing myeloablative BMT (Sartori et al. 2005; Brooks et al. 1970) provide anecdotal evidence for the involvement of clotting cascade activation of the development of SOS. In one study of 53 consecutive pediatric patients receiving BMT, children who developed VOD had significant increases in plasminogen activator inhibitor type I, tissue plasminogen activator, and D-dimer and significant decreases in prothrombin time, antithrombin, and α2-antiplasmin at either 2 days prior to or 1 day after clinical diagnosis of VOD, as compared to patients who did not develop VOD (Sartori et al. 2005). Several retrospective analyses in BMT patients have demonstrated less frequent symptoms and lower incidences of SOS in cohorts receiving prophylaxis therapy with heparin, defibrotide, and/or prostaglandin E1, providing further support for a causal or pathogenic role of thrombosis and hypercoagulability in the development of SOS (Chalandon et al. 2004; Rosenthal et al. 1996; Simon et al. 2001). Given the widespread morphological similarities between classic RILD and SOS, one may speculate that aberrant coagulation cascade activation may also play a role in the pathogenesis of classic RILD, although no clinical studies to date have adequately addressed this possibility.

Despite their pronounced etiological and clinical differences, the morphological similarities between VOD and SOS suggest that SOS may be an important disease model from which we can gain a better understanding of classic RILD. Analogous to the postulated mechanism of RILD, liver sinusoidal endothelial cells appear to be the primary target of drugs that produce SOS (DeLeve 1994, 1996, 1998). Of particular significance is the fact that all of these

compounds are (a) detoxified by glutathione (GSH) and (b) selectively more toxic to SECs than to hepatocytes (DeLeve 2007). Depletion of GSH due to metabolism of each of these compounds precedes SEC toxicity in vitro, suggesting that metabolite conjugation by GSH may play a protective role in preventing SEC damage and SOS caused by these drugs (DeLeve 1994, 1996, 1998).

In summary, it is plausible that, as in SOS, damage to SECs may precede the development of central vein obstruction in classic RILD. In SOS, central vein involvement appears to worsen the severity of disease (Shulman et al. 1994; Rollins 1986). It is equally plausible that the scenario is analogous for radiation-induced liver damage, as injury limited to SECs may produce only subclinical disease, whereas obstruction of downstream central and sublobular veins results in clinically manifest RILD.

3.3.3 Activation of Hepatic Stellate Cells

In addition to endothelial cell damage, several other mediators of hepatic damage are thought to contribute to the development of RILD. Hepatic stellate cell (HSC) activation, in particular, has been observed in patients who developed severe congestive changes characteristic of RILD in the months following RT for biliopancreatic cancer, prior to the development of fibrosis (Sempoux et al. 1997). In a study of six such patients by Sempoux and colleagues, activated HSCs, characterized by expression of the α-isoform of smooth muscle actin (α-SMA), were variably identified throughout congested irradiated areas and found within thickened central vein walls and adjacent to or within congested centrilobular sinusoids (Sempoux et al. 1997), while activated HSCs were not present in all samples from all patients and were unevenly distributed in congested areas, their presence did appear to coincide with severity of fibrosis and architectural distortion. α-SMA positive cells were also notably absent from nonirradiated areas, suggesting an association between hepatic irradiation and stellate cell activation. While the small patient population ($n = 6$) and lack of statistical analysis limits our ability to draw any conclusions from this study, the observations of stellate cell activation in RILD are nonetheless intriguing and warrant further investigation.

3.3.4 Transforming Growth Factor-β

The transforming growth factor-β (TGF-β) family consists of the TGF-β1, TGF-β2, and TGF-β3 precursor isoforms (Blobe et al. 2000; Khalil 1999). The propeptides are cleaved by proteolytic cleavage from the active TGF-β peptide growth factor that exists functionally as a dimer held together by disulfide bonds. TGF-β is ubiquitous as nearly every cell in the human body produces TGF-β and has receptors for it (Blobe et al. 2000). TGF-β is integral in the interaction between cells and the extracellular matrix in the processes of inflammation, immune response, and wound healing. It is also important in cell cycle regulation and in the apoptotic pathway. The reactive interaction between parenchymal cells, nonparenchymal cells, and the extracellular environment occurs through the language of cytokines. TGF-β proves to be one of the most important cytokines associated with tissue injury and wound healing (Amento and Beck 1991; Barcellos-Hoff 2005a, b; Barcellos-Hoff et al. 2005). The pathogenesis of RILD, though still unclear, may have less to do with direct parenchymal damage and more likely is a result of the tumor microenvironment as a result of irradiation.

As such, TGF-β has been implicated in playing a role in the fibrogenesis leading up to RILD. Fibrin deposition in the sinusoids and subendothelial space has been shown to occur after liver irradiation (Fajardo and Colby 1980). After a stable period of fibrin deposits, fibroblasts migrate to the region of injury and undergo proliferation and production of collagen under the influence of TGF-β (Amento and Beck 1991). TGF-β is not necessarily associated with radiation injury; rather, it is present in a non-specific manner in many types of liver disease, such as cirrhosis, chronic hepatitis, or chemotherapy-induced liver disease (Anscher et al. 1993; Castilla et al. 1991).

Anscher et al. described the dose dependence of the level of TGF-β in irradiated liver; they also showed that the level of TGF-β in hepatocytes was higher in the region of more extensive fibrosis (Anscher et al. 1990). After creating an association with TGF-β, dose, and fibrosis, they were able to identify a temporal or cause-and-effect relationship by demonstrating a fibrotic reaction in healthy rat livers after injection with TGF-β (Anscher et al. 1990). Rodent models of VOD and RILD have been elusive (as described in Sect. 3.2.3). Anscher and colleagues reported that the level of TGF-β in normal human hepatocytes was higher than that in normal rat hepatocytes, raising a possible reason why humans have a greater tendency to develop VOD as compared to rats (Anscher et al. 1990). The same group reported separately that patients who received induction chemotherapy prior to BMT and high-dose chemotherapy and developed VOD after treatment had significantly higher levels of pretransplantation TGF-β as compared to patients who did not develop VOD and to normal controls (Anscher et al. 1993).

TGF-β may not be the only factor contributing the mechanism of RILD, but it is certainly significant in the pathogenesis. Furthermore, it is a compelling hypothesis that TGF-β may play a role in determining why humans develop VOD more readily than other animal models.

3.3.5 Other Cytokines

Aside from TGF-β, there are a number of other cytokines and downstream reactants that participate in the response to

tissue injury. The inflammatory condition that leads to cytokine release is typically associated with injury (e.g. burns, trauma), exposure to endotoxins, or exposure to foreign materials (e.g. infection). The importance of the inflammatory response in these conditions is in recruiting leukocytes to the site of stress so that the host may react to the damage. Gourmelon et al. has shown that a similar cytokine release pattern occurs in nonhuman primates subsequent to whole body irradiation (Gourmelon et al. 2005). A number of authors have similarly demonstrated the release of inflammatory cytokines with irradiation of various organs or cell types (Fedorocko et al. 2002; Linard et al. 2003; Beetz et al. 1997; Meeren et al. 1997; Hosoi et al. 2001; Ishihara et al. 1993).

Similarly, Christiansen et al. showed that irradiation of rat liver in vivo induces upregulation of proinflammatory cytokines IL-1-beta, IL-6, and tumor necrosis factor alpha (Christiansen et al. 2007). The same group demonstrated that in vitro irradiation of isolated hepatocytes alone showed no effect versus irradiation of hepatocytes in a medium supplemented with the proinflammatory cytokines, which induced the upregulation of hepcidin, an acute phase reactant (APR). Moriconi et al. were able to show that hepatocytes had upregulation of chemokines after irradiation in vivo (Moriconi et al. 2008). Similarly, they showed that in vitro hepatocytes had upregulation of these chemokines only in the presence of proinflammatory cytokines. Although higher dose tolerance has been shown for partial liver irradiation (Dawson and Ten Haken 2005), the whole liver is sensitive to irradiation, with greater than a 5 % risk of toxicity above doses of 30–35 Gy in 2-Gy fractions (Ingold et al. 1965; Emami et al. 1991; Austin-Seymour et al. 1986). Conversely, hepatocytes irradiated in vitro have been demonstrated to be relatively radioresistant (Jirtle et al. 1984; Jirtle et al. 1982; Jirtle et al. 1981; Alati et al. 1988, 1989a, b). Therefore, hepatocytes irradiated in vivo or in a medium of proinflammatory cytokines demonstrate a weakened state that confers the overall radiosensitivity of the whole liver. The proinflammatory cytokines are not released from the hepatocytes themselves, but are released from nonparenchymal cells (i.e. Kupffer cells and SECs) and via a paracrine affect can induce hepatocyte production of APRs (Christiansen et al. 2007; Moriconi et al. 2008; Ramadori and Armbrust 2001).

In other types of liver injury, chemokines play a central role in the recruitment of leukocytes (Ley 1996; Mehendale 2005), which likely contribute to the development of fibrosis. However, despite the upregulation of chemokines from hepatocytes after irradiation, Moriconi et al. did not observe significant leukocyte recruitment in the liver (Moriconi et al. 2008).

4 Clinical Syndromes

4.1 Clinical Endpoints

A variety of endpoints characterize radiation-induced liver injury. It is sometimes useful to categorize the endpoints, albeit somewhat arbitrarily, as shown in Table 2. Note that the cytokine changes have been demonstrated primarily in preclinical models, and are not ready to be used routinely in a clinical setting.

4.1.1 Liver Toxicity Subtypes

Liver toxicity has not always been separated into "classic" and "non-classic" RILD in the literature, which has contributed to some challenges in understanding the different pathophysiology and the dependence on radiation dose and volume for different liver toxicities that may occur following irradiation. Below, potential liver toxicities that may occur following liver irradiation are described. Of note, "non-classic RILD" includes any serious liver toxicity that may not fit into the other categories, and with time it is possible that different nonclassic RILD toxicities may be better understood and separated as entities of their own.

4.1.1.1 Classic RILD

As described previously, the most commonly studied hepatic toxicity following liver irradiation is classic RILD, a clinical syndrome mimicking VOD following stem cell transplantation, presenting with anicteric ascites and hepatosplenomegaly (Lawrence et al. 1995). RILD typically occurs between 2 weeks and 3 months after the completion of irradiation. Patients typically present with fatigue, rapid weight gain, increased abdominal girth, and, occasionally, right upper quadrant pain or discomfort, in the absence of icterus or jaundice. Ascites and hepatomegaly may be seen on physical examination. Laboratory findings usually consist of significant elevations in alkaline phosphatase (3–10 times upper limit of normal) and mildly increased aspartate transaminase (AST) and alanine transaminase (ALT) levels ($\sim$2 times upper limit of normal), with other liver function tests, including bilirubin, within normal limits (or at baseline pre treatment levels). RILD is defined in the absence of intrahepatic progression of cancer, as progressive cancer may mimic or mask RILD.

The clinical manifestations and course of RILD differ significantly from that of acute liver failure. Patients in acute liver failure typically present with more acute symptoms of nausea, vomiting, abdominal pain, dehydration, and jaundice. While RILD can progress to fulminant hepatic failure, particularly in the presence of underlying

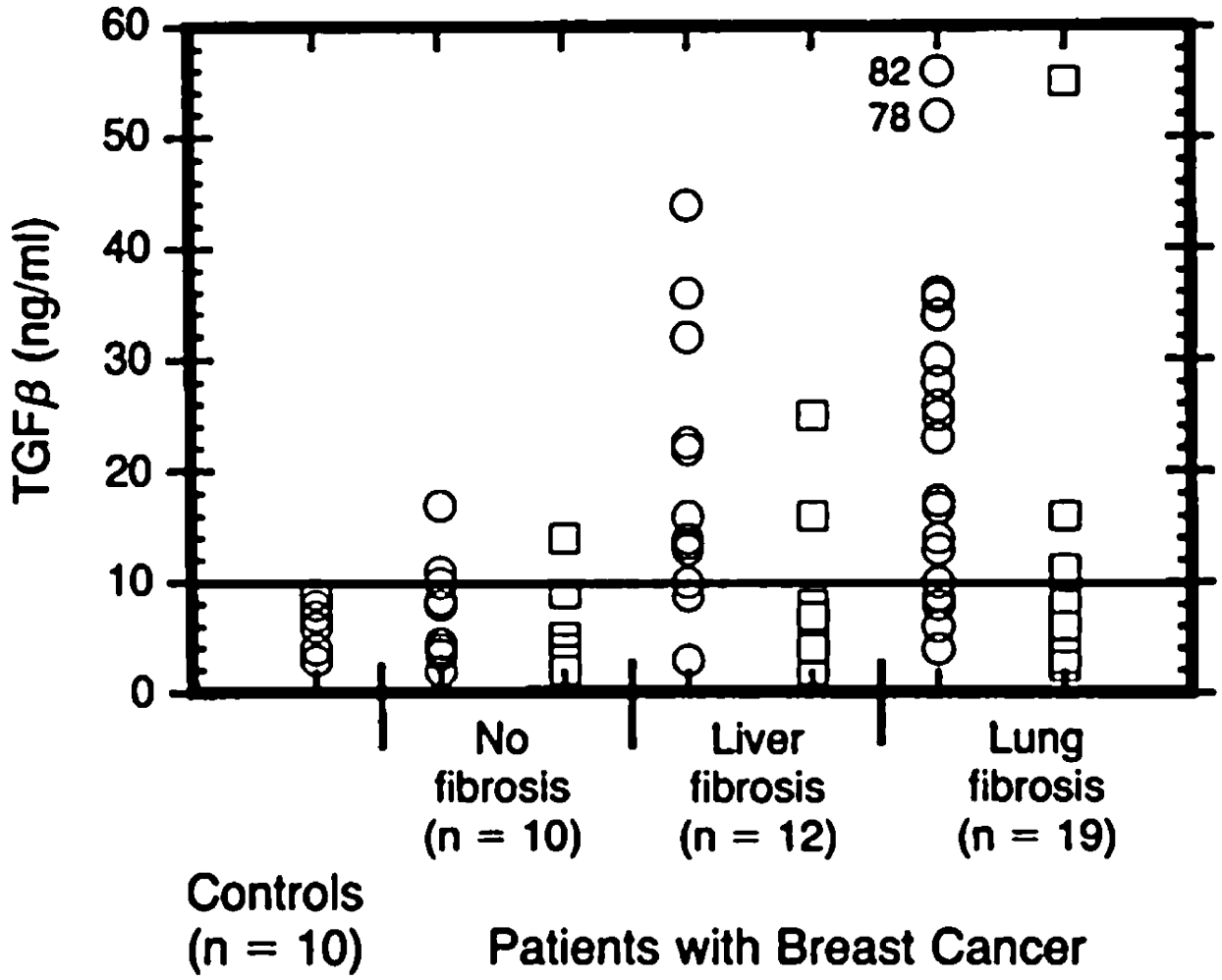

Fig. 6 Transforming growth factor β as a predictor of liver and lung fibrosis after autologous bone marrow transplantation for advanced breast cancer by Anscher et al. (1993). Individual TGFβ plasma concentrations in the four study groups. Healthy blood donors served as controls. One roup of patients did not have pulmonary fibrosis or hepatic veno-occlusive disease after high-dose chemotherapy and autologous bone marrow transplantation (no fibrosis); the two other groups had either hepatic veno-occlusive disease (liver fibrosis) or pulmonary fibrosis (lung fibrosis). TGFβ was measured before (*circles*) and after (*squares*) high-dose chemotherapy and transplantation (Anscher et al. (1993) shows the timing of the regimens). The *solid horizontal line* indicates the value (10 ng per milliliter, or 2 SD above the mean value determined in the controls) that was used as a cutoff point to determine the ability of pretransplantation TGFβ measurement to predict the development of hepatic or pulmonary toxicity after transplantation. To convert values for TGFβ to millimoles per liter, multiply by 4×10^{-8} (with permission from Anscher et al. 1993)

hepatic dysfunction, patients rarely present in acute liver failure. Figure 6 outlines the clinical workup, differential diagnosis, and management of classic RILD.

4.1.1.2 Nonclassic RILD

Nonclassic RILD is defined as elevated liver transaminases more than five times the upper limit of normal or CTCAE grade 4 levels in patients with baseline values more than five times the upper limit of normal within 3 months after completion of RT or a decline in liver function (measured by a worsening of Child-Pugh score by 2 or more), in the absence of classic RILD or progression of intrahepatic cancer (Pan et al. 2008). This endpoint has been described most commonly in patients with hepatocellular carcinoma who have compromised baseline liver function (hepatitis B infection, Child-Pugh B or C liver function) (Cheng et al. 2003; Liang et al. 2006).

A confounder of classic and nonclassic RILD, especially in populations with pre-existing liver dysfunction, is the baseline decline in liver function within this population that occurs with time due to pre-existing liver disease and/or progressive liver cancer. In a randomized trial in unresectable hepatocellular carcinoma of placebo versus Sorafenib, a multitarget kinase inhbitor, there was a 54 % rate of serious adverse events among the placebo group due to progression of cirrhosis and/or cancer (Llovet et al. 2008).

Table 1 Child-Pugh scoring system to assess severity of liver disease or toxicity

Criterion	1 point	2 points	3 points
Bilirubin (total)	<2 mg/dL	2–3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
INR	<1.7	1.71–2.20	>2.20
Ascites	None	Controlled with medication	Refractory
Hepatic encephalopathy	None	CTCAE grade I–II (or controlled with medication)	CTCAE grade III–IV (or refractory)

Points	Class	2-year survival (%)
5–6	A	85
7–9	B	57
10–15	C	35

INR international normalized ratio, *CTCAE* common terminology criteria for adverse events

Table 2 Representative endpoints of radiation-induced liver injury segregated as clinical vs. subclinical and global vs. focal, as shown

	Focal	Global
Subclinical	Regional changes on contrast CT Regional changes on contrast MR Regional changes in MR SPECT	Ascites Hepatosplenomegaly Increased ALP Increased liver enzymes (ALT, ALP) Increased Hepatitis B antigen Thrombocytopenia Changes in albumin, bilirubin, and INR Changes in indocyanine green (ICG) extraction Elevated TGF-β Elevated IL-1β Elevated IL-6 Elevated TNF alpha Elevated N-terminal peptide of type III procollagen propeptide Reduced protein C
Clinical	Fibrosis in critical region of liver, e.g., common bile duct leading to biliary obstruction	Increased abdominal girth Right upper quadrant pain Weight gain Fatigue Edema Confusion Encephalopathy

Nontheless, liver function (e.g. Child-Pugh score) is an important endpoint to report following treatment, as a decline in liver function is clinically relevant, whether it is due to progressive liver cancer, underlying cirrhosis or treatment. Thus, in addition to reporting nonclassic RILD in patients without progression of liver disease, any change in liver function (as measured using Child-Pugh score, Table 1) at 3 months following irradiation is recommended to be reported in all patients irradiated, including patients with progressive disease.

4.1.1.3 Reactivation of Hepatitis B Virus

Some patients who develop elevation of their liver enzymes, as described in Sect. 4.1.2, likely had hepatitis B reactivation induced by irradiation (Cheng et al. 2004a). Reactivation of HBV has now been described following liver irradiation in animal models and in patients. Reactivation of HBV can occur following chemotherapy, and thus, it is likely more common following combined chemotherapy and radiation in HBV carriers.

Patients planned to be treated with radiation therapy should be considered for tested for hepatitis B surface antigen (HBsAg) and anti-HCV. If either test is positive, further confirmatory testing should be done including HBV DNA or HCV RNA, and a referral to a hepatologist is recommended for treatment of viral hepatitis prior to irradiation.

4.1.1.4 Post Transplant Veno-Occlusive Disease

VOD is a frequent, serious, and often life-threatening complication of hematopoietic stem cell or bone marrow transplantation. It is believed to be caused by hepatic

endothelial cell injury from the high-dose cytoreductive conditioning regimens used during stem cell and bone marrow transplant protocols, often in combination with total body irradiation (TBI) (DeLeve et al. 2002; Bearman et al. 1993). Hepatocytes in zone 3 of the liver acinus are also injured by direct chemotherapy toxicity and ischemia due to endothelial clotting in the terminal hepatic venules.

Patients present with hyperbilirubinemia, fluid retention, and hepatomegaly. VOD has been defined as bilirubin $\geq$2.0 mg/dL, weight gain $\geq$2.5 % from pretransplant weight, and hepatomegaly and/or right upper quadrant pain, occurring within 2 weeks of transplantation, in the absence of other explanations for these signs or symptoms. The primary difference between transplant-associated VOD and RILD is the rapid elevation of bilirubin which may occur in transplant VOD within days following chemotherapy or TBI. Risk factors for VOD include previous hepatitis, mismatched or unrelated donor transplants, and high-dose chemotherapy regimens (i.e. high-dose Cyclophosphamide, or Cyclophosphamide and Busulfan). Interestingly, the use of TBI and the doses used in preparative regimens do not appear to be strongly associated with the risk of VOD occurring (Ganem et al. 1988).

VOD occurs in up to 50 % of patients following stem cell transplantation. 50 % of cases are irreversible and can lead to multiorgan failure. Disease prognosis generally depends on the degree of liver injury and the resulting severity of the hepatic dysfunction. Mild disease may not develop liver failure, and may reverse with supportive treatment. Moderate VOD includes evidence of liver dysfunction, and treatment with diuretics for fluid retention, and analgesics for right upper quadrant pain are often required. Fifty percent of patients present with severe and life-threatening VOD. These patients have the most dramatic rises in serum bilirubin, the fastest weight gain, the highest rates of ascites, and the most severe hepatic dysfunction. Prevention of VOD with heparin, prostaglandin E, and ursodeoxycholic acid have not definitively been shown to prevent or mitigate transplant-related VOD. Treatment with supportive care does not usually alter the course of this toxicity, and these patients often die of severe renal and cardiac failure. The day +100 post stem cell transplant mortality for these patients approaches 100 % (Bearman et al. 1993).

4.1.2 Grading of Toxicity

The Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, grades hepatobiliary toxicity according to clinical criteria including jaundice, asterixis, and encephalopathy or coma for grades 2, 3, and 4, respectively. These serious adverse events are rare following radiation therapy. Acute changes in liver enzymes or liver function tests are far more common during and/or following radiation therapy. Such liver enzyme abnormalities are classified under the CTCAE metabolic/laboratory category.

The Child-Pugh scoring system to assess liver dysfunction is based on an assessment of the clinical and laboratory parameters shown in Table 1. It can be used to characterize baseline liver function and also post-treatment changes in liver function.

4.2 Detection (Liver Function Tests)

4.2.1 Serum Markers

Assessment of liver function is an important component of evaluation of patient with liver cancer or other cancers in whom radiation therapy may be used for treatment. Serial measures of liver function are also useful in estimating the severity of radiation toxicity, and in predicting survival following development of classic or non-classic RILD. Hepatic synthetic function is assessed by measurement of serum albumin, bilirubin, and prothrombin time, which are critical components of the Child-Pugh scoring system. Decrease in platelet count and white blood cell counts may reflect the degree of portal hypertension and associated hypersplenism.

Other tests such as isocyanine green retention and 99m-Tc GSA (diethylenetriamine-penta-acetic acid-galactosyl human serum albumin) scintigraphy have been described as more specific indicators of hepatic reserve in preparation for resection, but have not convincingly surpassed the Child-Pugh classification as a predictor of post-operative complications and liver failure.

4.2.2 Indocyanine Green Clearance

The pathophysiology of RILD, as described in Sect. 3, leads to portal venous congestion and thereby altered vascular outflow from the liver. Cao et al. concluded that hepatocyte function was altered in the area of hypoperfusion using an indocyanine green (ICG) extraction study (Cao et al. 2008). While ICG clearance has been used as a measure of liver function, there have been discrepancies when compared with histological findings. ICG is taken up from plasma almost exclusively by hepatocytes, and subsequently secreted into bile. However, this function of hepatocytes does not measure the synthetic function or conjugative abilities of hepatocytes. Furthermore, ICG analysis measures whole liver function, and it is unable to identify specific regions of diminished functionality. Therefore, the outcome of the ICG test ultimately defines whether perfusion of the whole liver is adequate, where functionality of one portion of the liver can overshadow the dysfunction of another part of the liver. A more meaningful analysis would be to measure the function of the irradiated portion of the liver.

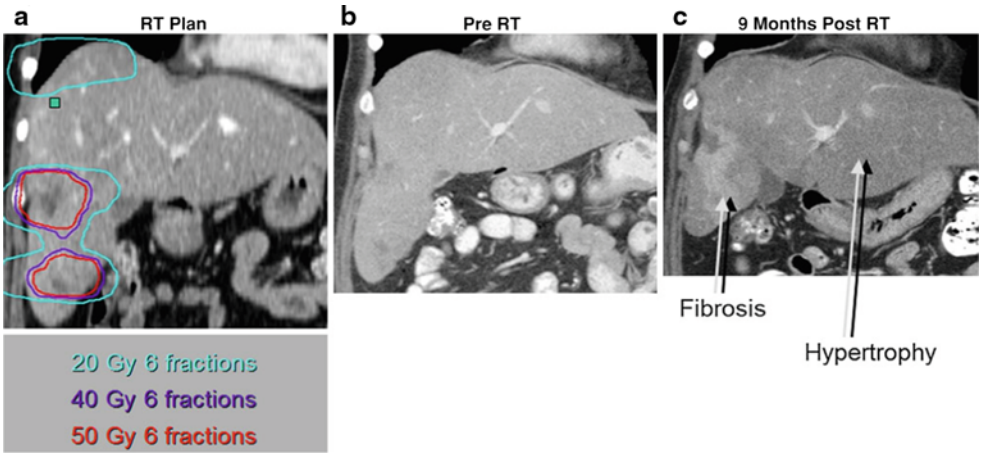

Fig. 7 Coronal views of preradiation therapy CT scans, with **a** and without **b** the radiation dose distribution shown, of a patient with multiple liver metastases, compared to CT 9 months following radiation therapy **c**, with fibrosis occurring in the liver irradiated to high doses and hypertrophy of the spared left lobe

4.3 Diagnosis (Imaging)

Focal changes in irradiated liver were documented on scintillation scanning as early as 1967 (Concannon et al. 1967). Changes in computed tomographic (CT) and MRI contrast enhancement have been seen within regions of the liver irradiated to high doses (Herfarth et al. 2003). Ultimately, the liver volume irradiated to high doses becomes fibrotic while the spared liver hypertrophies, as shown in Fig. 7. The threshold doses for these effects is a topic of ongoing research.

Characterizing RILD by noninvasive imaging has been challenging and the techniques are evolving. The CT findings of RILD were first described in a report of three patients who received partial liver irradiation (Jeffrey et al. 1980). The post-irradiation CTs showed low density of the irradiated portion of liver, sharply demarcated from the liver outside of the radiation ports. On follow-up CT scans between 4 and 14 months after radiation therapy, the low-density band had resolved and liver function was returned to normal unless affected by progression of the primary cancer (Jeffrey et al. 1980).

Unger et al. later described the CT and MR imaging findings of two cases reports of RILD (Unger et al. 1987). This group confirmed the CT findings of low attenuation in the portion of irradiated liver, again sharply demarcated from unirradiated liver. This area of low density could represent increased water or fat content. An MR of the same patients showed decreased signal intensity on T1-weighted images, increased signal intensity on T2-weighted images, and increased signal intensity on proton spectroscopic imaging in the portion of liver corresponding to the low attenuation on CT, indicating that the irradiated liver consisted of increased water content. On follow-up CTs, there was resolution of the low attenuation portion of liver, and shrinkage of the irradiated liver segment (Unger et al. 1987).

As seen above, CT and MR imaging provides anatomical data in RILD. Unger et al. also performed CT angiography on one patient and found that the liver in the radiation ports demonstrated delayed filling of contrast as compared to unirradiated liver, alluding to the outflow congestion pattern found on pathology (Unger et al. 1987). This was the first step toward identifying the perfusion changes of the liver as it relates to RILD.

Noninvasive CT imaging and the estimation of blood flow by the gradient method was first described for the kidney (Peters et al. 1987a, b). The quantification of blood flow was later described in a mathematical model using information obtained from dynamic CT and read on a color scale (Miles 1991; Miles et al. 1991). Although some groups have used the gradient method to measure liver perfusion (Miles et al. 1993; Blomley et al. 1995; Bader et al. 1998), the liver poses a unique challenge given that it has dual vascular input from the hepatic artery and the portal vein. Materne et al. first developed and validated a method to quantify liver perfusion using the "dual-input, one-compartment" model to account for the dual inflow (Materne et al. 2000).

The finding of VOD in RILD implies that the vascular outflow will be altered, namely in a post-hepatic obstruction manner beginning at the level of the central veins and further distally to the hepatic veins. CT perfusion is an imaging technique that can identify and quantify this vascular flow aberrancy (Cao et al. 2008).

MR single-photon emission computerized tomography (SPECT) has been used to measure asialoglycoprotein receptor (ASGPR). ASGPRs are receptors found in abundance on the sinusoidal surface of hepatocytes that mediate the removal of serum glycoproteins, lipoproteins, immunoglobulin A, fibronectin, and apoptotic cells. They, therefore, can serve as a surrogate for hepatic function. Iguchi et al. (2003) have shown that ASGPR SPECT correlates well with liver fibrosis (Hoefs et al. 2006).

Table 3 SOMA grading system for liver injury

Liver				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain RUQ	Occasional and minimal	Intermittent and tolerable	Peristent and intense	Refractory and excruciating
Objective				
Abdominal findings Edema Weight gain Alertness Bleeding	Hepatomegaly Occasional leg edema	Soft ascites Intermittent leg edema ≤5 % Change in attentiveness and sleep pattern	Tense ascites Anasarca responsive to diuretics >5–10 % Confusion Correctable	Anasarca unresponsive to diuretics >10 % Coma Unresponsive
Management				
Pain Abdominal findings Bleeding	Occasional non-narcotic	Regular non-narcotic Intermittent diuretics Iron therapy	Regular narcotic Permanent diuretics Occasional transfusion of fresh frozen plasma	Continuous narcotic Frequent transfusions
Analytic				
AST/ALT/Alk phos	<2.5 × normal	2.5–5.0 × normal	>5.0–20.0 × normal	>20.0 × normal
Bilirubin	<1.5 × normal	1.5–5.0 × normal	>5.0–10.0 × normal	>10.0 × normal
PT/PTT	<1.25 × normal	1.25–1.5 × normal	>1.50–2.0 × normal	>2.0 × normal
Serum alb (gm/dl)[3]	>3.0	>2.5–3.0	>2.0–2.5	≤2.0
Platelets (1,000)	>75.0	>50.0–75.0	>25.0–50.0	≤25.0

5 Radiation Tolerance and Predicting Liver Toxicity

5.1 Clinical Parameters

Pre-existing liver dysfunction makes patients more susceptible to radiation-induced liver injury, as summarized in Table 3. Patients with Child-Pugh B or C scores have a higher risk of radiation-associated liver toxicity than those with Child-Pugh A scores (Liang et al. 2006; Hata et al. 2006; Ten Haken et al. 2006). Additional risk factors include hepatitis B carrier status (Cheng et al. 2004a), prior transarterial chemoembolization (TACE) (Liang et al. 2006), concurrent chemotherapy (Dawson et al. 2002), portal vein tumor thrombosis (Kim et al. 2007; Liang et al. 2006; Seong et al. 2003), tumor stage (Liang et al. 2006), male sex (Dawson et al. 2002), and cancer of the liver Italian program (CLIP) staging system (Liang et al. 2006; Seong et al. 2003, 2007).

As a measure of baseline liver reserve, baseline indocyanine green retention rate at 15 min was investigated and found to correlate with hepatic insufficiency following proton ion therapy for 30 patients with hepatocellular carcinoma (Kawashima et al. 2005). Eight patients developed hepatic insufficiency, presenting as anicteric ascites, elevated transaminases and/or asterixis, 1–4 months following therapy. No hepatic insufficiency was observed if the retention rate was less than 20 %, whereas 3 of 4 patients with retention rates greater than 50 % developed hepatic insufficiency.

The tolerance of the liver to whole organ irradiation does not appear to be substantially altered by the concomitant use of fluoropyrimidines. In contrast, whole liver irradiation in combination with alkylating agents or mitomycin C is associated with an increased risk of liver toxicity (Lawrence et al. 1995; Haddad et al. 1983; Schacter et al. 1986). In one study investigating the partial volume tolerance of the liver to irradiation, the use of concurrent hepatic arterial bromodeoxyuridine (BUdR) chemotherapy increased the risk of RILD compared to concurrent hepatic arterial fluorodeoxyuridine (FUdR) (Dawson et al. 2002).

5.2 Dosimetric Parameters

5.2.1 Whole Liver Tolerance

The classic paper by Ingold et al. published in 1965 is the first report of a dose-complication relationship for whole liver irradiation (Ingold et al. 1965). RILD occurred in 1 of 8 patients who received 30–35 Gy over 3–4 weeks and 12 of 27 patients who received 35 Gy or more to their whole liver. Since then, many clinical series have been published supporting that the whole liver tolerance to radiation of

30–35 Gy in 2 Gy per fraction associated with a 5 % risk of RILD. In 1973, whole liver doses of 2.25 Gy × 8 fractions were reported to be safe, but 3.5 Gy × 8 was associated with a high rate (8/25) of liver toxicity (Wharton et al. 1973; Perez et al. 1978), showing the importance of fraction size. An apparent lower whole liver threshold was seen in patients treated with the 'moving strip technique', where RILD was observed following 22–25 Gy delivered to the whole liver (Schacter et al. 1986). However, there is much uncertainty of the actual doses delivered using the 'moving strip techniques', and the delivered doses were likely higher than the planned whole liver doses. In the 1991 report by Emami et al., the TD 5/5 for whole liver radiation was estimated to be 30 Gy in 2 Gy fractions (Emami et al. 1991).

Hyperfractionation was investigated as a strategy to reduce toxicity, but the tolerance to whole liver irradiation did not improve substantially. In a Radiation Therapy Oncology Group (RTOG 8405) dose escalation study of accelerated hyperfractionation, none of the 122 patients who received 27–30 Gy in 1.5 Gy fractions twice daily to the whole liver experienced RILD, whereas 5 of 51 who received 33 Gy in 1.5 Gy fractions developed RILD (Russell et al. 1993).

Another study (RTOG 7609) investigated whole liver radiation therapy for palliation of 103 patients with liver metastases. The fractionation schedules (and number of patients) were 26 Gy in 16 fractions (n = 38), 30 Gy in 10 (n = 19), 15 (n = 2), or 19 (n = 5) fractions, 20 Gy in 10 fractions (n = 19), or 21 Gy in 7 fractions (n = 18). Although no RILD was reported, the median survival was 11 weeks, and approximately 23 % of patients did not complete their planned treatment. Progressive disease may have masked RILD or led to early death before RILD could manifest, limiting a detailed interpretation of these data. As 17 of the 18 patients treated with 21 Gy in 7 fractions completed treatment as planned, this regimen has been recommended as the fractionation of choice of those studied (Borgelt et al. 1981).

More recent experience has suggested that the whole liver doses associated with a 5 % risk of classic RILD are 32 and 37 Gy in 1.5 Gy twice daily for patients with primary liver cancer and metastases, respectively (Dawson et al. 2002). In 2 Gy per fraction, the mean liver doses estimated to be associated with a 5 % risk of classic RILD for primary and metastatic liver cancer are 28 and 32 Gy.

5.2.2 Partial Liver Tolerance

In 1965, Ingold et al. safely delivered 55 Gy to parts of the liver (Ingold et al. 1965). The first quantitative analysis of RILD as a function of dose and volume was performed by Austin Seymour et al. in 1986. Dosevolume histograms (DVHs) from 11 patients treated with charged particles for pancreatic or biliary cancer (one of whom developed liver toxicity) were reviewed. Patients were treated with a total dose of 52–70 Gy. It was concluded that doses in excess of 35 Gy should be limited to 30 % of the liver when 18 Gy was delivered to the whole liver (equivalent to photon 2 Gy/day).

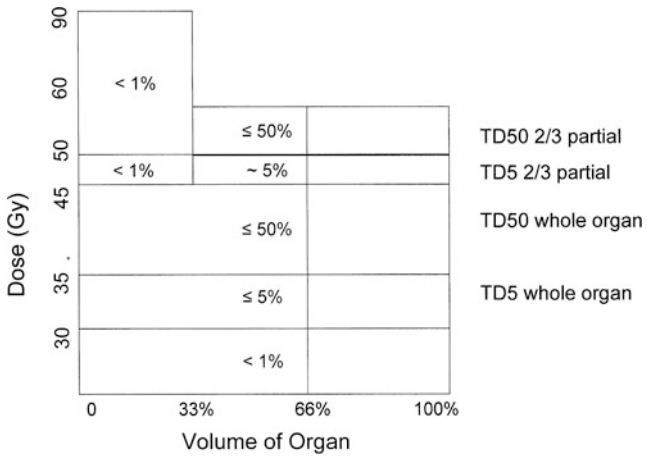

Fig. 8 Dose–volume histogram for liver toxicity, illustrating the relationship between volume and tolerance doses, assuming uniform partial volume irradiation

In 1991, Emami et al. reported estimates of the tolerance doses for 5 % and 50 % risk of liver toxicity (TD 5/5 and TD 50/5 respectively) following uniform liver RT (Emami et al. 1991). For one-third, two-thirds, and the whole liver tolerances, the estimated TD 5/5 were 50 Gy, 35 Gy, and 30 Gy, respectively, (at 1.8–2 Gy/day) and the estimated TD 50/5 were 55, 45, and 40 Gy, respectively (at 1.8–2 Gy/day) (Emami et al. 1991). These estimates were based primarily on clinical judgment from retrospective reports of suspected radiation injury in less than 30 patients, as detailed partial dose and volume data were not generally available at the time of this report.

Since Emami's review, there has been many published reports of patients treated with partial liver irradiation using photons (Cheng et al. 2003; Liang et al. 2006; Ten Haken et al. 2006; Dawson et al. 2002, 2005), protons (Hata et al. 2006; Chiba et al. 2005; Ohara et al. 1997), and hypofractionated stereotactic body radiotherapy (SBRT) (Herfarth et al. 2001, 2004; Uematsu et al. 2000). Clinically significant liver toxicity is not common following focal proton therapy (Hata et al. 2006; Chiba et al. 2005; Ohara et al. 1997) or SBRT (discussed in Sect. 5.4). Figure 8 summarizes the whole and uniform partial volume tolerances of the liver.

The largest series of patients treated with partial liver radiation therapy is from the University of Michigan (Dawson et al. 2002). Dose was prescribed based on the DVH of the normal liver (the effective volume (V_{eff}) of

Table 4 Series of fractionated partial liver irradiation and rates of RILD from Pan et al. (2008), with permission

Study group	N	Diagnosis	Baseline Child-Pugh score	Prescription dose fractionation	Crude percent RILD	Mean normal liver dose in patients with versus without RILD	Factors associated with RILD
Michigan (Dawson et al. 2002; Dawson and Ten Haken 2005)	203[a]	PLC + LMC	203 A	1.5 Gy bid	9.4 % (19/203)	37 Gy versus 31.3 Gy	PLC versus LMC Mean liver dose
Taipei (Cheng et al. 2004b)	89[b]	HCC	68 A 21 B	1.8–3.0 Gy	19 % (17/89)	23 Gy versus 19 Gy	HBV, liver cirrhosis
Shanghai (Xu et al. 2006; Liang et al. 2006)	109[b]	PLC	93 A 16 B	4–6 Gy	15.6 % (17/109)	24.9 Gy versus 19.9 Gy	Liver cirrhosis
Guangdong (Wu et al. 2004)	94 [b]	HCC	43 A 51 B	4–8 Gy	17 % (16/94) Note: 4 fatal	Not stated	Liver cirrhosis
S Korea (Seong, Park) (Park et al. 2002; Seong et al. 2003)	158[b]	HCC	117 A 41 B	1.8 Gy	7 % (11/158)	Not stated	Dose
S Korea (Kim) (Kim et al. 2007)	105[b]	HCC	85 A 20 B	2.0 Gy	12.3 % (13/105)	25.4 Gy versus 19.1 Gy	Total liver volume receiving 30 Gy or more above 60 %

[a] Patients also received FUdR or BUdR; in this series, the mean normal liver dose was calculated as corrected for 1.5 Gy bid equivalent dose, and the comparison of patients with versus without RILD refers to the median value of mean normal liver dose, whereas for other series the comparison is between the average (mean) of mean normal liver dose in each group

[b] At least 77 % of patients in these series also received trans-arterial chemoembolization (TACE)

HCC hepatocellular carcinoma; *PLC* primary liver cancer; *HBV* hepatitis B viral infection

normal liver irradiated) and patients were prospectively followed for RILD (Ten Haken et al. 1993). The 203 patients with primary and metastatic liver cancer were treated with 3D conformal radiation therapy delivered concurrently with hepatic arterial chemotherapy (FUdR or BUdR). All patients had Child-Pugh A liver scores. This experience demonstrated that small portions of the liver can be irradiated to very high doses (up to 90 Gy in 1.5 Gy twice daily), and that mean liver dose is strongly associated with risk of RILD (as discussed in Sect. 5.2.3.2).

Cheng et al. reported on liver toxicity that developed in 17 of 89 patients with hepatocellular carcinoma treated with focal photon RT and TACE (Cheng et al. 2005). The majority of these patients had a diagnosis of hepatitis B (73 %) and hepatitis C (21 %), and 24 % had Child-Pugh B scores at baseline. The majority of the complications were non-classic RILD (elevated serum transaminases, 15 patients) versus classic RILD (2 patients). Multivariate analysis revealed that hepatitis B virus and Child-Pugh liver score were independently associated with increased risk of liver toxicity. In all patient subgroups, the tolerance of the liver to radiation was lower than that reported from the University of Michigan, perhaps due to the sequential use of TACE which may have decreased the liver reserve and the patient population which included patients with hepatitis B and poor liver function (Child-Pugh B).

Table 4 includes series in which toxicity has been described and quantified after partial liver irradiation. In most, the key factor predicting RILD was the baseline condition of the liver, but dosimetric parameters (e.g. mean liver dose and volume receiving 30 Gy or more (V30)) were also associated with increased toxicity risk. In each series, where mean normal liver dose was reported for patients with or without RILD, the mean dose for patients with RILD was higher (Pan et al. 2008). V30 has been studied mostly in hepatocellular carcinoma patients, with both classic and nonclassic RILD endpoints combined. V30 segregates higher risk patients from lower risk patients in some studies at cutoff levels of 28–60 % (Kim et al. 2007; Liang et al. 2006; Yamada et al. 2003); however, the effect of V30 is not uniformly observed (Cheng et al. 2002). Other studies suggest the importance of V20–V40 (Kim et al. 2007) and V5–V40 (Liang et al. 2006), but only for Child-Pugh A patients in the latter study.

5.2.3 Normal Tissue Complication Probability Models

5.2.3.1 Lyman NTCP Model

The Lyman normal tissue complication probability (NTCP) model has been used to describe the volume dependence of RT normal tissue toxicity (Lyman 1985). It assumes a

sigmoid relationship between the dose of uniform radiation given to a volume of an organ and the chance of a complication occurring. The Lyman model uses three parameters: $TD_{50}(1)$, the whole liver dose associated with a 50 % probability of toxicity, 'm', characterizing the steepness of the dose–response at $TD_{50}(1)$, and 'n', a volume effect parameter which indicates a larger volume effect as it increases (range 0–1). The Lyman NTCP model was first applied to clinical data in 1991 by Burman et al. (1991), who used the estimated partial liver tolerances by Emami et al. to calculate the Lyman model parameters. The value of $TD_{50}(1)$, 'm', and 'n' were 45 Gy, 0.15, and 0.32, respectively.

In 1992, Lawrence et al. analyzed the DVHs of 79 patients with hepatic malignancies (9 with RILD) using the Lyman NTCP model with the KB Veff DVH reduction scheme (Lawrence et al. 1992). The $TD_{50}(1)$ and 'm' parameters were similar to the previous estimates; however, a larger volume effect parameter ($n = 0.69$) was found. More recently, data from 204 patients (19 with classic RILD) were evaluated using the Lyman model (Dawson et al. 2002). The volume effect parameter was again higher than previously estimated, with a value of 0.97.

In addition to dosimetric factors, the influence of clinical and demographic factors on the development of classic RILD in these 203 patients were investigated using a multivariate analysis (Dawson et al. 2002). Mean liver dose ($p < 0.0001$), primary hepatobiliary carcinoma diagnosis ($p = 0.005$), BUdR chemotherapy ($p < 0.0001$), and male sex (0.002) were statistically significant factors associated with RILD. Lyman NTCP model parameters were then fit for subgroups that were predicted to have different risks of RILD. In 169 patients treated with FUdR, 'n' and 'm' were fit to the entire group, but $TD_{50}(1)$ was separately fit for patients with primary liver cancer ($TD_{50}(1)_{HB}$) (n = 84) and liver metastases ($TD_{50}(1)_{LM}$) ($n = 85$). The parameters and 95 % CI's were as follows: 'n': 0.97 (0.69, 2.3), 'm': 0.12 (0.07, 0.25), and $TD_{50}(1)_{HB}$: 39.8 Gy (38.8, 41.1) and $TD_{50}(1)_{LM}$: 45.8 Gy (43.4, 50.4), ($D = 66.0$, $p > 0.99$), indicating a higher tolerance of the liver to radiation for patients with liver metastases compared to primary hepatobiliary malignancies and a strong correlation of RILD risk with the mean liver dose. The tolerance doses for one-third and two-thirds uniform partial liver irradiation associated with a 5 % risk of RILD are >100 and 54 Gy, respectively, for metastases, and 93 and 47 Gy, respectively, for primary liver cancer (in 1.5 Gy bid) (Dawson et al. 2002).

The Lyman NTCP model has also been used to estimate partial liver tolerance to irradiation in patients with hepatocellular caricinoma irradiated in Asia. In the Taiwanese (Cheng et al. 2003) and Chinese (Liang et al. 2006; Ten Haken et al. 2006) series (including mostly hepatitis B patients), the tolerance of the liver to radiation was less predictable. The most common toxicity was elevation of transaminases rather than classic RILD. In the Taiwanese series of RILD (15 nonclassic, 2 classic) in 17 of 89 patients with hepatocellular carcinoma treated with focal photon RT and TACE (Cheng et al. 2005), 'n' was low ($n = 0.26$) in patients with hepatitis B, and closer to 1 ($n = 0.86$) in nonhepatitis B patients. The tolerance of the liver to radiation was lower than that reported from the University of Michigan. In other Asian studies, both classic and nonclassic RILD were also included as toxicity endpoints. The range of estimates of the parameters generated among patients with Child-Pugh A or better liver function and no hepatitis B virus (HBV) infection are as follows: n, 0.86–1.1; m, 0.12–0.31; and TD_{50}, 39.8–46.1 Gy. For patients with HBV or Child-Pugh B liver dysfunction, the ranges are as follows: n, 0.26–0.7, m, 0.4–0.43, and TD_{50}, 23–50 Gy, demonstrating a lower tolerance to irradiation in these patients. In some of these series, larger fraction sizes were used, which may have also contributed to the differences in TD_{50} values between these series and the Michigan experience (Ten Haken et al. 2006).

5.2.3.2 Mean Liver Dose Model

An 'n' of 1 in the Lyman NTCP model suggests a large volume effect and a strong correlation of NTCP with mean liver dose. For patients studied in the University of Michigan experience, beyond a threshold mean liver dose of 30 Gy (below which no patient developed RILD), Lyman NTCP increased by approximately 4 % per Gy increase in mean dose. The mean liver dose associated with a 5 % risk of RILD for patients with metastatic and primary liver cancer are 37 and 32 Gy, respectively, in 1.5 Gy per fraction, and 32 and 28 Gy in 2 Gy per fraction, respectively, (assuming an α/β of 2 for the liver) (Fig. 9). The risk of classic RILD associated with different mean liver doses can be estimated by correcting for differences in dose per fraction.

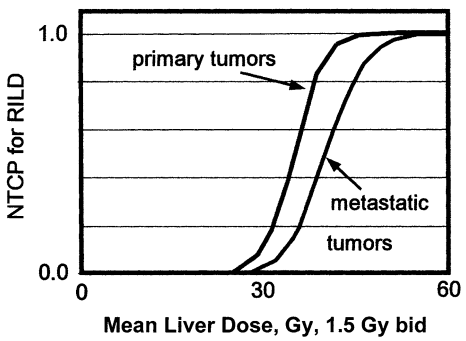

Fig. 9 Mean liver dose, corrected with LQ modeling for 1.5Gy per fraction, versus Lyman normal tissue complication probability (NTCP) of radiation-induced liver disease (RILD) for primary and metastatic liver cancer, redrawn from Dawson and Ten Haken (2005) with permission

5.2.3.3 Local Damage: Organ Injury NTCP Model

As the Lyman model is simply a sigmoid dose–response function, efforts have been made to develop models that will accommodate biological data when they are available. These "damage-injury" (D-I) models try to use statistical principles to derive the RT tolerance of an organ from dose–response characteristics of individual functional subunits. These models are most appropriate for organs with parallel architecture, such as the liver, where it is assumed that the organ functions (sustains damage) until a critical fraction of the organ becomes incapacitated (and injury occurs).

In 1995, Jackson et al. analyzed an extension of the University of Michigan's original dataset using a D-I NTCP model (Jackson et al. 1995). The model fits the data from 95 patients well; however, uncertainties in the functional reserve distribution and subunit radiosensitivity were highly correlated. The D-I model parameters were as follows: D_{50} (the dose associated with a 50 % probability of voxel or subvoxel damage) = 42 Gy; k (describing the steepness of the "local damage" function) = 1.95; F_{50} (the fraction of the total organ incapacitated which would produce a 50 % complication rate) = 0.497; and σ_v (describing the steepness of the "organ" response function) = 0.05. The partial liver volume threshold, below which the complication risk becomes near zero for all doses, was 0.4.

Data from more patients (203) were subsequently fit using the D-I NTCP model (Dawson and Ten Haken 2005), and the most substantial differences were in the F_{50} and σ_v parameters ($F_{50} = 0.4$, $\sigma_v = 0.08$), suggesting a lower threshold and a shallower slope for population cumulative functional reserve than previously estimated, predicting more complications for a lower fractional damage (Dawson et al. 2005). The revised RT volume threshold for complications was 0.25. Of note, the 68 % confidence intervals for the D-I NTCP model parameters are very large, and thus much more clinical data is required to validate the D-I NTCP model parameters. Nonetheless, such a model motivates the search for functional imaging that will measure functional subunit tolerance to irradiation.

In another analysis from the Taiwan group of patients with hepatocellular carcinoma and gastric cancer, valid fits were only obtained for the nonHBV carriers with local damage parameters of $D_{50} = 25$ Gy, $k = 60$; and fraction of liver injury required for RILD parameters of $F_{50} = 0.59$, $\sigma = 0.12$(Cheng et al. 2005).

5.2.3.4 Sensitivity of NTCP models

The largest uncertainty in NTCP model parameters is likely due to the model fitting, and relatively small number of events (i.e. complications), compared to the 3 or 4 parameters required to be fit. As values for some parameters can be measured or estimated with better certainty, the uncertainty of other NTCP model parameters will decrease and the utility of NTCP models will increase. Other geometric and dosimetric uncertainties can also impact the confidence intervals of NTCP parameter estimates.

The liver is relatively easy to identify on simulation CT scans. The magnitude of the errors introduced by including the biliary duct system and hepatic vasculature in the "liver volume" is unclear, though probably minimal, as most series likely contoured the liver in a similar manner. Of note, the liver minus the gross tumor volume was used for the Michigan analysis and most others. NTCP values may differ if another liver volume is used for analysis of NTCP.

Liver motion due to breathing has been shown to alter the delivered radiation doses. The technique used to deliver irradiation also influences the uncertainty in delivered doses with larger uncertainties, with older techniques such as the moving strip technique, and also with more modern techniques of intensity modulated radiation therapy in the absence of image guidance.

Changes in dose per fraction may also alter NTCP model parameters, compared to the fractionation in which they were obtained.

5.3 Intensity Modulated Radiation Therapy

Few papers on liver tolerance have focused on intensity modulated radiation therapy (IMRT), and the effects of different spatial dose distributions are not well established. IMRT lead to a low dose 'bath' delivered to a larger volume compared with simpler plans which usually completely spare RT to a portion of the liver. This bath of low dose may impact the partial tolerance of the liver to RT, and it may reduce the possibility for a compensatory increase in function. For the same mean dose to the liver, a bath of low dose to a larger volume has been hypothesized to be associated with a higher risk of RILD compared to higher doses delivered to a smaller volume, based on an analysis of the Michigan data using principal component analysis (Dawson et al. 2005).

5.4 Stereotactic Body Radiation Therapy

RILD is uncommon following SBRT for liver metastases, but has occasionally been reported (Blomgren et al. 1995; Hoyer et al. 2006; Mendez et al. 2006). In order to keep the risk of liver toxicity low, a substantial volume of liver must be spared from irradiation. This can be done by keeping the dose to 700 cc of uninvolved liver less than 15 Gy in three fractions (Kavanagh et al. 2006) or ensuring that no more than 50 % of the liver receives 15 Gy in 3 fractions (or 7 Gy in one fraction), and no more than 30 % of the liver receives 21 Gy in 3 fractions (or 12 Gy in one fraction) (Herfarth et al. 2004).

Mendez-Romero et al. observed 1 classic and 1 non-classic case of RILD among 8 patients with hepatocellular carcinoma (HCC) treated on a trial of SBRT for liver tumors; another patient with baseline Child-Pugh B liver dysfunction and HCC experienced portal hypertension and concomitant nonhepatic infection and died 2 weeks after treatment. No grade 4 or 5 toxicity occurred among the 17 patients with liver metastases treated on the trial, consistent with the finding that hepatocellular carcinoma patients are more susceptible to liver toxicity (Mendez et al. 2006). In a phase II study involving 61 patients treated with 3 fraction SBRT for colorectal metastases, Hoyer et al. observed liver toxicity in 1 patient following SBRT. In this case, 60 % of the liver received 10 Gy or higher, with a median dose of 14.4 Gy. This patient died of hepatic failure 7 weeks after treatment, but the authors could not prove that the cause was radiation-induced liver toxicity (Hoyer et al. 2006). In a Princess Margaret Hospital study of patients treated with 6 fraction SBRT for hepatocellular caricnoma or intrahepatic cholangiocarcinoma, 17 % patients experienced progression from Child-Pugh A to B within 3 months after treatment (Tse et al. 2008), although this was more common in patients irradiated to low doses, with intrahepatic cancer progression.

In the University of Colorado trial of SBRT for liver metastases, a modification of a critical volume model (Yaes and Kalend 1988) was applied to attempt to avoid liver toxicity. A minimum "critical volume" required to be spared from radiation therapy was estimated from surgical series to be 700 cc. The maximum dose allowed to the critical volume was 15 Gy in 3 fractions (Schefter et al. 2005). No RILD or other severe toxicity has been observed after SBRT for 18 patients with liver metastases (Schefter et al. 2005). The median mean liver dose (to liver minus the tumor volume) in patients treated was 15.3 Gy (3.3–23.9 Gy), in 3 fractions. Figure 10 displays the mean DVH from the first 18 patients treated with SBRT in Colorado, without toxicity.

A potential concern related to the use of high dose per fraction treatment is the observation of extrahepatic portal vein occlusion following high-dose intraoperative radiation therapy (IORT). Mitsunaga and colleagues observed this in 12 of 53 patients who underwent pancreaticoduodenectomy for periampullary disease followed by 20 Gy IORT to the resection bed (Anscher et al. 1993).

5.5 Compensatory Response

Following partial liver irradiation, shrinkage of the high-dose irradiated volume is seen on follow-up CT and MR imaging. A compensatory increase in liver volume in the unirradiated regions is also commonly seen, as shown in Fig. 7 (Herfarth et al. 2003; Ohara et al. 1997).

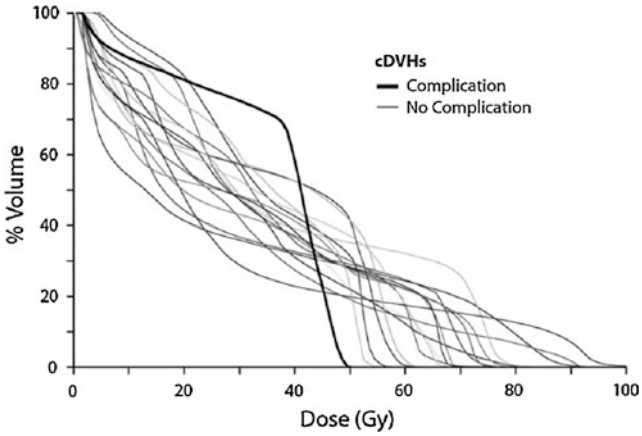

Fig. 10 All cumulative partial liver (minus GTV) cumulative dose–volume histograms (cDVHs) with Lyman NTCP of 1%. The cDVH associated with complication is shown in bold. This cDVH had a larger dose to a smaller volume, compared to the other cDVHs with a larger volume treated to a higher dose, from Dawson et al. (2005), with permission

5.6 Recommended Dose/Volume Constraints

Recommendations for dose/volume constraints are outlined in Table 5. These dose/volume recommendations are associated with some uncertainty and they will vary depending on the technique used, concurrent therapies, and patient population investigated.

6 Chemotherapy

Many chemotherapy agents have the potential for producing liver damage. Determining the cause of abnormal liver function tests developing during chemotherapy can be complex and may relate to pre-existing liver dysfunction, reactivation of a dormant virus, or directly related to hepatic toxic drugs. The cause of liver toxicity in patients with liver metastases or liver cancer can also be challenging, as progressive disease or systemic symptoms of metastatic disease, such as nutritional deficiencies, may be responsible. Therefore, baseline evaluation of patients' prechemotherapy should include liver function tests and typically a CT scan or ultrasound (U/S) which are usually done as part of staging. This assessment of liver function before chemotherapy aids in the choice of drug and dose. Repeat evaluation of liver function during therapy can detect the evolution of hepatic dysfunction and help determine if progressive disease is partially responsible. These tests can also help determine the need for dose modification during treatment.

The following overview outlines the different patterns of liver toxicity and their manifestations. Table 6 outlines some of the most common chemotherapy-related liver toxicities. For a more extensive review, we refer the reader

Table 5 Suggested dose–volume constraints, from (Pan et al. 2008) and Quantec

Palliative whole liver doses for 5 % or less risk of RILD
Liver metastases
≤30 Gy, in 2 Gy per fraction
21 Gy in 7 fractions (Borgelt et al. 1981)
Primary liver cancers
≤28 Gy, in 2 Gy per fraction
21 Gy in 7 fractions (Abrams et al. 1997)
Therapeutic partial liver radiotherapy (standard fractionation)
Mean normal liver dose (liver minus GTV)
<28 Gy in 2 Gy fractions for primary liver cancer
<32 Gy in 2 Gy fractions for liver metastases
Nonuniform liver recommendations (SBRT, 3–6 fractions)
Mean normal liver dose (liver minus GTV)
<13–20 Gy for primary liver cancer
<15–22 Gy for liver metastases
Critical volume model-based
≥700 cc of normal liver receives ≤ 15 Gy in 3–5 fractions (Schefter et al. 2005)

to references focusing on chemotherapy-related toxicities (Davila and Bresalier 2008; King and Perry 2001).

6.1 Mechanisms of Toxicity

- *Toxic hepatitis*. This form of hepatic injury is usually due to a direct effect of either the parent drug or a metabolite and the pattern of injury is predictable. It typically manifests as elevations of hepatic enzymes preceding increases in total bilirubin as cellular damage occurs. As the toxic effect progresses, fatty infiltration and cholestasis may occur with severe toxicity resulting in hepatocellular necrosis.
- *Idiosyncratic reactions*. Most toxicity is idiosyncratic and thought to be due to host response and possibly immunologic mechanisms. This form of toxicity is unpredictable, not dose-dependent, and can occur with nearly every drug in clinical use. There is no relationship between the drug dose and the occurrence of the drug reaction. Rechallenge with the offending agent is not recommended as there is usually a recurrence of symptoms, particularly if the reaction was immunologically based.

6.2 Patterns of Drug-Induced Liver Injury

Acute drug-induced liver may present as hepatocellular damage, cholestasis, fibrosis, or steatosis. The presentations range from asymptomatic, mild biochemical abnormalities to an acute illness with jaundice that resembles viral hepatitis to acute liver failure. Withdrawal of the offending drug usually leads to reversal of the injury. However, some types of toxicity can be associated with a progressive course, possibly leading to fibrosis or cirrhosis, despite discontinuation of the drug. Other drugs can cause endothelial damage or thrombosis leading to vascular complications such as sinusoidal obstructive syndrome (SOS).

- *Hepatitis*. Drug-induced acute hepatocellular injury is similar to that seen in viral hepatitis and includes hepatocellular necrosis, steatosis, and cellular degeneration. A characteristic finding on laboratory testing is an elevation in serum aminotransferases. Acute hepatocellular injury is associated with a mortality rate of up to 10 % overall and up to 80 % or higher if acute liver failure develops (Ostapowicz et al. 2002; Speeg and Bay 1995). A serum bilirubin >3 times the upper limit of normal is the best predictor of mortality in the setting of acute hepatocellular injury (Bjornsson 2006).
- *Cholestasis*. Cholestatic reactions are typically associated with elevated alkaline phosphatase and bilirubin levels with a lower rise in aminotransferases. Gemcitabine, a fluorine analogue, has broad antitumor activity and is used in the treatment of a variety of cancers. It frequently causes transient, reversible elevations in transaminases although there are reports of fatal cholestatic hepatotoxicity (Coeman et al. 2000; Robinson et al. 2003). Pre-existing liver metastases and/or bilirubin level higher than 1.6 mg/dL at treatment onset are risk factors for developing liver failure (Rodriguez-Frias and Lee 2007; Sessa et al. 1994).
- *Steatosis/steatohepatitis*. Nonalcoholic fatty liver disease ranges in severity from nonprogressive steatosis to steatohepatitis, characterized by inflammation and hepatocyte injury that can progress to cirrhosis and fibrosis. Although a causative association is unproven, radiographic evidence of steatosis is seen in 30–47 % of patients treated with fluorouracil (Zorzi et al. 2007). The association between irinotecan and steatohepatitis has been confirmed in a number of studies (Zorzi et al. 2007; Vauthey et al. 2006; Pawlik et al. 2007). This has important implications particularly when these agents are given in the neoadjuvant setting prior to resection for hepatic metastases related to colorectal cancer. Steatohepatitis is a contraindication to major liver resection and irinotecan should be avoided in patients with known steatosis or steatohepatitis in whom major hepatic resection is planned. To prevent adverse outcomes from chemotherapy-associated liver injury, extended preoperative chemotherapy should be avoided and several studies indicate that a longer interval between chemotherapy and hepatic resection reduces hepatotoxicity and surgical

Table 6 Summary of chemotherapy-associated liver toxicities

Agents	Toxicity	Frequency	Comments
Nitrogen mustards			
Chlorambucil	Fibrosis and cirrhosis	Rare	Severe damage reported
Cyclophosphamide	VOD in high doses or transplantation	10–25 % of BMT patients	Severe and life threatening
Ifosfamide	↑ Transaminases and bilirubin	Uncommon	Dose reduce with significant dysfunction
Melphalan	VOD, hepatitis, and jaundice ↑ Transaminases	VOD 10–25 % of BMT patients. Common at high doses	May be severe Usually transient
Nitrosoureas			
Carmustine	↑ Transaminases, ALP, and bilirubin	20–25 % of patients	Usually mild and reversible
Lomustine	↑ Transaminases, ALP, and bilirubin	Common	Usually mild and reversible
Streptozocin	Raised LFTs	Common (15–67 % of patients)	Usually asymptomatic and reversible
Platinum agents			
Carboplatin	↑ ALP, transaminases	Common	Transient
Cisplatin	↑ Transaminases Steatosis and cholestasis	Common at high doses Rare	Transient
Oxaliplatin	↑ Transaminases and bilirubin Sinusoidal obstruction syndrome and perisinusoidal fibrosis	Common Rare. Usually with combination therapy	SOS may increase morbidity after liver resection
Other alkylating agents			
Dacarbazine	Hepatic vein occlusion	Rare	Usually with combination chemotherapy
Busulfan	VOD in high doses Cholestatic hepatitis	Common in BMT (10–25 %) Rare	Prior XRT, chemotherapy, and stem cell transplant increase the risk of VOD
Folate analog			
Methotrexate	Cirrhosis and portal fibrosis ↑ Transaminases	More common with chronic use More common with high dose	Potentially irreversible Transient
Antimetabolites			
Fludarabine	Abnormal LFTs, liver failure	Rare	
Mercaptopurine	Intrahepatic cholestasis and focal centrilobular necrosis ↑ Transaminases, ALP, and bilirubin	Common at doses > 2.5 mg/kg/day	Dose reduce in patients with hepatic dysfunction
Capecitabine	Hyperbilirubinemia Hepatic failure, hepatic fibrosis, and hepatitis	Common—up to 25 % of patients Rare	
Cytarabine	↑ Transaminases (acute) VOD Hyperbilirubinemia, liver abscess, liver damage, and necrotizing colitis	Common Uncommon Rare	Reversible With high doses
Gemcitabine	↑ Transaminases Cholestatic hepatotoxic reactions	Common (up to 60 %) Rare	Usually transient and reversible Can be fatal
Antitumor antibiotics			
Bleomycin	Hepatotoxicity	Rare	
Doxorubicin	↑ Transaminases and bilirubin	Rare	Toxicity increased with hepatic dysfunction
Epirubicin	↑ Transaminases	Rare	Dose ↓ with mild/moderate hepatic dysfxn
Mitoxantrone	↑ ALP, transaminases, and γGT	> 10 %	Dose decrease with hepatic dysfunction
Dacarbazine	Fulminant hepatic failure	Rare	Can be life threatening

(continued)

Table 6 (continued)

Agents	Toxicity	Frequency	Comments
Other agents			
Etoposide	VOD in high doses Hepatitis	10–25 % of BMT patients Rare	Severe
Docetaxel	↑ Transaminases, bilirubin, and ALP	≥ 10 %	dose decrease in pts with hepatic dysfunction
Paclitaxel	↑ Transaminases, bilirubin, and ALP	≤37 % patients with high doses	Dose ↓ in patients with hepatic dysfunction
Vinorelbine	↑Transaminases and bilirubin	Common	Dose ↓ in patients with hepatic dysfunction
Irinotecan	Steatosis and steatohepatitis ↑Transaminases and bilirubin	Up to 50 % patients Up to 25 % patients	May ↑morbidity after liver resection Usually reversible
Topotecan	↑Transaminases and ALP	Uncommon	Reversible

VOD veno-occlusive disease, *BMT* bone marrow transplant, *ALP* alkaline phosphatase, *LFTs* liver function tests, *XRT* radiation therapy, *γGT* gamma glutamyltransferase

complications for patients with colorectal liver metastases (Kopetz and Vauthey 2008; Welsh et al. 2007). Tamoxifen, a selective estrogen receptor modulator, used in the treatment of estrogen receptor-positive breast cancer is associated with steatosis, reported in up to 30 % of cases and is associated with a two-fold increased risk of developing steatohepatitis, especially in overweight women (Bruno et al. 2005; Ogawa et al. 1998).

- *Sinusoidal obstruction syndrome* (*SOS*). Sinusoidal Obstruction Syndrome (SOS), described in Sect. 3.3.2, results from blockage of venous outflow in the small centrilobular and sublobular hepatic vessels and manifests clinically as marked elevations in serum enzymes and bilirubin, ascites, painful hepatomegaly, and weight gain from fluid retention. Hepatic SOS is one of the most serious and life-threatening toxicities of hematopoietic stem cell transplantation, with the highest risk in patients treated with high-dose cyclophosphamide with or without busulfan. The frequency of SOS after allogeneic transplantation varies, but is estimated to be 10–25 %. Pre-existing liver disease or previous liver irradiation might increase susceptibility and the radiation dose has been suggested to increase the risk of SOS, although it also occurs frequently without radiation therapy conditioning. Treatment is mainly supportive. Sinusoidal injury has been reported with oxaliplatin, with an incidence of 19–52 % in patients receiving preoperative oxaliplatin for colorectal liver metastases, although this does not appear to be associated with increased morbidity or mortality (Vauthey et al. 2006; Pawlik et al. 2007; Klinger et al. 2009).
- *Viral hepatitis*. Similar to irradiation, hepatic toxic drugs can cause reactivation of hepatitis B virus, possibly due to an increase in viral synthesis when the patient is immunosuppressed, followed by a rebound in the host immune response to infection when therapy is discontinued. Risk factors for hepatitis B reactivation include detectable hepatitis B virus DNA prior to chemotherapy, male sex, and use of steroids. This toxicity may occur with many chemotherapy regimens, including low-dose methotrexate. Prophylactic antiviral therapy (Lamivudine) appears to reduce the risk of reactivation. There is a less clear relationship between chemotherapy and hepatitis C reactivation. However, the presence of hepatitis C virus prior to chemotherapy does increase the risk of liver toxicity, likely due to the impaired liver reserve. No prophylaxis is established for Hepatitis C.

6.3 Targeted Molecular Agents

Monoclonal antibodies and tyrosine and nontyrosine kinase inhibitors are increasingly being utilized in the treatment of cancer. The common agents in use and their associations with hepatotoxicity are listed in Table 7 (Carlini et al. 2006; Ho et al. 2005; Saif 2008).

7 Special Topics

7.1 Pediatrics

There is no literature suggesting that the tolerance of the pediatric liver is less to radiation, despite the fact that many pediatric protocols recommend far lower doses to be delivered to the liver than in adult populations. This is partially due to the fact that many treatment strategies in pediatrics consist of combined chemotherapy and radiation therapy either in combination or in sequence, and that there are less studies of the tolerance of the pediatric liver to radiation, specifically the partial pediatric liver tolerance.

Table 7 Summary of molecular targeted agents and associated liver toxicities

Agents	Toxicity	Frequency	Comments
Gefitinib	Increased transaminases, ALP	Uncommon	Usually reversible
Erlotinib	Increased transaminases	1–10 %	Usually reversible
Sorafenib	↑ Transaminases, bilirubin	Uncommon	Not studied in severe hepatic dysfxn
Sunitinib	↑ Transaminases, ALP, and bilrubin	Common	Transient
Temsirolimus	↑ Transaminases, ALP	Common	avoid in severe hepatic dysfunction
Lapatinib	↑ Transaminases and bilirubin	Rare	May be severe
Imatinib	↑ Transaminases, ALP, and bilirubin Hepatic necrosis	Uncommon Rare	Usually after 1–3 months

Doses of 5–10 Gy in one fraction and 15–25 Gy over 2 weeks have been delivered to pediatric patients with hepatic hemangiomas, without development of RILD or other liver toxicities (Order and Donaldson 2003).

7.2 Radioisotope Therapy

Hepatic radiation injury due to interval deposits of radionuclides was first recognized with the use of thorium dioxide (Thorotrast), an alpha emitter used in the 1950s as a contrast medium for radiography of the liver, speen, and blood vessels in the 1940s. The mechanism is ingestion by Kupfer cells. Since $Thorium^{232}$ has a long half-life (1.4×10^{10} years), its persistent deposition decades later, can result in neoplastic transformation of the liver i.e. cholangiosarcomas, and hepatomas, cirrhosis (Rubin and Levitt 1964), and peliosis hepatitis, characterized by blood-filled cavities throughout the liver (Jirtle et al. 1990), hypothesized result from endothelial sinusoidal injury (Gushiken 2000) or hepatocyte necrosis.

The Therapeutic use of Au^{198} as a radiogold colloid was first utilized by Rubin in treating disseminated reticular endothelial cell neoplasm, prior to effective chemotherapy for Non-Hodgkin's Lymphoma. The rationale was when lymphomas infiltrate the liver, the cellular infiltrates diffuse and radiogold would be deposited in a parallel diffuse fashion in Kupfer cells of the liver. Patient treated had extreme hepatomegaly, splenomegaly, and bone marrow infiltration. He was hospitalized for bone marrow aplasia and recovered. The patient survived for decades. Kaplan subsequently developed a protocol to treat Stage III/IV Hodgkin's if the spleen was involved with disease, post splenectomy (Rubin and Levitt 1964), radiogold was administered intravenously to selectively eradicate microdeposits of Hodgkin's disease infiltrates (Rubin and Levitt 1964).

Since then, hepatic arterial delivery of radioisotopes (Welsh et al. 2006; Gray et al. 2001; Stubbs et al. 2001; Kennedy et al. 2006; Tian et al. 1996) has been used more extensively to treat primary and metastatic liver cancers. A variety of radioisotopes have been investigated, but Yttrium-90 (Y^{90}), tagged glass, or resin microspheres is what is commercially available and most commonly used. Y^{90} has an effective pathlength of 5.3 mm (i.e. 90 % of the energy is deposited within a 5.3 mm radius of the microsphere). A typical prescribed dose is 120–150 Gy, where the microspheres (and dose) are primarily deposited at the periphery of the tumor (Kennedy et al. 2004).

Classic and nonclassic liver toxicity have been observed following Y^{90} microsphere therapy, but they are not common, despite delivery of very high focal liver doses (Neff et al. 2008). The safe delivery of high dose Y^{90} to small volumes appear consistent with the partial volume estimates from conformal radiation and SBRT series, as the estimated effective liver volume irradiated following Y^{90} microsphere therapy, is small (<20 %), due to rapid dose fall off of dose around each microsphere.

In a review of toxicities in 121 patients treated with hepatic arterial Y^{90}, liver toxicity was the most common toxicity, seen in 14 patients. At baseline, portal vein thrombosis was present in 25 % of patients, ascites in 19, and 20 % of patients had a Child-Pugh score of B. Risk factors associated with 90 day mortality, a surrogate for serious acute toxicity, were evaluated. Seven variables were studied, including five liver reserve variables (infiltrative tumor, tumor volume greater than 70 % of liver, tumor volume greater than 50 % of liver and albumin ≤3 g/dL, bilirubin ≥2 mg/dL, AST/ALT ≥5 times upper limit of normal) and 2 nonliver reserve variables (lung dose >30 Gy, non HCC diagnosis). Ninety day mortality was 49 % in 33 'high risk' patients with at least one adverse variable and 7 % in 88 'low risk' patients with no adverse variables. Eleven of the 12 fatal treatment related toxicities were in the 'high risk' group, which predominantly included patients with poor underlying liver function (Goin et al. 2005). In the 99 'low risk' patients, the most frequent toxicities were ascites, elevated bilirubin, and elevated transaminases, which were mostly transient. Elevated pretreatment bilirubin level and radiation dose were significantly associated liver toxicity in the 'low risk' patients ($p = 0.001$ and $p = 0.08$ respectively). Furthermore, shorter time between treatments in 23 patients who had two or more Y^{90} courses was

associated with an increased risk of liver toxicity ($p = 0.05$) (Goin et al. 2005). The lack of a validated dose distribution in Y^{90} treatment makes partial liver tolerance analysis challenging for Y^{90} therapy.

Intravenous radiolabeled monoclonal antibodies, antibody fragments, and low molecular weight peptides, can also cause liver toxicity, if radioisotopes deposit dose locally within the liver. Liver toxicity is usually not dose limiting, and the risk depends on the chemical and physical characteristics of the molecule and its clearance pathways.

7.3 Brachytherapy

Brachytherapy (percutaneous or at laparotomy) is a less common strategy to deliver radiation to liver cancers (Thomas et al. 1993; Donath et al. 1990; Ricke et al. 2004). Brachytherapy with applicators placed at laparotomy has not been associated with liver toxicity. Serious toxicity has been reported following percutaneous brachytherapy. In a phase II study of percutaneous Iridium-192 in 20 patients with liver cancer (19 metastases, 1 cholangiocarcinoma; mean diameter 7.7 cm (5.5–10.8 cm) for peripheral lesions and 3.6 cm (2.2–4.9 cm) for hilar cancers; dose range 12–25 Gy), two serious complications were observed. An intrahepatic hemorrrhage on removal of the brachytherapy sources was seen, and obstructive jaundice occurred 14 days after brachytherapy with elevated bilirubin and subsequent liver failure 9 months later, perhaps associated with biliary injury from high dose radiation. Mild increases in liver enzymes and bilirubin without clinical symptoms were common. (Ricke et al. 2004).

7.4 Biliary and Gallbladder Tolerance

Bile duct epithelium is relatively resistant to radiation injury. Biliary toxicity includes acute edema induced biliary obstruction (following irradiation of pending obstructing lesions) and late biliary strictures. Biliary toxicity has not been commonly reported following conventional fractionated external beam radiation therapy or SBRT, but has been described following intraductal brachytherapy.

Rabbit and dog animal models have revealed that single radiation doses above 30 Gy caused biliary duct stenosis which may lead to biliary cirrhosis over time (Todoroki 1978; Sindelar et al. 1982).

Biliary strictures have been seen years following hypofractionated proton therapy for hepatocellular carcinoma (Chiba et al. 2005). Totally, 3 of 162 patients treated with hypofractionated proton therapy developed biliary stenosis, or biomas 13, 29, and 38 months following therapy. This was most common with the fractionation schemes that used more than 4 Gy per fraction (72 Gy in 16 fractions and 50 Gy in 10 fractions).

The possibility for acute biliary obstruction following SBRT was reported in patients with cholangiocarcinoma treated with 5 Gy fractions or more, likely due to treatment-induced edema (Tse et al. 2008), suggesting that lower fraction sizes and/or prefraction steroids to reduce edema could reduce the possibility for treatment-induced edema and biliary obstruction or cholangitis.

There is little known about the gallbladder tolerance to radiation therapy. In theory, stricture of the cystic duct may result in edema or perforation of the gall bladder, so very high doses and high doses per fraction should be used with caution in this region. It is not known what the tolerance of the gallbladder wall is to irradiation.

Longer follow-up of patients treated with SBRT is required before the biliary tolerance for stricture and gallbladder tolerance to different doses per fraction is better understood.

8 Prevention and Management

8.1 Prevention

Animal models have investigated various interventions to mitigate and prevent classic and nonclassic RILD. No radioprotective effect of the highest tolerable doses of salicylates were found in rat models (Kinzie et al. 1972). Anticoagulation with warfarin have been suggested to be a potential mitigating treatment for classic RILD (Lightdale et al. 1979), but this has not been compared in a prospective setting, and there are risk of anticoagulation therapy in patients with liver disease, who are often those who require irradiation.

Several analyses in BMT patients have demonstrated less frequent symptoms and lower incidences of VOD in patients receiving heparin, defibrotide, and/or prostaglandin E1 (Chalandon et al. 2004; Rosenthal et al. 1996; Simon et al. 2001), suggesting a possible mitigating role of these agents for VOD liver toxicity. Randomized trials of these therapies in high-risk patients are warranted.

8.2 Management

Once any radiation therapy induced liver toxicity has been detected, a referral to a hepatologist is recommended. As in chronic liver disease, fluid and salt restriction, along with other conservative measures may delay the progression to liver failure.

No established standard exists for the treatment of RILD. Management is typically conservative, and limited to

supportive care with diuretics, paracentesis, and steroids. Classic reports have described the natural course of RILD as self-limited, with most patients' symptoms resolving over several months (Lawrence et al. 1995). The patients who do not respond to supportive management may develop chronic liver fibrosis, marked by portal hypertension, jaundice, ascites, coagulopathy, and general liver failure. Mortality rates from RILD range from 10 to 20 %, to 76 % (in patients with chronic viral hepatitis and/or liver cirrhosis), emphasizing the importance of preserving the liver function after radiation therapy when possible.

8.2.1 Supportive Therapy

Many noncytotoxic drugs administered concurrently with chemotherapy can cause abnormal liver function and should be considered potentially causative in the setting of abnormal liver function tests occurring during treatment. Allopurinol, commonly given with chemotherapy to prevent uric acid nephropathy and secondary gout, has been linked to fulminant hepatic failure, presumably due to a hypersensitivity reaction. Several antibiotics and antifungal agents can cause significant hepatic injury. While penicillins have a record of low hepatotoxicity, raised transaminases, and cholestatic jaundice have been reported with the commonly used antibiotic piperacillin-tazobactam, the potential of erythromycin and several other macrolides to cause (usually cholestatic) hepatitis is well established and fluconazole can cause hepatitis and can produce abnormal liver enzymes without significant liver biopsy changes. The 5HT3 receptor antagonists, ondansetron, and granisetron are associated with transient, reversible increases in transaminases and cholestatic jaundice and biliary stasis can occur with prochlorperazine, particularly during the first few months of treatment. With the current popularity of alternative medicines the occurrence of hepatotoxicity has led to the recognition of "herbal hepatitis". Up to 50 % of patients with cancer might not tell their doctor about use of alternative medications so a careful history is important.

9 Future Research

There are still many unanswered questions about radiation-induced liver toxicity, and research to better understand the pathophysiology of classic and nonclassic RILD are warranted. No intervention currently has been proven in patients to prevent or reverse the effects of RILD. By examining the mechanisms behind the pathogenesis of RILD, key areas of investigation to develop potential mitigating and preventative therapies may be identified. Some areas of active research include hepatocyte and stem cell rescue of liver injury, and development of antistellate cell and anti-TGF-β therapies.

The impact of concurrent or sequential systemic treatment on the radiation tolerance of the liver needs to be better defined, as there is a rationale to combine radiation therapy with systemic therapy in many clinical situations.

Improvements in the understanding of the partial liver tolerance to the liver may occur with collaborative efforts, and pooling of dose–volume information, clinical factors, and measurements of liver function pre- and post-radiation therapy is suggested. With such efforts, we may have more power to better understand how different dose distributions, and fractionations alter the tolerance of the liver to radiation therapy. Knowledge of the dose thresholds for subregional injury and of the doses associated with preservation of liver function and liver hypertrophy following therapy should help future NTCP modeling of injury and prevention of injury. Improved measured of liver function, and of the spatial differences in liver function, i.e., with novel imaging, would allow radiation plans to be developed to better avoid the best functioning portions of the liver, and possibly reduce the risk of hepatic toxicities. Finally, more research and clinical data on potential hepatobiliary toxicities that may occur following very high dose per fraction, i.e., SBRT, are also needed.

10 Review of Literature Landmarks (History and Literature Landmarks)

In 1954, Phillips et al. described one of the first cases of possible liver toxicity that occurred in one of 36 patients with liver metastases who were treated with estimated whole liver doses of 20–37 Gy in 8 fractions (Phillips et al. 1954). Subsequent reports of liver toxicity in the 1960s confirmed the low tolerance of the whole liver to irradiation (Ogata et al. 1963; Ingold et al. 1965; Schacter et al. 1986). In 1965, Ingold et al. described liver toxicity in 13 of 40 patients irradiated for abdominal diseases. Symptoms of rapid weight fain, increased abdominal girth, hepatomegaly were seen within 3 months following irradiation (Ingold et al. 1965). The liver enzymes, particularly the alkaline phosphatase, were elevated. Most of the patients recovered but a few died of liver failure. In 1966, Reed and Cox described the pathology in these cases, establishing features of classic radiation-induced liver disease (RILD) (Reed and Cox 1966). The early estimations of the whole liver tolerance to irradiation, 30–35 Gy with conventional fractionation, have remained largely unchanged.

Although Ingold reported that 55 Gy could be delivered safely to a portion of the liver in 1965, it was not until decades later that the partial liver tolerance to irradiation was quantified. With CT-based radiation therapy planning and clinical experience in partial liver irradiation, the relationship between radiation dose, liver volume irradiated,

and risk of liver toxicity has been described using mathematical models in various populations (Cheng et al. 2003; Liang et al. 2006; Dawson et al. 2001, 2002; Chiba et al. 2005; Jackson et al. 1995). These models show that the risk of toxicity increases as the irradiated liver volume, the dose, and the dose per fraction increase, at least for some of the liver toxicity endpoints (e.g. classic RILD). Clinical factors associated with increased risk of toxicity include tumor type (primary liver cancer versus metastases), type of chemotherapy used, and presence of hepatitis B virus (Cheng et al. 2004a). For classic RILD, the mean liver dose is a good estimate of toxicity risk, with 5 and 50 % risks of toxicity occurring with mean liver doses of 32 and 40 Gy, in 1.5 Gy twice daily, for patients with primary liver cancer, with a Child-Pugh score of A. Similar mean liver doses associated with 5 and 50 % risk levels for patients with metastases (without underlying liver disease) are 37 and 47 Gy, in 1.5 Gy twice daily. Reduced tolerance doses have been reported in Asian populations with hepatocellular carcinoma, where the incidence of Hepatitis B or C and cirrhosis is very high.

Bone marrow transplant and hematopoietic stem cell transplant, with and without TBI, has also been associated with liver toxicity, which is similar in clinical presentation to RILD, with the primary exception that RILD is anicteric, whereas transplant and TBI associated liver toxicity presents with an elevation in bilirubin.

Liver directed radioisotope therapy has been used to treat primary and metastatic liver cancers, and these therapies are also associated with a risk of liver toxicity. Although the risk of liver toxicity appears low in appropriately selected patients, both classic and nonclassic RILD can be seen following radioisotope therapy.

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Adverse Late Effects of Radiation Treatment in the Pancreas

Suzanne Russo, Roger Ove, Luis Fajardo, and Joel Tepper

Contents

Abstract

- Histology: Each acinus is made up of an irregular cluster of pyramidal secretory cells with apices projecting toward the lumen of a small central duct.
- Endocrine secretions enter the blood by way of a fine reticular network of fenestrated capillary beds surrounding the islets of Langerhans, which consist of groups of endocrine cells of various sizes.
- Symptoms: Pancreatic exocrine dysfunction and malabsorption are the most commonly reported complications following pancreatic radiation.
- Patients may more rarely develop an abnormal glucose tolerance test. Patients may or may not also demonstrate accompanying abnormal random or fasting plasma glucose levels.
- Radiology: Imaging of the pancreas following radiation is often normal but sometimes radiographic changes consistent with chronic pancreatitis can be observed.
- Multiple Fractions: At 45 Gy, pancreatic exocrine insufficiency with or without malabsorption has been reported.
- Hypofractionation. The estimate risk of diabetes is 16% in childhood cancer survivors who have received at least 10 Gy to the tail of the pancreas, with a dose response up to 20 to 29 Gy, and a plateau at higher radiation doses. Stereotactic body radiosurgery has recently been utilized to deliver a range of hypofractionated radiation treatments to patients with pancreatic tumors. Up to 25 Gy delivered in a single fraction has been used for treatment, including some patients who received prior chemotherapy and fractionated external beam radiation.

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No pancreatic complications were reported in these studies though the number of evaluable patients is small.
- Recommended dose-volume: As radiation-induced damage to pancreatic function is rarely life threatening and is usually well treated with medical management, dose-volume constraints have not been formally evaluated as with other critical normal tissues.
- Management: Because pancreatic exocrine deficiency can be managed with replacement therapy, pancreatic injury has not routinely been considered a serious complication compared to other normal tissue damage that may occur from abdominal radiation, such as radiation enteritis. Nonetheless, the risks associated with diabetes and the association with pancreatic tail irradiation in childhood cancer survivors may significantly contribute to public health issues. Hence, the pancreas should be identified as a critical organ for radiation planning purposes, especially in children receiving abdominal irradiation. Long-term follow-up of patients receiving abdominal irradiation should include diabetic screening.

Abbreviations

bcl-2	B cell lymphoma-2
bax	B cell lymphoma-associated X
gEUD	Generalized equivalent uniform dose
GPx	Glutathione peroxidase
IL-1	Interleukin-1
IMRT	Intensity modulated radiation therapy
QUANTEC	Quantitative analyses of normal tissue effects in the clinic
SOD2	Superoxide dismutase
TNF-α	Tumor necrosis factor-alpha

1 Introduction

Radiation therapy is often incorporated into the multimodality treatment for a number of abdominal malignancies, including gastric, hepatobiliary, intra-abdominal lymphomas, retroperitoneal sarcomas, and intra-abdominal metastases. Many of the normal tissues in the gastrointestinal tract are made up of rapidly multiplying mucosal epithelial cells, rendering them susceptible to acute radiation injury. In contrast, both exocrine and endocrine cells of the pancreas have very low cell turnover rates (Fajardo and Berthrong 1981; Hauer-Jensen et al. 1995; Hellerstrom et al. 1976; Rubin and Casarett 1968), and acute radiation injuries, including pancreatitis and pancreatic endocrine and exocrine insufficiency, have been rarely reported. For this reason, many believe that pancreatic tissue is radioresistant. There have been a few reports of chronic pancreatic complications as a result of late radiation injury. Radiation can result in progressive changes in the microenvironment and fibrovascular tissue in the treatment area, which manifests as ischemia. Such changes can contribute to damage to the pancreas and resultant clinical manifestations.

Unlike other organs, such as lung, where a variety of dose-volume parameters have been linked to radiation injury and provide a rationale for clinical guidelines, there are very limited data for radiation-induced pancreatic damage. In addition, where predictive models for RT-induced injury are suboptimal for most tissues, they are not at all defined for the pancreas. This is partially due to the lack of objective measures of pancreatic injury and the difficulty in separating tumor effects from the effects of the therapy. In this chapter, we will review the data for radiation-induced pancreatic injury and provide dose/volume guidelines for the clinician. The bio-continuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Gross Anatomy

The pancreas arises embryogenically from endoderm. It is covered by a loose connective tissue capsule that penetrates the pancreas and separates the parenchyma into lobules. The pancreas is a long gland that lies transversely across the central posterior abdomen and extends from the duodenum to the splenic hilum. The organ is divided into three parts; the head with a small uncinate process, the body, and the tail. The head of the pancreas lies in the curve of the duodenum, while the body lies posterior to the transverse colon and greater curvature of the stomach. The pancreas lies anterior to the upper abdominal aorta, the first and second lumbar vertebral bodies, and the superior poles of the kidneys (Fig. 2).

Rich vascular and lymphatic networks surround the pancreas. Regional lymph node basins are associated with specific locations within the pancreas. The pancreatic head region drains primarily to the lymph nodes along the common bile duct, common hepatic artery, porta hepatis, anterior and posterior peri-pancreatic soft tissues, and the superior mesenteric chain. The pancreatic body and tail may drain to the common hepatic artery, celiac axis, splenic artery, and splenic hilum. The posterior pancreas also drains to the para-aortic lymph nodes.

2.2 Histology and the Functional Subunit

The exocrine component of the pancreas consists of closely packed secretory acini, which drains into a branched ductal

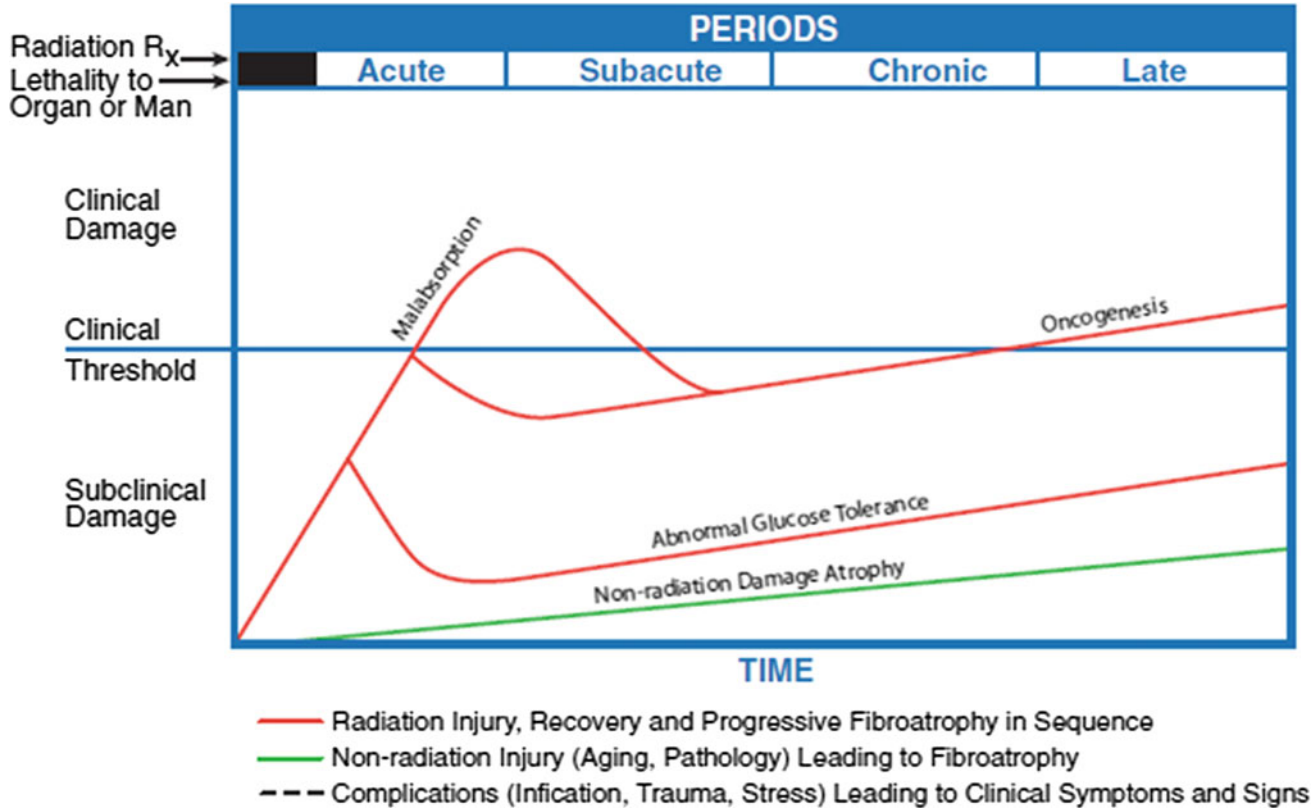

Fig. 1 Bio-continuum: Pancreatic acinar cells are known to be radioresistant to irradiation, even with larger doses and chemoradiation combo-based regiments, since modern radio techniques (IMRT, SERT) tend to spare a significant volume of this elongated organ, acute pancreatitis has not been reported clinically. Malabsorption has been reported but is transitory. With experimental radiation injury to the exocrine pancreas, islet of Langerhans appear to be spared, and although late diabetes has not been reported, it has been observed as a late effect in long-term survivors of childhood malignancies who have received abdominal irradiation. Oncogenesis with second malignant causes have been observed (with permission from Rubin and Casarett 1968)

system. Each acinus is made up of an irregular cluster of pyramidal secretory cells with apices projecting toward the lumen of a small central duct. The acinar cells are typically protein-secreting (zymogenic) cells with the apices packed with zymogen secretory granules, which secrete into the central duct in response to cystokinin, produced by enteroendocrine glands of the duodenum. In addition, a bicarbonate-rich fluid produced by terminal intercalated ducts located in the acinar cell walls is secreted into the central duct in response to secretin, also from the duodenal enteroendocrine glands. This secretion serves to neutralize acidic gastric chyme. (Fig. 3a, b).

The small central ducts are lined with cuboidal epithelium, that becomes stratified as the ducts become progressively larger in size. The dense connective tissue that comprises the wall of the ducts becomes thicker as they increase in size, and the main pancreatic duct contains smooth muscle. The branched ductules join together and drain into the main pancreatic duct, which joins the common bile duct and drains into the duodenum via the ampulla of Vater through the duct of Wirsung and the more proximal duct of Santorini.

Endocrine secretions enter the blood by the way of a fine reticular network of fenestrated capillary beds surrounding the islets of Langerhans, which consist of groups of endocrine cells of various sizes. During embryologic development the endocrine cells migrate from the duct system and aggregate around capillaries to form isolated clumps of cells scattered throughout the exocrine pancreas. Islets of Langerhans are most numerous in the tail. Each islet is supplied by as many as three arterioles, which branch into the fine capillary network and is drained by about 6 venules passing between the exocrine acini into the interlobular veins.

Both sympathetic and parasympathetic nervous systems innervate the islets of Langerhans, influencing secretions. The endocrine pancreas is composed of four types of secretory cells. The alpha and beta cells mainly secrete polypeptide hormones, glucagon, and insulin, respectively, which mainly regulate carbohydrate metabolism and have a wide variety of other effects on energy metabolism, growth,

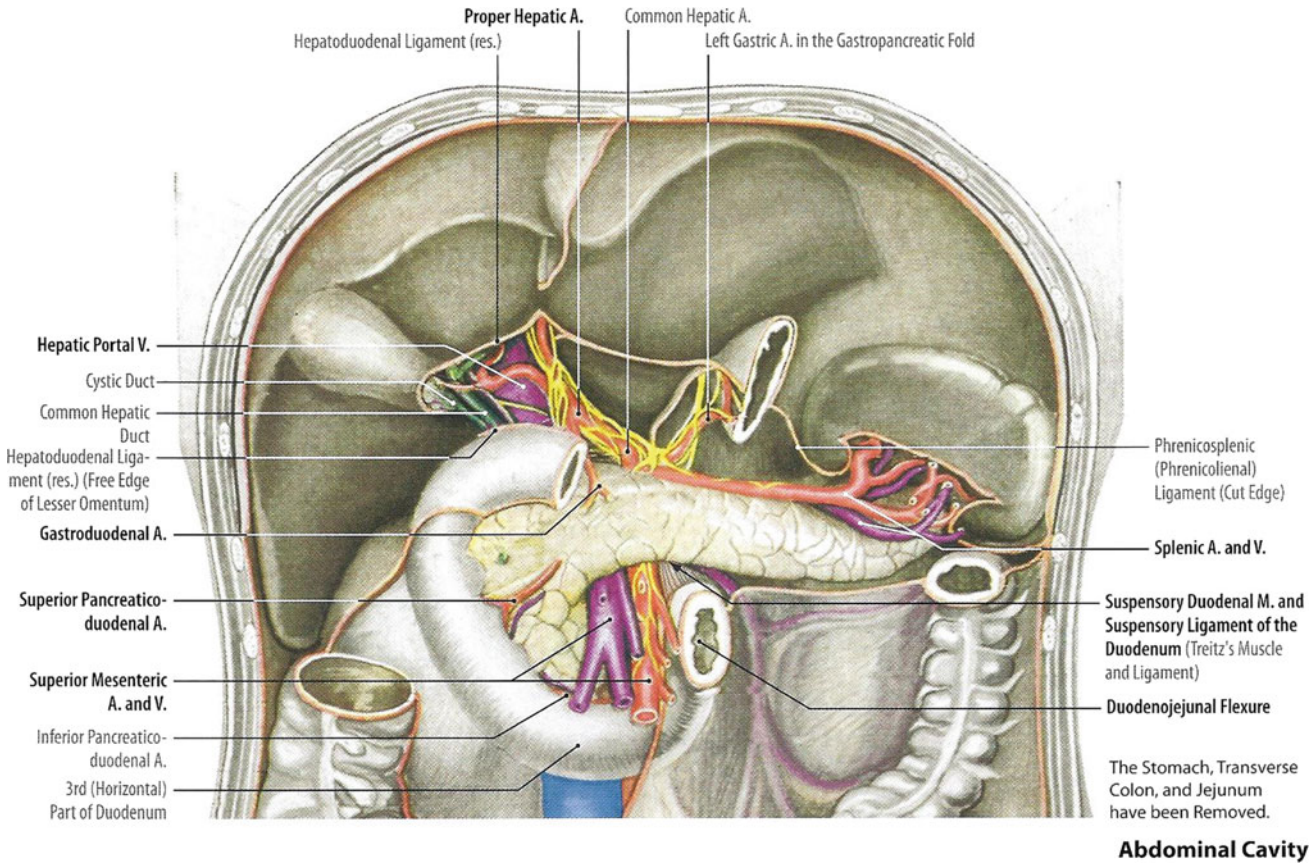

Fig. 2 Anatomy of pancreatic area (with permission from Tillman 2007)

and development. Insulin promotes the uptake of glucose by liver, skeletal muscle, and adipose tissue, which lowers plasma concentration of glucose. Glucagon has metabolic effects opposite to the actions of insulin, resulting in a balanced carbohydrate metabolism. Generally, the glucagon-secreting alpha cells tend to be distributed at the periphery of the islets. Somatostatin is secreted by the delta cells of endocrine pancreas and has a wide variety of effects on gastrointestinal function, and may also inhibit insulin and glucagon secretion. The F cells secrete pancreatic polypeptide, which is involved in the regulation of endocrine and exocrine secretions.

3 Biology, Physiology, and Pathophysiology

3.1 Biology (Molecular Changes)

As an early event, ionizing radiation produces free radicals that lead to DNA damage and mitotic cell death, which is unlikely to produce sufficient damage for prolonged progression of injury. It is believed that the initial radiation event requires additional mechanisms that lead to late radiation-induced normal tissue damage, including endothelial dysfunction, increased vascular permeability, inflammation, and fibrosis. Although this phenomenon has not been well studied for the pancreas, it has been extensively researched for a number of other tissues.

Oxidative tissue damage and apoptosis plays an important role in abdominal irradiation, as assessed by increased lipid peroxidation, myeloperoxidase activity, and caspase-3 levels in the intestinal and pancreatic tissue. Pancreatic, as well as hepatic and intestinal myeloperoxidase activity and malondialdehyde levels are significantly increased following irradiation in an animal model (Olgac et al. 2006; Erbil et al. 2005). These phenomena may provide an amplifying mechanism for continued oxidative stress after the initial production of reactive oxygen and nitrogen species leading to prolonged progression of oxidative injury. In this study, the imbalance between oxygen-derived free radicals and antioxidant capacity appeared to be mitigated by treatment with octreotide (Olgac et al. 2006) or glutamine (Erbil et al. 2005) prior to, and following radiation, with significantly

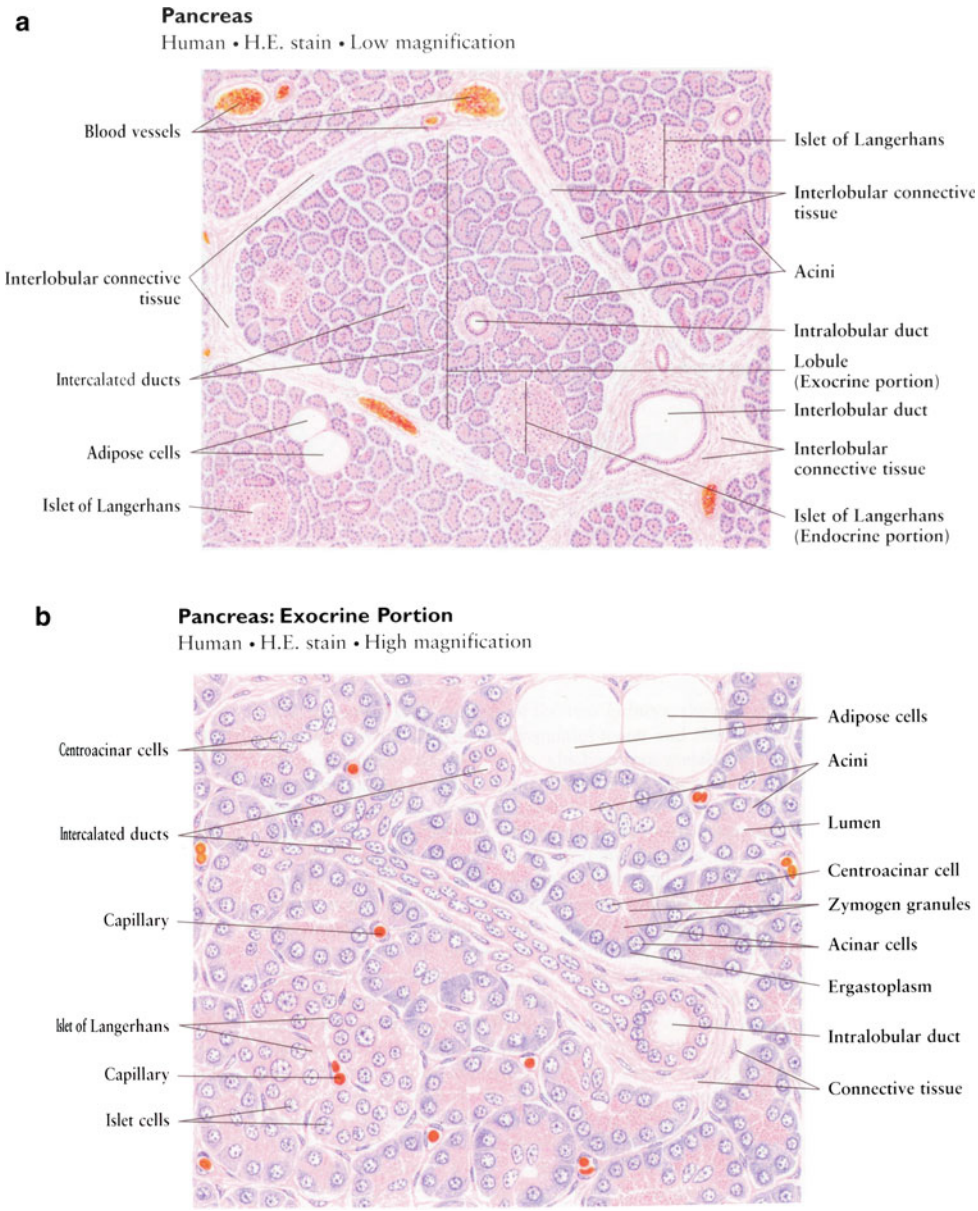

Fig. 3 Histology of pancreas. **a** Low magnification, **b** High magnification (with permission from Zhang 1999)

less elevation in pancreatic myeloperoxidase activity and malondialdehyde levels and accompanying inflammation compared to untreated animals.

It is presumed that an inflammatory process in which various mediators, such as eicosanoids, cytokines, and reactive oxygen metabolites contributes to the pathogenesis of radiation-induced normal tissue injury. Radiation-induced activation of a number of cytokines has been shown to play a key role in the development of chronic normal tissue injury after exposure to radiation in a number of studies. Nuclear Factor Kappa B (NFκ-B) is activated by a wide variety of agents, including hydrogen peroxide, irradiation, reactive oxygen intermediates, interleukin-1 (IL-1), Tumor necrosis factor-alpha (TNF-α), among others, and depends on the cellular redox potential. Once activated, NFκ-B transcriptionally regulates many cellular genes involved in acute phase response, and inflammatory responses (Jobin and Sartor 2000; Schmid and Adler 2000; Schmid et al. 1996).

In the prior studies, elevated pancreatic myeloperoxidase activity and malondialdehyde levels along with histological evidence of inflammation and increased apoptosis of pancreatic tissue following radiation have been correlated with NFκ-B overexpression (Olgac et al. 2006; Erbil et al. 2005) and increased caspase-3 activity (Erbil et al. 2005), both of which may contribute to late radiation-induced injury

Table 1 Physiology of pancreas cell sub-types

Cells	Secretory product	Physiologic actions
Acinar	Secretin	Stimulates high bicarbonate level (HCO_{-3})
Acinar	Amylase	Digestion of starch
Acinar	Lipase	Digestion of fat
Acinar	Trypsin	Digestion of protein
Alpha	Glucagon	Catabolic, stimulates glycogenolysis and gluconeogenesis, raises blood glucose
Beta	Insulin	Anabolic; stimulates glycogenesis, lipogenesis, and protein synthesis; lowers blood glucose
Delta	Somatostatin	Inhibits secretion of alpha, beta, D_1, and acinar cells
D_1	Vasoactive intestinal polypeptide (VIP)	Same as glucagon; also regulates tone and motility of the gastrointestinal tract and activates 3′,5′ cyclic adenosine monophosphate (cAMP) of intestinal epithelium
PP	Human pancreatic polypeptide (hPP)	Stimulates gastric enzyme secretion, inhibits intestinal motility and bile secretion

through apoptosis, and prolonged inflammation. There is no direct evidence regarding long-term complications, as animals were sacrificed 10 days after treatment, however. Both glutamine and octreotide also decreased the overexpression of NFκ-B and increased caspase-3 activity in response to radiation (Olgac et al. 2006; Erbil et al. 2005).

BCL (B Cell Lymphoma)-2 (bcl-2) is the prototype for a family of mammalian genes and the proteins they produce which govern mitochondrial outer membrane permeabilization, and can be either proapoptotic or antiapoptotic. BCL (B Cell Lymphoma)-associated X (bax) promotes apoptosis by competing with Bcl-2. Bcl-2 and bax expression have also been implicated in injury and apoptotic cell death following radiation. Radiation-induced effects on cell proliferation, expression of bcl-2 and bax proteins, and apoptosis in pancreatic tissue have been investigated utilizing a mouse model. Cell proliferation and bcl-2 expression decreased by exposure to a single dose of radiation, whereas the cell apoptosis rate and bax expression were increased (Liu and Zhong 2004).

Although the molecular mechanisms of radiation injury to the pancreas are not well characterized, they appear to be complex and involve prolonged oxidative stress, increased apoptotic death through cytokine activation and disturbed regulation of certain genes. Further investigation is warranted.

3.2 Physiology

The pancreas has two functional unites: the acinar glandular system and the islets of Langerhans, these are exocrine and endocrine components respectively. Pancreatic secretions are under neural and hormonal control (Table 1).

Acinar: Secretin provides high (HCO_3) to neutralize the acid from the stomach. Enterokinases are key enzymes that are essential for digestion of starch, fat, and protein in diets. Cholicystokinin allows for reabsorption of bile.

Islet hormones: the islets are scattered and well vascularized aggregates of endocrine cells. There are four major cell types, each secreting one specific peptide hormone. Each are responsible for important physiologic functions. Most widely discussed is insulin, essential for glucogenesis and regulation gylcogenolysis.

3.3 Pathophysiology

Radiation-induced injury has traditionally been divided into an early inflammatory phase, which typically occurs between 6 and 16 weeks after radiation exposure, and a late fibroproliferative phase, which occurs much later and is characterized by diffuse fibrosis. The pathogenesis of radiation injury of the pancreas has been proposed to arise from endothelial cell damage of the microcirculation supplying acinar cells, adding ischemia to direct radiation cell damage. Acute stromal edema as a result of increased capillary permeability also plays a role (Fajardo et al. 2001). Radiation injury to myoepithelial cells and intimal fibroblasts also result in progressive fibrosis and ischemia from arterial and venular lesions and add to long-term pancreatic damage (Fajardo et al. 2001) (Fig. 4a, b, c).

3.3.1 Animal Studies

A few animal studies have focused on radiation-induced vascular and ductal damage. The vascular and connective tissues appear to have similar radiosensitivity as tissues elsewhere in the body. Zook et al. observed moderate radiation-induced occlusive vascular disease in dogs receiving abdominal neutron or photon radiation and postulated that this phenomenon could contribute to acinar and duct cell changes (Zook et al. 1983). In another study,

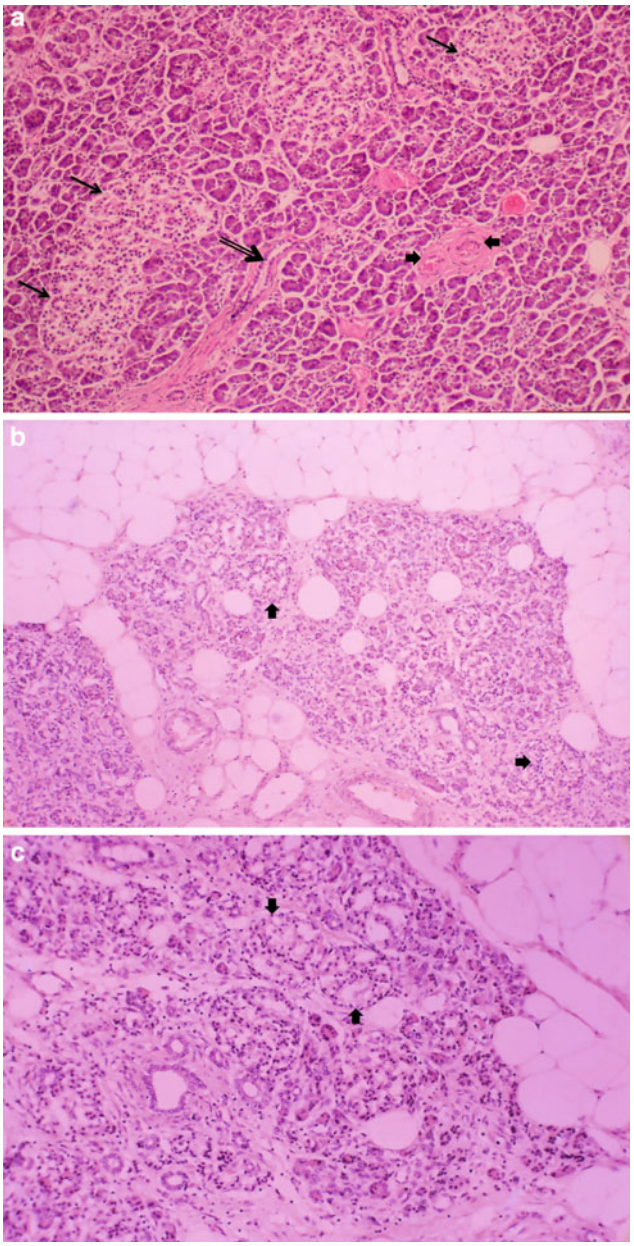

Fig. 4 **a** Normal pancreas. Hematoxylin and eosin (H and E) prepared normal pancreas from postmortem specimen. Most of the field consists of small, dark acini, the exocrine galnds. Three islets of Langerhans are in the upper-left half of the field (*thin arrows*). A small duct (*thick arrow*) is in the low center. Various blood vessels are in the right center (*arrow heads*). **b** Late radiation injury. Figures 4b and c demonstrate H and E prepared human pancreas several months after exposure to several thousand centigray (cGy) of megavoltage radiation to the pancreas delivered for an adjacent abdominal neoplasm. There is marked loss of the parenchyma, especially of the exocrine glands, with replacement by adipose tissue (fat cells framing the picture) in the midst of atrophic acini. The atrophic acini are dilated and separated from each other. Several islets appear to be intact (*arrow heads*)

80 Gy was delivered to rat abdomens and histological changes were observed at intervals following exposure (Kovacs 1976). In the acute phase of radiation injury during the first 2 weeks following radiation, most of the acini remain intact with rare small necrotic foci. Edema, inflammation, and dilatation of efferent ductules with stasis consequently leads to atrophy of the acini associated with the efferent ducts over the next several months. During this period, the number of capillaries diminishes, and the number of necrotic foci increase in areas where no capillaries are visible (Kovacs 1976). These progressive late structural changes are thought to contribute to functional changes over time.

Early radiation-induced pancreatic injury results in the decline in bicarbonate and enzyme secretion shortly following radiation to the pancreas in canines and other animals (Corring et al. 1975; Pieroni et al. 1976; Volk et al. 1966). One canine study utilizing intraoperative pancreatic radiation doses of 17.5–40 Gy resulted in a progressive decrease in exocrine pancreatic function, which was evaluated by measuring N-benzoyl-l-tyrosyl-para-aminobenzoic acid, which correlated with weight loss and percentage of normal appearing acinar cells (Ahmadu-Suka et al. 1988). Autopsies performed on the dogs at 135 days following radiation demonstrated a dose-dependent degree of pancreatic atrophy in the irradiated dogs (Ahmadu-Suka et al. 1988).

In contrast islet cell damage appears to be rapidly repaired without alterations in blood glucose levels (Sarri et al. 1991). Most investigators believe that islet cells are more resistant than the acinar tissue to radiation effects (Fajardo and Berthrong 1981; Cameron and Flecker 1925; Zook et al. 1983; Ahmadu-Suka et al. 1988; Spaulding and Lushbaugh 1955). One study demonstrated that degeneration of beta cells occurs approximately 1–4 days after a single large fraction of pancreatic radiation with complete regeneration at 18 days (Cameron and Flecker 1925). Another investigator delivered single large doses of radiation to monkey pancreas and found necrosis of islet cells at 8 h, with beta cells more resistant that alpha cells (Spaulding and Lushbaugh 1955). In both studies there were no morphologic changes noted in the acinar cells during a short follow-up period (Cameron and Flecker 1925; Spaulding and Lushbaugh 1955). In addition, data suggest that the insulin function of a pancreas in rats exposed to a single 4 Gy dose is maintained at a level sufficient for ensuring adequate regulation of glucose homeostasis and of carbohydrate metabolism (Shkumatov 2004).

Similar studies evaluating histological changes and endocrine function have been performed in primates who underwent irradiation in preparation for pancreatic transplantation. Eight or 10 Gy whole body radiation was delivered over 4–5 weeks, with a maximum of 2 Gy weekly. Although the animals remained normoglycemic, insulin release was significantly reduced in both groups during irradiation and was associated with mild glucose intolerance. Histological changes included necrosis of the

islet cells and acinar tissue, and cytocavitary network changes of alpha and beta cells, including degranulation, vacuolization, mitochondrial destruction, and an increase in lysosomes (Du Toit et al. 1987).

Other animal studies utilizing fractionated or single doses of radiation have demonstrated acinar gland damage (Pieroni et al. 1976; Volk et al. 1966; Wellmann et al. 1966). Early ultrastructural changes include acinar cell degeneration, mitochondrial injury, and vesicles in endoplasmic reticulum cisternae, which are evident within 1 h following single dose radiation exposure (50–90 Gy) on electron microscopy and are associated with reduced enzyme secretion (Volk et al. 1966). After 8 days following radiation, numerous membrane-bound cytoplasmic bodies, endoplasmic reticulum containing entrapped degenerating mitochondria, and reduced zymogen granules are observed (Volk et al. 1966).

Acini exposed to radiation are known to exhibit increased autophagy, however, these changes do not appear to be related to radiation-induced lysosomal degradation of intracellular proteins (Somosy et al. 1996; Telbisz et al. 2002). Islet cells show similar degenerative organelle changes that are repaired efficiently and last up to 3 weeks, during which time there is no alteration in blood glucose levels (Cameron and Flecker 1925; Volk et al. 1966; Spaulding and Lushbaugh 1955). Longer follow-up demonstrates a recovery period from 3–5 weeks, consisting of increasing endoplasmic reticulum and gradual disappearance of autophagic remnants. After about 5–12 months, the ultrastructure of the cells returns to normal morphologic appearance with the exception of persistent interstitial fibrosis. Conversely, pancreatic function does not completely recover, and continues to exhibit a persistent decrease in enzyme production compared to pretreatment (Wellmann et al. 1966).

In another early study utilizing fractionated pancreatic radiation (45–50 Gy over 30 days) in nine dogs whose pancreas had been surgically mobilized in the abdomen, Archambeau et al. performed functional studies of blood glucose and pancreatic secretions obtained through fistulae (Archambeau et al. 1966). Samples of the pancreatic head and tail were also obtained at 2, 3, and 6 months after radiation demonstrated progressive interstitial fibrosis with distorted normal pancreatic architecture, and preserved acini and the islet morphology. No changes in secretory volume, serum, and pancreatic electrolytes or blood glucose were detected, but there was an initially elevated serum amylase, which declined progressively (Archambeau et al. 1966).

Injury to small- and medium-sized ducts resulting in occlusion of the lumen by cell debris has been demonstrated after 50 Gy fractionated radiation combined with 25 Gy intraoperative radiation to the pancreas in dogs. Over time, severe interstitial fibrosis was observed and by 135 days small- to medium-sized arteries and veins were narrowed with medial and adventitial fibrosis (Ahmadu-Suka et al. 1988). Others have demonstrated that local radiation impairs microcirculatory blood flow in healthy pancreas in a rat ductal pancreatic tumor model. A single fraction of 15 Gy resulted in increased tumor apoptosis but no change in tumor blood flow, whereas blood flow and functional capillary density in the normal pancreas was impaired 5 days after radiation, resulting in hypoperfusion (Ryschich et al. 2003). These changes are thought to contribute significantly to decline in pancreatic exocrine dysfunction and late parenchymal structural damage.

3.3.2 Human Studies

There is even less data describing radiation damage in humans following radiation to the pancreas. As mentioned earlier, Case and Warthin described atrophy of the acinae and degeneration and necrosis of pancreatic ducts in 3 patients with radiation-induced hepatitis (Case and Warthin 1924). Subsequently, in 1955, Brick observed pancreatic fibrosis during autopsies of three men who received radiation to the para-aortic lymph nodes for testicular cancer (Brick 1955). In another report, autopsies of patients treated with abdominal radiation for lymphoma demonstrated peripancreatic stromal fibrosis, sometimes severe, with myointimal proliferation in arteries. The authors described the appearance as similar to chronic pancreatitis with lack of active inflammation and necrosis (Fajardo 1982). Woodruff et al. performed postmortem studies of 22 patients who received radiation for pancreatic cancer using 50–60 Gy over 30 fractions delivered with helium ions. After a median of 9 months following radiation, approximately 85 % of patients demonstrated radiation injury in the nontumor bearing pancreas consisting of dense fibrosis, mainly located in the exocrine parenchyma. They reported that no patient died of pancreatic insufficiency and only one patient developed hyperglycemia (Cohen et al. 1985; Woodruff et al. 1984).

Because of the paucity of human specimens, very little is known regarding early radiation injury to the human pancreas and we predict early radiation damage by extrapolating from the animal studies previously described. After about 10–20 Gy, acinar injury is observed, similar to animal studies. Inflammatory cells are abundant and the number of secretory granules is reduced and the cytoplasm becomes vacuolated. Similar to other tissues, the amount of cellular damage increases with increasing fraction size. Zonal necrosis and ductule degeneration are observed at 60 Gy. Although larger ducts may only demonstrate mild cell changes and enlargement, smaller ducts develop distended lumens and plugging by cellular debris. Acute injury to arterioles and venules may also be present and associated with edema of the stroma and acute inflammation in regions

Table 2 Representative endpoints that might reflect radiation-induced pancreas injury, segregated (somewhat arbitrarily) as shown

	Focal	Global
Subclinical	Regional imaging abnormalities; e.g., calcifications on planar images, hyperenhancement on CT, or biliary duct abnormalities on retrograde cholangiopancreatography	Latent diabetes mellitus, glucose intolerance, malabsorption of proteins and fats, reduced levels of pancreatic enzymes in small intestine, or abnormalities in urinary bentiromide
Clinical	Cancer induction	Diabetes mellitus, steatorrhea

of early parenchymal necrosis. In contrast, islet capillaries show relatively normal anatomical structure during the early injury phase without endothelial enlargement or fibrin thrombi, and islets of Langerhans appear normal (Fajardo et al. 2001).

Pathologic examination of patient pancreas specimens examined at 6 months or more after treatment with radiation demonstrate shrunken, fibrotic pancreas with thickening of the fibrous capsule and adhesions to the surrounding tissues grossly. Lobulation becomes less prominent, and large ducts may be dilated (Fajardo et al. 2001). Microscopic examination of irradiated pancreas at the same time interval demonstrate fibrotic parenchyma with severe acinar cell loss, abundant collagen, hyaline, and atypical fibroblasts similar in appearance to chronic pancreatitis. Despite these structural changes, islet cells appear normal. Occasionally fat necrosis and calcifications may be found (Case and Warthin 1924; Levy et al. 1993). At this time point, very little inflammation is found with the exception of small collections of lymphocytes trapped within the dense fibrous connective tissue. Arteriole walls are thickened with fibrosis of the intima and narrowed lumens while smaller arteries and veins demonstrate fibrous intimal plaques comprised of foam cells (Berthrong 1986). The number of ductules are reduced or atrophied, and plugged with cellular debris while larger ducts are dilated with enlarged nuclei (Fajardo et al. 2001).

Others have studied pancreatic function following abdominal radiation. In one study, the early and late effects of intraoperative radiation on the exocrine and endocrine functions of the residual pancreas were examined in 54 patients with pancreatic head resection, 20 whom underwent intraoperative radiation, and 34 who did not (Yamaguchi et al. 2000). Fasting blood sugar levels and glucose tolerance tests demonstrated no change at 2 months, but at 6 months the glucose tolerance was compromised compared to the preoperative baselines in both groups, while fasting blood sugar levels remained normal. The total amount of pancreatic juice drainage in the irradiated patients was about half as much as that in nonirradiated group. In addition, univariate and multivariate regression analyses demonstrated that intraoperative radiation was a significant independent factor in the decline of pancreatic exocrine function (N-benzol-L-tyrosyl-p-aminobenzoic acid excretion) in the early postoperative period (Yamaguchi et al. 2000).

4 Clinical Syndromes (Endpoints)

A variety of endpoints can be considered to reflect RT-associated pancreatic dysfunction, as shown in Table 2. It is sometimes useful to categorize the endpoints, albeit somewhat arbitrarily, as shown.

4.1 Detection (Symptoms)

Pancreatic complications are rarely reported following abdominal irradiation. There are reports, however, of exocrine abnormalities, pain, and diabetes occurring after abdominal irradiation.

Pancreatic exocrine dysfunction and malabsorption are the most commonly reported complications following pancreatic radiation. Exocrine dysfunction can present as painful acute episodes or slow, relatively asymptomatic destruction of the pancreas.

Because pancreatic exocrine deficiency can be managed with replacement therapy, pancreatic injury has not routinely been considered a serious complication. Pancreatic lipase is responsible for the hydrolysis of triglycerides and without this enzyme, fat absorption is inhibited and steatorrhea arises. The absence of pancreatic proteases also contributes to protein malabsorption. The evaluation of pancreatic exocrine insufficiency is cumbersome and is rarely performed. Jejunal or duodenal contents detecting pancreatic enzymes or bicarbonate production can be evaluated following a specific meal or hormonal stimulation. A less invasive approach is evaluation of urinary bentiromide, which measures chymotrypsin production by determining whether para-aminobenzoic acid is cleaved off an ingested carrier and excreted through the kidneys. In most cases, a clinical history is obtained that reveals greasy, light-colored, buoyant stools reflective of high lipid content, and continued weight loss despite adequate nutritional intake.

Patients may more rarely develop an abnormal glucose tolerance test. Patients may or may not also demonstrate accompanying abnormal random or fasting plasma glucose levels. Glucose tolerance is tested by ingesting 75 g of glucose after fasting. A 2-h glucose level between 140 and 200 mg/dl, and an intervening value greater than 200 mg/dl

is reflective of impaired tolerance. Patients demonstrating impaired tolerance are at increased risk for development of overt diabetes mellitus. It is difficult to determine whether or not glucose intolerance is attributed to radiation in many occasions, as there is often underlying destructive pancreatic pathology present, such as pancreatic cancer, as an underlying etiologic factor contributing to development of endocrine dysfunction.

In addition to radiation-induced pancreatic damage resulting in functional changes, late radiation-induced oncogenesis has been reported, although the mechanism of oncogenesis has not been defined. Low-level radiation has been linked to pancreatic cancer (Cohen 1980). Ductal adenocarcinomas have been found in long-term survivors who have received pancreatic radiation as a late event after a long latent period (Deutsch et al. 1999; Lambert et al. 1998; Travis et al. 1997). A case of adenocarcinoma of the head of the pancreas arising in a previously irradiated volume 14 years after extended field irradiation for Stage II A Hodgkin's disease has been reported (Deutsch et al. 1999). Similarly, cancers of the pancreas were increased in patients irradiated for peptic ulcer disease with a relative risk of 1.87 (Carr et al. 2002; Griem et al. 1994). Travis et al. reported 1,406 s neoplasms in 28,843 men irradiated to the abdomen for testicular cancer. The pancreas was among the organs at significant risk with an observed: expected ratio of 2.21, higher than many other organs (Travis et al. 1997). In irradiated patients, risk of cancer increased significantly from 1 to 45 Gy (a low to a high-dose level) for stomach and pancreas (Suit et al. 2007).

4.2 Diagnosis (Imaging)

Radiation changes in the pancreas have received little attention because imaging findings are usually nonspecific and may not be of any clinical significance. Imaging of the pancreas following radiation is often normal but sometimes radiographic changes consistent with chronic pancreatitis can be observed. Abdominal X-rays may reveal diffuse calcifications. Because many patients receiving pancreatic radiation have underlying pancreatic carcinoma, it is difficult to distinguish whether the observed radiologic changes are due to the tumor or radiotherapy (Charnsangavej et al. 1994; Hori et al. 1982) (Fig. 5).

Following radiation to the pancreas, endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography may demonstrate gross ductal changes similar to chronic pancreatitis, with a "chain of lakes"-like appearance.

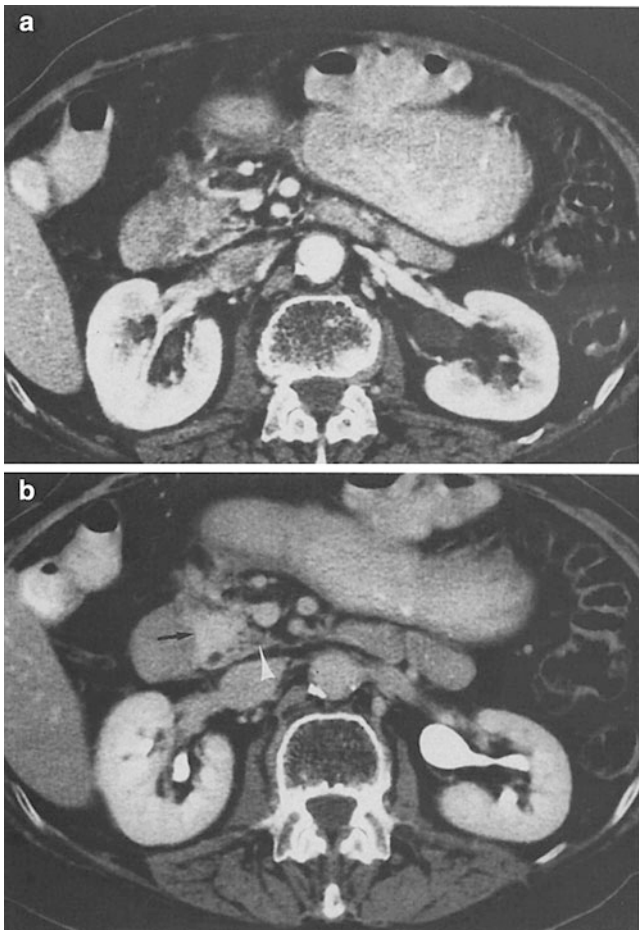

Fig. 5 Diagnosis: This CT scan demonstrates postradiation changes 6 months after radiotherapy to the head of the pancreas in an asymptomatic patient with cholangiocarcinoma. **a** CT scan during the bolus phase of IV contrast enhancement shows normal enhancement of the head of the pancreas. **b** Delayed scan 4 min later shows abnormal hyperdense enhancement of the pancreatic head (*arrows*) that is indistinguishable from chronic pancreatitis. The uncinate process (*arrowhead*) is what the pancreatic head "should normally look like" on these 4 min delayed images. Computed tomography images courtesy of Chuslip Charnsangavej M.D., Department of Diagnostic Radiology, University of Texas, M.D. Anderson Cancer Center, Houston, TX

5 Radiation Tolerance and Predicting Radiation-Induced Injury

5.1 Dose Time Fractionation

The majority of patients that receive curative doses of radiation to the abdomen for malignancy have relatively short survival intervals, therefore there are little data to define the precise dose of radiation that results in 5 % of

patients with pancreatic complications at 5 years. Nonetheless, diabetes has been reported as a late effect following radiation, although many factors may contribute to the development of the onset of diabetes in addition to radiation exposure in most settings (Levy et al. 1993). Some argue that even though islets of Langerhans appear histologically intact, function may be altered.

At 45 Gy, pancreatic exocrine insufficiency with or without malabsorption has been reported (Case and Warthin 1924). Recently, evidence of a dose-response relationship between pancreatic irradiation and subsequent risk of diabetes in a retrospective study of childhood cancer survivors. This study demonstrated that the risk of diabetes was strongly correlated with radiation dose to the tail of the pancreas, where islet of Langerhans are concentrated. The cumulative incidence of diabetes was 16% in 511 patients who had received 10Gy or more to the pancreatic tail. A dose response was seen up to 20 to 29 Gy before reaching plateau at higher radiation doses. The relative risk of developing diabetes was 11.5 for patients who received at least 10 Gy to the pancreatic tail compared to patients who did not receive radiation, and was most pronounced for patients under the age of 2 at the time of radiation. This association was not appreciated for radiation to other parts of the pancreas, and results were unchanged after adjustment for body mass index despite a strong independent effect (de Vathaire et al. 2012). There have also been reports of a chronic pancreatitis syndrome following abdominal radiation (Levy et al. 1993; Schoonbroodt et al. 1996). Levy et al. reported on five patients who received abdominal irradiation and developed pseudocysts, pancreatic calcifications, and morphologic changes resembling chronic pancreatitis at a median of 7 years following 36–40 Gy (Levy et al. 1993). There are little data to define a dose response for late radiation-induced pancreatic injury, however, histological evidence of pancreatic injury has been demonstrated with fractionated doses as low as 36 Gy (Levy et al. 1993), and a higher incidence of radiation-induced pancreatic complications has been reported at doses of 60 Gy (Fajardo and Berthrong 1981; Rubin and Casarett 1968; Berthrong 1986).

As targeting and delivery of radiation has improved with newer technologies, investigators have evaluated the potential for dose-escalation in an attempt to improve outcome for patients with intra-abdominal malignancies. One model investigated the use of intensity-modulated radiation therapy (IMRT) optimization for selective dose radiation escalation in patients with pancreatic cancer (Spalding et al. 2007). IMRT using lexicographic ordering, a hierarchical optimization technique, with generalized equivalent uniform dose (gEUD) cost functions, was used to increase the dose to pancreatic tumors and to areas of vascular involvement that precluded surgical resection. IMRT plans optimized by using gEUD-based cost functions resulted in inhomogeneous dose distributions that allowed substantial dose escalation to tumor and areas of vascular involvement compared with 3D conformal radiation treatment plans up to 66 Gy and 85 Gy, respectively, with significant dose reductions in nearby normal tissue organs at risk (Spalding et al. 2007). This model is currently being tested in clinical studies and the effect on normal pancreatic function has not yet been described. It is possible with better tumor control, survival of these patients may be improved, and late pancreatic normal tissue toxicity will be increasingly reported.

5.2 Hypofractionation

A study at Massachusetts General Hospital is currently evaluating the dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment (Kozak et al. 2007). Data for the first nine pancreatic cancer patients treated with neoadjuvant intensity-modulated radiotherapy (1.8 Gy × 28) had treatment plans generated using a 5 CGE × 5 fraction proton regimen. Improved dose conformality provided by the hypofractionated proton regimen resulted in significant reduction in the mean doses to surrounding normal tissue inclusive of kidneys, liver, and small bowel in both high- and low-dose regions (Kozak et al. 2007). The dose to uninvolved pancreas was not evaluated but this treatment planning technique may also be applied. Hypofractionated proton radiotherapy has not yet been tested in a Phase I clinical trial investigation. Similar to dose-escalated IMRT, we may encounter improved tumor control, improved survival, and longer term follow-up resulting in more pancreatic complications.

Stereotactic body radiosurgery has recently been utilized to deliver a range of hypofractionated radiation treatments to patients with pancreatic tumors. Up to 25 Gy delivered in a single fraction has been used for treatment, including some patients who received prior chemotherapy and fractionated external beam radiation. The largest series reported included 77 patients with unresectable adenocarcinoma of the pancreas who received 25 Gy in 1 fraction. The rates of grade two or greater late toxicity were 11 and 25 % and were due to bowel ulceration, stricture, or perforation, but no pancreatic complications were reported (Chang et al. 2009). Several other clinical studies utilizing this technology with a variety of fractionation schedules to treat pancreatic tumors have been reported, but patient numbers remain small, and median follow-up is short. Most studies

focus on intestinal toxicity as a major limitation, and there are no reports of pancreatic injury to date.

5.3 Recommended Dose-Volume Constraints

Both the pancreas and salivary glands show many histological and functional similarities. Both originate from endoderm and consist of acinar and ductal epithelial cells, which have similar exocrine function and microenvironments. In addition, investigators have compared two stem cell populations from pancreatic and salivary glandular tissues, which demonstrated similar phenotypes and analogous properties. During embryonic development the two exocrine glands originate from the foregut, which might be the explanation for these similarities (Gorjup et al. 2009). For this reason, some have postulated a similar tolerance to radiation.

As radiation-induced damage to pancreatic function is rarely life threatening and is usually well treated with medical management, dose-volume constraints have not been formally evaluated as with other critical normal tissues. Pancreatic exocrine dysfunction is the side effect most often encountered following pancreatic radiation therapy. If one extrapolates from similarities between salivary and pancreatic exocrine tissue, we may hypothesize similar radiation dose-volume effects. Dose-volume relationships have been well studied for parotid radiation (Blanco et al. 2005; Deasy et al. 2010; Eisbruch et al. 1999; Marmiroli et al. 2005; Roesink et al. 2001; Li et al. 2007; Maes et al. 2002).

Important studies not only evaluated quality of life, but also quantitatively measured salivary function at intervals following radiation and correlated the results with dose-volume data (Blanco et al. 2005). Based on these data, it is estimated that a mean parotid dose of 25.8 Gy, on average, is likely to reduce a single parotid gland's flow to 25 % of its pretreatment value, and the incidence of xerostomia as a result of radiation-induced exocrine dysfunction was significantly decreased when the mean dose of at least one parotid gland was kept to <25.8 Gy with conventional fractionation. Using this model, salivary function, in each gland, appeared to be lost exponentially at a rate of approximately 5 % per 1 Gy of mean dose (Blanco et al. 2005).

Most recently Deasy et al. reanalyzed available data on dose-volume relationships for salivary glands for the quantitative analyses of normal tissue effects in the clinic (QUANTEC) project (Deasy et al. 2010). Although he concluded that currently available predictive models are imprecise, the risk of severe xerostomia defined as long-term salivary function of <25 % of baseline, may be avoided if at least one parotid gland is spared to a mean dose of less than approximately 20 Gy or if both glands are spared to less than approximately 25 Gy (mean dose) (Deasy et al. 2010). This is somewhat consistent with the limited data published on radiation–induced pancreatic toxicity reporting exocrine dysfunction (Case and Warthin 1924; Brick 1955), and chronic pancreatitis-like syndrome as low as 36 Gy (Levy et al. 1993).

Hence, if we accept the hypothesis that radiosensitivity is similar for parotid exocrine function, we suggest that 50 % of the pancreas not involved by tumor receive a mean dose of less than 25 Gy. However, it should be recognized that radiation-induced pancreatic damage is rarely a limiting factor, which can usually be managed medically and concerns for intestinal or renal toxicity and/or tumor control usually prevail. In general, lower pancreatic mean doses will result in better function. Clinical judgment should play an important role in treatment planning when compliance with dose-volume constraints may not be achievable.

Radiation-induced pancreatic endocrine insufficiency is less commonly encountered but nonetheless, has been reported. Although there are no dose-volume data predicting this rare complication, one should assume that irradiating the entire pancreas to high dose would increase the risk of glucose intolerance, especially since there is a higher proportion of beta cells in the tail region. Analysis of the available literature aforementioned, tolerance dose $TD_5 = 45$ Gy, and the $TD_{55} = 60$ Gy is postulated.

6 Chemotherapy

The majority of data presented in this chapter predates the routine use of combined modality therapy, however, we acknowledge that exposure to chemotherapeutic agents may contribute to pancreatic sequelae resulting from treatment. Most current cancer treatment regimens for abdominal malignancies incorporate the use of sequential and/or concurrent chemotherapy in addition to abdominal radiation. To date, there have been only a few sporadic reports of acute pancreatitis associated with certain chemotherapy, mostly in children treated for all who did not receive abdominal radiation (Flores-Calderon et al. 2009; Alvarez and Zimmerman 2000; Adachi et al. 1988; McGrail et al. 1999), and patients receiving alloxan and streptozocin (Scarpelli 1989). To date, there have been no reports of pancreatic toxicity for agents commonly used for the treatment of abdominal malignancies, nor in patients who have received combined chemoradiation for treatment of abdominal malignancies.

7 Special Topics

7.1 Pediatrics

In the course of abdominal RT or TBI, damage to the islet cells of the pancreas can occur and there is now emerging evidence on the increased risk of diabetes mellitus (DM) in long-term survivors of childhood cancer. This may be the result of direct cytotoxicity to pancreatic cells from abdominal RT, but may also be a long-term implication from the metabolic syndrome. In a study of 8599 survivors from the CCSS, DM was reported in 2.5 % of the survivors compared with 1.7 % of the siblings. After adjustment for body mass index, age, sex, race/ethnicity, household income, and insurance, the survivors were 1.8 times more likely than the siblings to report DM. In adjusted models, TBI was associated with a sevenfold increased risk, abdominal irradiation with a 2.7-fold increased risk, alkylating agents with a 1.7-fold increased risk, and age 0–4 years at diagnosis with a 2.4-fold increased risk (Meacham et al. 2009). More recent data demonstrates a dose-response relationship between pancreatic tail irradiation and subsequent risk of diabetes. The cumulative incidence of diabetes was 16% in 511 childhood cancer survivors who had received 10Gy or more to the pancreatic tail. A dose response was seen up to 20 to 29 Gy before reaching plateau at higher radiation doses. The relative risk of developing diabetes was 11.5 for patients who received at least 10 Gy to the pancreatic tail compared to patients who did not receive radiation, and was most pronounced for patients under the age of 2 at the time of radiation (de Vathaire et al. 2012).

8 Prevention

The use of radioprotectant and free-radical scavengers for prevention of radiation-induced pancreatic damage has only been investigated in the laboratory. The first study to investigate this topic was published in 1967 (Volk et al. 1967; Wellmann et al. 1967). In this study dogs were either pretreated with a single small nondiabetogenic dose of alloxan monohydrate (15 mg/kg) or placebo and then received a single dose of 50–60 Gy to a surgically exposed pancreas. In the nontreated dogs, subsequent histological examination of partial pancreatectomy specimens demonstrated widespread focal cytoplasmic degeneration, endoplasmic reticulum and mitochondrial abnormalities, and reduction in size and number of zymogen granules similar to other studies. In addition, these dogs demonstrated marked decrease in amylase, aminopetidase, and lipase activities. In the alloxan treated dogs, the structural changes were not as pronounced, and the marked decrease in enzyme activity was not observed (Volk et al. 1967; Wellmann et al. 1967). A follow-up study evaluated dogs which received a single dose of alloxan at intervals of 2–14 days following radiation, as well as some which receive alloxan both pre- and post-treatment. No severe nor widespread cytological changes were noted in any animals and similar radioprotective effects were observed on enzymatic levels, especially when the dogs received both pre- and post-treatment alloxan (Wellmann et al. 1967). The authors proposed that the protective effect of alloxan may be in part due to interaction with amino acids, which modifies the structure and reduces synthesis of proteins, particularly those with –SH radicals (Doolittle and Watson 1966; Stocker et al. 1965). No studies have reported radioprotective effect of alloxan on the human pancreas.

Amifostine has been evaluated as a radioprotector in the clinical setting for both salivary function preservation in patients receiving radiation for head and neck cancers (Brizel et al. 2000) and as an rectal mucosa protector for patient receiving abdominal or pelvic radiation (Simone et al. 2008). Its effect on pancreatic function has been evaluated in the laboratory setting (Grdina et al. 2009). Amifostine was administered intraperitoneally to mice receiving radiation for transplanted tumors. The use of amifostine produced a delayed radioprotective effect correlating with elevated levels of the antioxidant enzyme, superoxide dismutase (SOD2) activity in selected tissues, including heart, liver, lung, pancreas, small intestine, spleen, and tumor 24 h after amifostine treatment. Other antioxidant enzyme, catalase, and glutathione peroxidase (GPx), activities remained unchanged except for significant elevations in the spleen. GPx was also elevated in the pancreas indicating a radioprotective effect (Grdina et al. 2009). There have been no clinical studies evaluating radioprotective effects of Amifostine in the pancreas in humans.

There have been no other agents formally evaluated as radioprotectants in the pancreas in humans. The only other two agents that demonstrated promising results in animal studies were octreotide and glutamine, which mitigated the radiation-induced changes in myeloperoxidase and caspase activity, and malondialdehyde and NFκ-B levels, as previously described (Olgac et al. 2006; Erbil et al. 2005).

9 Management

Because pancreatic exocrine deficiency can be managed with replacement therapy, pancreatic injury has not routinely been considered a serious complication compared to other normal tissue damage that may occur from abdominal radiation, such as radiation enteritis. In most cases, pancreatic enzyme supplementation is all that is needed to improve intestinal absorption of fats and proteins, reverse

weight loss, and normalize stools. Dosage and timing of enteric-coated pancreatic enzymes are important issues in the treatment of malabsorption. Nonenteric-coated enzyme preparations along with acid suppression (histamine-2 blockers or proton-pump inhibitors) are of limited to modest effectiveness in treating pain.

Chronic pain related to progressive fibrosis compressing splanchnic nerves sometimes responds to narcotic pain medication. The role of endoscopic ultrasound-guided celiac plexus block is sometimes useful and is limited to treating those patients whose pain has not responded to other modalities (Abdel Aziz and Lehman 2007). In the setting of pancreatic cancer, such pain is typically associated with tumor progression rather than radiation injury, however.

The management of patients with glucose intolerance and diabetes should ameliorate hyperglycemia and its symptoms and prevent hyperglycemic crises. The burden of such therapy falls on the patient, and education of the patient and/or caregiver is important. Home glucose monitoring is a component of glycemic control and relies on patient compliance. Most patients with glucose intolerance without evidence of hyperglycemia respond to dietary management. Exercise also contributes to weight control, cardiovascular fitness, and increases the body's sensitivity to insulin. Sulfonylurea oral hypoglycemic agents can sometimes be useful in patients with hyperglycemia to increase endogenous insulin secretion in response to meals and enhance peripheral sensitivity, however, approximately 25 % of patient with Type 2 diabetes will not respond. This number is thought to be higher in patients with radiation injury but the exact proportion of nonresponders is not known.

Most patients who develop hyperglycemia following radiation to the pancreas require insulin therapy. It has been postulated that patients who develop hyperglycemia following pancreatic radiation have blood glucose levels that are more difficult to control than a patient with Type I diabetes who did not receive abdominal radiation. There is convincing evidence that tighter glucose control is accompanied by decreased incidence and progression of chronic complications. Surveillance for early stages of diabetic complications such as retinopathy and neuropathy is important because progression can be delayed with appropriate intervention. Monitoring of hemoglobin A_{1c} may be helpful in predicting risk for these complications.

10 Future Direction and Research

a. The dose–response for reductions in *regional* pancreatic function (either exocrine or endocrine) are not known. Sophisticated imaging techniques might be able to detect these cellular functions and allow one to quantitatively relate regional RT doses to regional changes in function.
b. The relationship between the three-dimensional dose distribution and changes in global pancreatic function are not well defined. Studies that relate global function (e.g., glucose tolerance testing or fat absorption assessments) to the three-dimensional dose distribution could be performed. The pancreas should be identified as a critical organ for radiation planning purposes, especially in children receiving abdominal irradiation. Long-term follow-up of patients receiving abdominal irradiation should include diabetic screening as a component of survivorship plans.
c. The pancreas is often a target of intra-operative radiation. One could perform biopsies of the normal pancreas immediately before and after such intra-operative radiation to assess the acute molecular events triggered by radiation.

11 History and Literature Landmarks

1924: Case and Warthin: reported first clinical case of patient vigorously irradiated, who died 10 weeks post therapy over epigastrium with atrophy of acinous cells, vacuolar degeneration, and necrosis.

1935: Schurch and Vehlinger reported necrosis of pancreas of a dog following high-dose radium implantation.

1942: Friedman: reviewed literature suggesting islets of Langerhans were more radioresistant than acinar epithelium.

1955: Spalding and Lushbaugh: studied effects of massive radiation dose single exposure of pancreas in monkeys and rats and found pyknosis and necrosis of islet alpha cells which more readily injured than beta cells.

1955: Brick reported first observation of pancreatic fibrosis at autopsy of 3 patients following megavoltage irradiation for para-aortic lymph nodes.

1968: Rubin and Casarett: reviewed the literature concluding the pancreas is relatively radioresistant compared to other abdominal organs, i.e., stomach, intestine, colon, liver, and kidneys and was not dose limiting.

2012: de Vathaire et al. demonstrated a 16% cumulative incidence of diabetes in 511 childhood cancer survivors who had received 10Gy or more to the pancreatic tail, with a dose response identified for up to 20-29 Gy.

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Kidney and Ureter

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Abstract

- The kidneys are dose-limiting for radiation therapy of cancers of the upper abdomen, as well as for conditions treated with total body irradiation and bone marrow transplant or hematopoietic stem cell transplant.
- The architecture of the kidneys can be considered as subunits (i.e. nephrons) that are predominantly arranged "in parallel", but with some serial function.
- The nephron is the basic structural and functional unit of the kidneys. It depends on a complex vascular system.
- The major target for injury appears to be the arteriolar-glomerular area rather than the tubular epithelium, as the earliest cellular feature of RT-induced kidney injury is glomerular endothelial cell injury.
- The kidneys maintain the homeostasis of body fluids by filtering metabolites, including the urea and fixed acid of protein catabolism.
- Glomerular filtration rate (GFR) measurements may help to adjust the dosing of cytotoxic agents, and accurate chemotherapy dosing may reduce side effects of the cytotoxic agents, all the while retaining their benefit.
- Intra-renal TGF-beta is elevated in experimental radiation nephropathy, but it is not clear if it results from injury or initiates it.
- The bone marrow transplant (BMT) nephropathy syndrome, has been defined as azotemia (doubling of baseline serum creatinine level or a >50 % decrease in the glomerular filtration rate (GFR)), hypertension, and anemia after transplant, and it occurs ≈8–12 months post-transplant.

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- The time from bilateral kidney irradiation to clinical symptoms of radiation nephropathy can range from 1–9 months (in the acute presentation) to 18 years + (in the chronic presentation) of radiation nephropathy.
- Total dose associated with a 5 % risk of injury at 5 years, TD5/5, of 18–23 Gy, and a total dose associated with a 50 % risk of injury at 5 years, TD50/5, of 28 Gy, in 0.5–1.25 Gy per fraction.
- TBI dose appears to be related to risk of renal toxicity post hematopoietic stem cell transplant.
- Unilateral kidney irradiation may be followed by injury, as shown by Thompson et al. who observed a dose response for kidney atrophy and clinical kidney toxicity many years following unilateral kidney RT (Thompson et al. 1971). The effective dose associated with scintigraphic changes in 50 % of the patients (ED50) was 27 Gy when 10 % of the bilateral kidney volume was irradiated. Neonates appear to have an increased sensitivity to RT. Doses of 12–14 Gy at 1.25–1.5 Gy per fraction to the entire neonate kidney have been associated with a decreased GFR (Peschel et al. 1981).
- The therapeutic efficacy of radiolabeled antibody fragments can be limited by renal toxicity, particularly when the kidney is the major route of extraction from the circulation.
- Ureteric strictures following irradiation were first reported in 1934 following pelvic irradiation and radium brachytherapy for gynecological malignancies (Everett 1934).
- Chemotherapy related injury may manifest itself as acute renal failure (ARF), chronic renal failure, or specific tubular defects.
- Animal models of BMT nephropathy have shown that angiotensin converting enzyme (ACE) inhibitors, dexamethasone, or acetylsalicylic acid can prevent and treat chronic renal failure (Moulder et al. 2007); (Verheij et al. 1995; Cohen et al. 1997; Cohen et al. 2007); (Moulder et al. 1987, 1998a, b).
- In chronic kidney disease, a reduction in renal workload by low protein diet, and salt restriction may delay the progression to renal failure.

Abbreviations

(ACE) Angiotensin converting enzyme
(ARF) Acute renal failure
(BMT) Bone marrow transplant
(CrCl) Clearance of creatinine
(DVH) Dose–volume histogram
(GFR) Glomerular filtration rate
(HSCT) Hematopoietic stem cell transplant
(HUS) Hemolytic uremic syndrome
(NTCP) Normal tissue complication probability
(NT) Nephrotoxic
(RT) Radiation therapy
(TBI) Total body irradiation

1 Introduction

The kidneys are dose-limiting for radiation therapy of cancers of the upper abdomen, as well as for cancers treated with total body irradiation for bone marrow transplant or hematopoietic stem cell transplant. The kidneys are vitally important, for filtering waste metabolites and electrolytes from the blood, for producing erythropoietin to stimulate red blood cell production, and for modulating blood pressure via fluid/electrolyte balance. The incidence of radiation-associated kidney injury, i.e., radiation nephropathy, is likely underreported due to its long latency, and to the occurrence of more common causes of renal failure that may make it difficult to diagnose radiation nephropathy.

The pathophysiology of radiation nephropathy is poorly understood. Its presentation may be acute, severe, and irreversible leading to acute renal failure (ARF), or more subtle, presenting with a gradual change in glomerular filtration rate (GFR) and very late clinical sequelae.

A variety of dose/volume parameters have been linked to renal injury and can be used to provide clinical guidelines (see Sect. 5). However, predictive models for radiation nephropathy are suboptimal, and these models require future validation. Although progress has been made in the mitigation of radiation nephropathy with several compounds in animal models, there are less data on prevention or mitigation in patients (see Sect. 8). In this paper we will review radiation nephropathy and provide dose/volume recommendations for the clinician.

Figure 1 summarizes the biocontinuum for renal injury.

2 Anatomy and Histology

2.1 Gross Anatomy

The kidneys are paired organs, located in the posterior abdomen within the retroperitoneum, ranging in length from 9 to 13 cm, the left slightly larger than the right (Fig. 2). Surrounding organs include the liver, the diaphragm, and the spleen. The right kidney is slightly lower than the left. They are surrounded by fat and renal fascia, and they are mobile. Renal motion during respiration ranges from 5 to 30 mm, in a coronal body plane. Each kidney is attached to a ureter which drains the urine to the bladder for excretion. Congenital absence of one kidney can occur, but occurs in

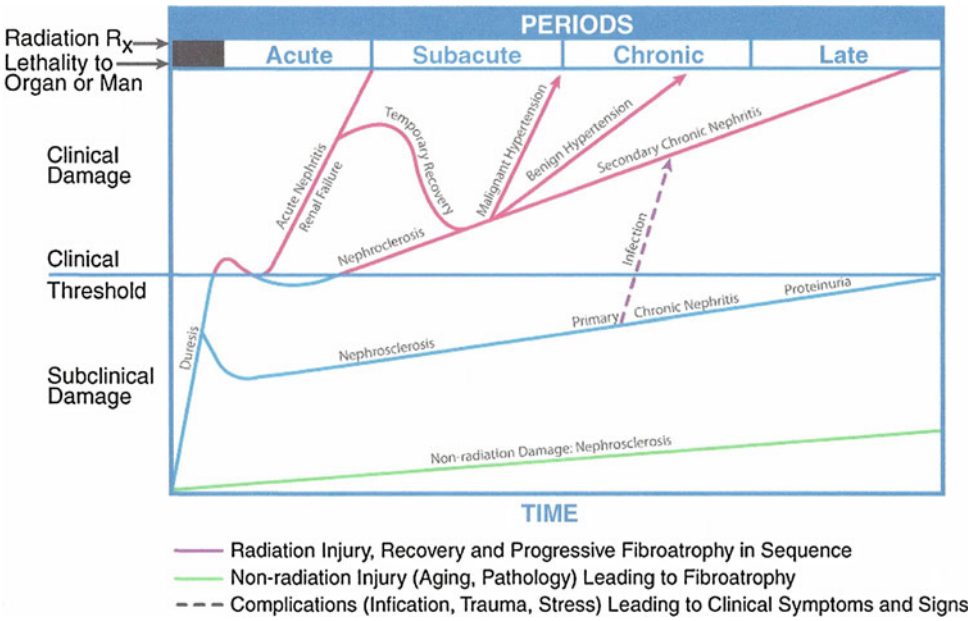

Fig. 1 Biocontinuum: The time course of renal symptoms in patients treated with radiation therapy (with permission from Rubin and Casarett 1968)

only 1 in 1000 births. One in about 500 people is born with a horseshoe kidney, which forms from the fusion of two kidneys, and is usually located within the pelvis (Fig. 2).

2.2 Histology and the Functional Subunit

The nephron is the basic structural and functional unit of the kidney. It depends on a complex vascular system. Afferent vessels become tufts of capillaries in the renal glomeruli, then empty into the efferent arterioles. The glomerular capillary blood pressure provides the force for water and solutes to be filtered out of the blood into a space contained in a fibrous sac referred to as Bowman's capsule that opens to the proximal tubule. The tubule is the portion of the nephron that contains the tubular fluid filtered by the glomerulus. Draining each glomerulus, the tubules are: the proximal convoluted tubule, then Henle's loop, the medullary thick ascending limb, and finally the distal convoluted tubule and collecting ducts, each section with specific functions. There are cortical nephrons, located superficially, and juxtamedullary nephrons, located more deeply in the kidney, which have somewhat different excretory and urine concentrating abilities. Histologic examples are shown in Fig. (3a, b, c).

The architecture of the kidney can be considered as subunits predominantly arranged "in parallel", but with some serial function. For example, the collecting system is "in series", because an injury to the central collecting system or fibrosis/stenosis of the ureter will render the upstream kidney non-functional. In contrast, a portion of the kidney can be injured without cessation of global organ function, because nephrons function relatively independently, as subunits arranged "in parallel". Resection or injury to a region of kidney will not immediately compromise function of adjacent regions. However, over the long term, after loss of sufficient kidney mass, "overwork" of the remaining nephrons may stress them and lead to their injury, with subsequent decline of overall kidney function (referred to as "hyperfiltration" (Brenner 1983)).

3 Biology, Physiology, and Pathophysiology

3.1 Tissue, Cellular, and Molecular Mechanisms

The pathogenesis of RT-induced kidney injury is not well understood. The major target for injury appears to be the arteriolar-glomerular area rather than the tubular epithelium, as the earliest cellular feature of RT-induced kidney injury is glomerular endothelial cell injury. Of the many cell types in kidneys, glomerular, then interstitial capillary endothelia have the highest mitotic indices (Nadasdy et al. 1994). This may explain the predominance of glomerular injury in radiation nephropathy. On light and electron microscopy, glomerular endothelial injury and mesangiolysis are characteristic. Progressive replacement of capillary walls and lumina lead to glomerular sclerosis (Glatstein et al. 1977), which proceeds tubular injury (Jaenke et al. 1993). Tubular cell loss occurs, probably by both direct irradiation injury and secondarily, from ischemia, due to the vascular radiation injury. The cortical tubules tend to be disrupted more than the medullary tubules.

Following Hematopoietic Stem Cell Transplant (HSCT) and TBI, thrombotic microangiopathy is an additional, systemic feature commonly observed. Although it has been seen

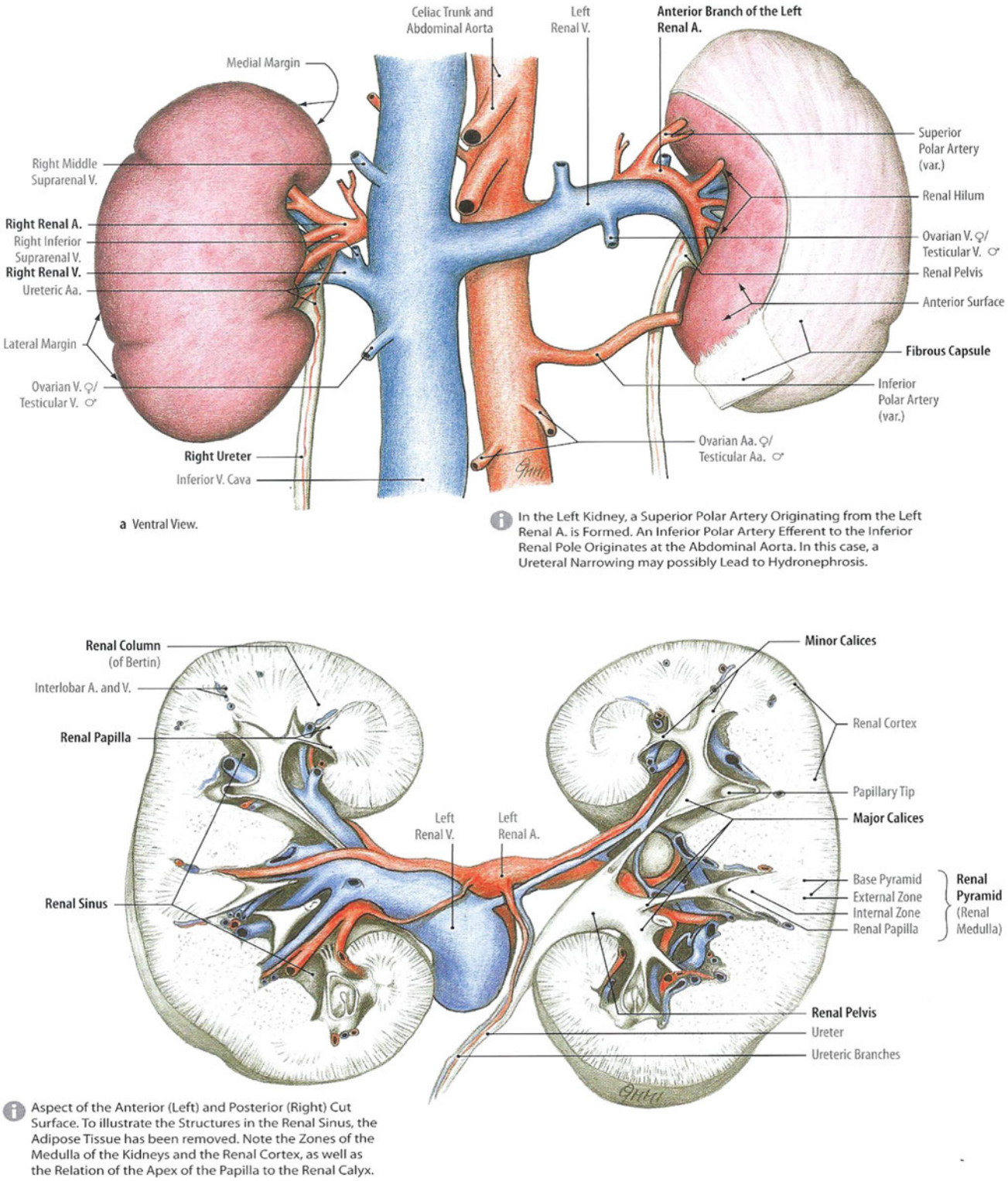

Fig. 2 Gross anatomy of the kidney (with permission from Tillman 2007)

following non-TBI kidney irradiation (Cogan and Arieff 1978), it is unusual in this setting. The development of thrombotic microangiopathy may be influenced by extra-renal endothelial injury caused by RT.

At the cellular and molecular levels, a cascade of events begins immediately after exposure to RT and proceeds during a prolonged period of clinically occult injury (Rubin et al. 1995; Johnston et al. 1996; Fleckenstein et al. 2007).

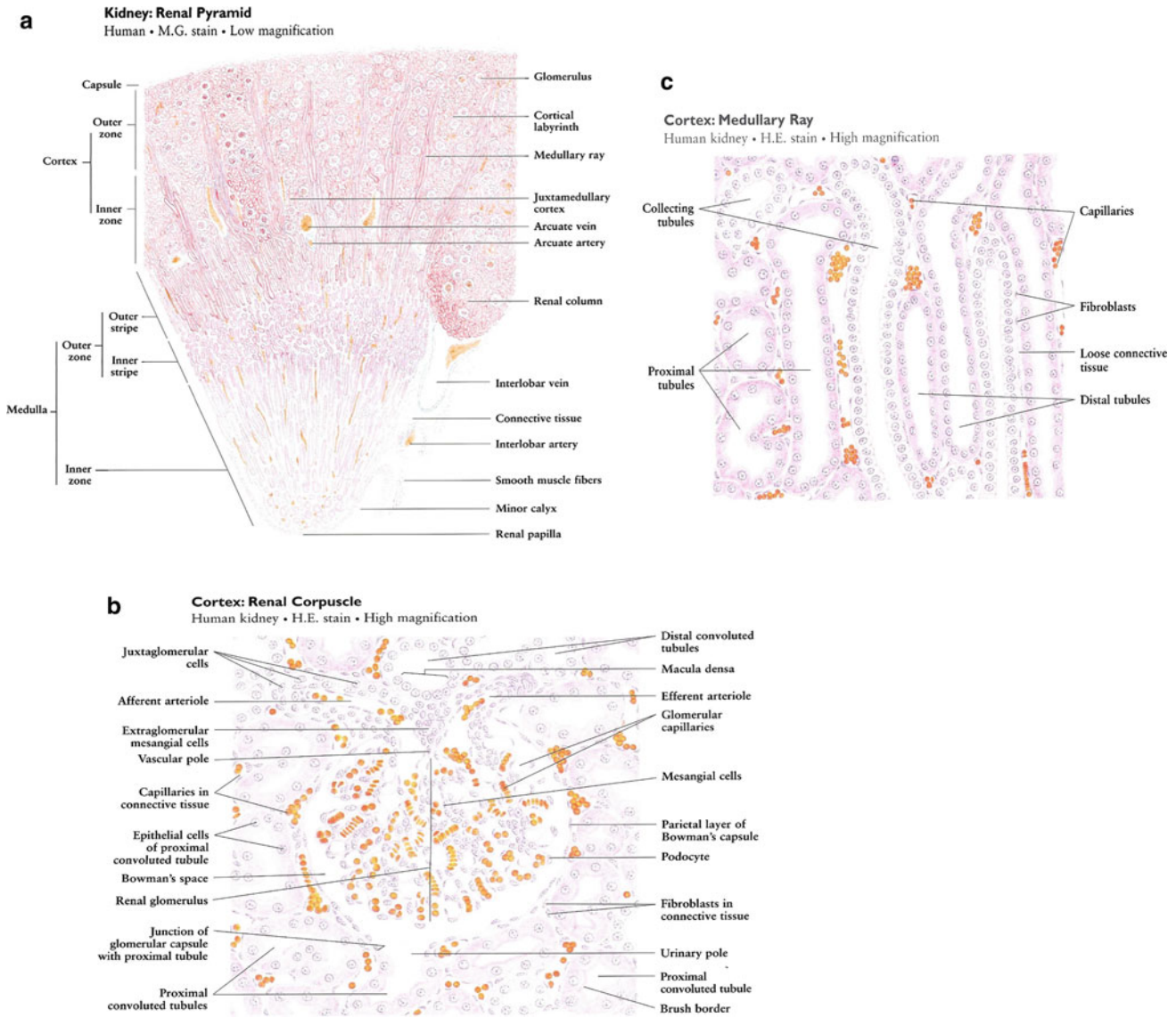

Fig. 3 Renal histology low (**a**) and high (**b**) and (**c**) magnification (with permission from Zhang 1999)

Endothelial cell death in mitosis can result in increased vascular permeability, edema, inflammation, and fibrosis (Vujaskovic et al. 2001; Jackson et al. 2006; Fleckenstein et al. 2007; Novakova-Jiresova et al. 2007) (Vujaskovic Anscher et al. 2001; Jackson Batinic-Haberle et al. 2006). Free radicals are formed by the ionizing radiation, leading to DNA damage and mitotic cell death. In general, this transient increase in reactive oxygen and nitrogen species is unlikely to be sufficient on its own to produce prolonged progression of injury. Subsequent chronic oxidative stress and inflammation might perpetuate the production of free radicals and activate cytokines that may contribute to the development of chronic injury. On the level of mediators, intra-renal TGF-beta is elevated in experimental radiation nephropathy, but it is not clear if it results from injury or initiates it. (Datta et al. 1999) (Cohen et al. 2000) As for the role of oxidative stress, in animal models, there is thus far no clear evidence that chronic oxidative stress plays an essential role in radiation nephropathy.

Animal studies have investigated the dependence of radiation fraction size on radiation nephropathy. In rodents, for fraction sizes of 1 Gy or higher, an α/β ratio of 1.5–3 Gy was found for radiation nephropathy (Stewart et al. 2001). The inter-fraction interval has also been shown to be important in animal models, with an estimated half-time for repair of 1–2 h (similar for fraction sizes from 2 to 7 Gy). The time to expression of renal damage has also been shown to be dose dependent in animal models, with larger doses

Table 1 Renal physiology

Function	Test
Glomerular filtration fraction (GFR)	Insulin clearance test
Tubular reabsorption limitation (TRM)	Para-amino hippurate test
Antidiuretic hormone (ADH) secretion	Urine osmolality and volume test Blood urea level test
Angiotensin converting enzyme (ACE)	Blood pressure serial Na + Cl Levels
Potassium, calcium, and phosphate excretion	Serum: K, Ca, Ph levels
Bicarbonate production and reabsorption	Urine U_{ta} concentration Urine U_{nh4} ammonium concentration

causing shorter latency times. The histology of radiation nephropathy is the same, regardless of the fractionation.

3.2 Physiology and Pathophysiology

The kidneys are organs that have many roles. They maintain the homeostasis of body fluids by filtering metabolites, including the urea and fixed acid of protein catabolism. The kidneys are the regulators of blood pressure, mainly via sodium excretion and the renin-angiotensin system. The kidneys accomplish their functions independently and through coordination with the cardiovascular and endocrine system. Thus, for instance, sodium balance depends in part on adrenally secreted aldosterone, which increases sodium ion reabsorption in the distal convoluted tubules of the kidneys. Water balance depends on detection of changes in plasma osmolarity by the hypothalamus. Increased plasma osmolarity leads to enhanced renal conservation of water, and that is dependant on the antidiuretic hormone, vasopressin, which is secreted by the posterior pituitary gland in response to the hypothalamic detection of changed osmolarity. The renal conservation of water closes the feedback loop. The kidneys secrete a variety of hormones, including erythropoietin, urodilatin, renin, and vitamin D, and they regulate glucose metabolism (Table 1 and Fig. 4a, b, c).

The renin-angiotensin system appears to play a role in radiation nephropathy. In animal models, angiotensin-converting enzyme (ACE) inhibitors are very effective in preventing, mitigating, and treating radiation nephropathy (Cohen et al. 1997), and conversely, angiotensin II infusion exacerbates radiation nephropathy (Cohen et al. 1999). However, activation of the renin-angiotensin system (systemically or locally within the kidney) has not been confirmed in radiation nephropathy (Cohen et al. 2002). Thus, the exact role of the renin-angiotensin system in this model is not well-defined.

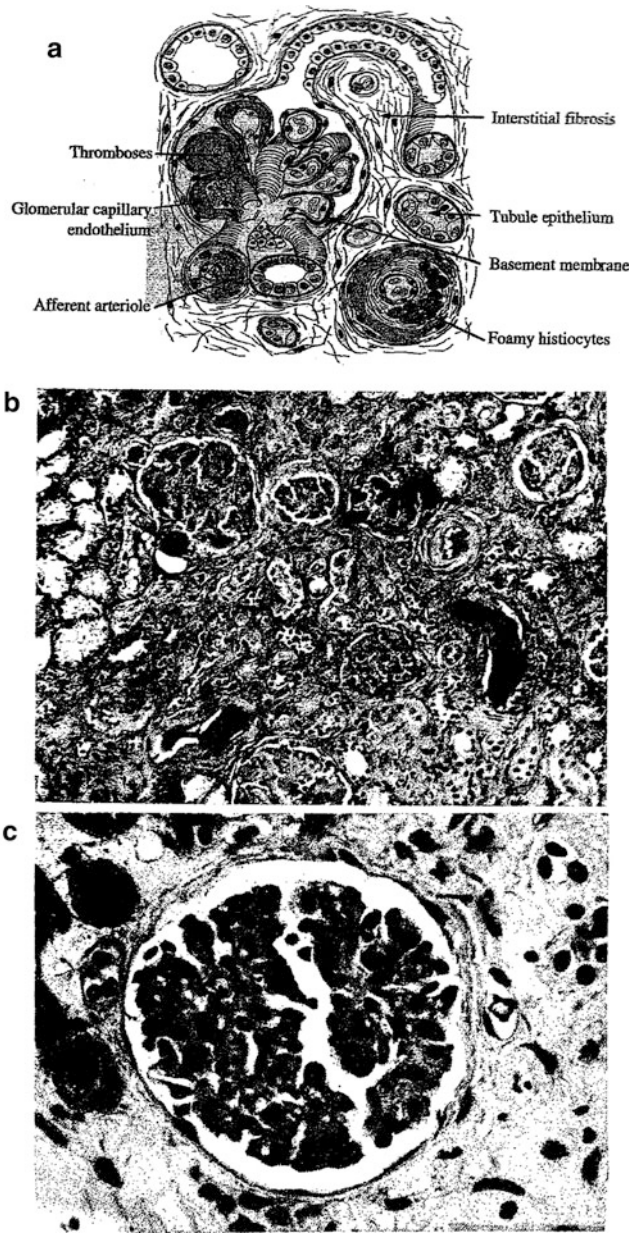

Fig. 4 **a** Pathology—schematic of glomerular sclerosis. With permission from Rubin 2001, **bc** Glomerular sclerosis demonstrates the withering and loss of glomeruli. (**b**) Low mag, (**c**) High mag. The radiation response in the renal parenchyma. The responsive cell types are in the endothelium and epithelium. There is fibrinoid and hyaline accumulation associated with endothelial swelling in the afferent arterioles, which may spread beneath the glomerular capillary endothelium. The basement membrane thickens. Vascular compromise promotes thromboses, possibly leading to infarct. The tubular epithelium presents a variable picture, but there is some degree of interstitial fibrosis. As the vascular compromise develops, larger vessels may be affected, with focal necrosis and accumulations of foamy histiocytes. (From White (1975) with permission)

3.2.1 Glomerular Function

The serum creatinine concentration is used to evaluate renal function, despite its substantial variability. Creatinine is freely filtered by the glomeruli, and its tubular secretion is less important than its filtration. The clearance of creatinine (CrCl) from the body approximates the actual GFR. Measurement of GFR is particularly important in cancer patients, as many cytotoxic agents are eliminated primarily by the kidneys. GFR measurements may help to adjust the dosing of cytotoxic agents, and accurate chemotherapy dosing may reduce side effects of the cytotoxic agents, all the while retaining their benefit.

GFR can be measured using radiolabelled isotopes, contrast media, or inulin. Twenty-four hours urine collection is another method to measure creatinine clearance. Since the serum creatinine level depends on its release from creatinine in muscle, normal serum creatinine levels are dependent on age and sex. Different mathematical formulas have been used to estimate GFR, which take into account the age, size, and gender variability of the serum creatinine. Most of these formulas have not been validated in cancer patients, but they are used commonly as they provide rapid and simple estimations of GFR.

Clinically relevant differences between calculated GFR values and measured GFR values have been observed (Holweger et al. 2005). Measurement of GFR of low-molecular-weight proteins, such as cystatin C and ss-trace protein, may be more useful than CrCl or mathematically estimated GFR. The optimal strategy for measuring GFR in cancer patients is not clearly defined (Holweger et al. 2005)

3.2.2 Tubular Function

The normal tubules reabsorb much of the glomerular filtrate, to achieve acid–base balance and maintain body tonicity. Therefore, tubular injury may manifest as changes in tubular excretion of normally reabsorbed substances, abnormalities in urine pH, or body tonicity. Beta-2 microglobulin levels in blood or urine can be useful in identifying a tubular injury, as this protein is usually almost completely reabsorbed by the proximal tubules. Tubular injury can also lead to changes in cation and anion excretion.

Illustrations of the histology of RT effects on the kidney are shown in Fig. 4. The effects of RT on the microvasculature of the glomerulus are shown in Fig. 5. Various metrics used to quantify renal function are provided in Table 1.

4 Clinical Syndromes (Endpoints)

The findings associated with radiation nephropathy can be divided into subclinical and clinical (Table 2). The SOMALENT system also provides a means to segregate and grade

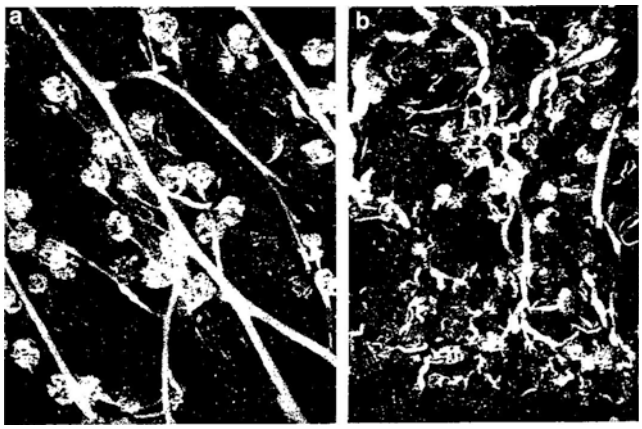

Fig. 5 Pathophysiology: Pathology of acute clinical periods: microradiographs of cortical region of the kidney. **a** Microangioradiograph of cortical region of normal dog kidney, showing relatively normal filling of interlobular arteries, afferent arterioles, and glomeruli with the radiopaque medium (×25). **b** Microangioradiograph of cortical region of normal dog kidney 6 months after receiving a single X-ray dose of 1000 rads, showing the effects of the occlusive changes in interlobular arteries and afferent arterioles in terms of decreased and irregular filling of these vessels and glomeruli with the radiopaque medium (×25) (From J. G. Maier and G. W. Casarett: Patho-Physiologic Aspects of Radiation Nephritis in dogs. University of Rochester, with permission)

renal injury (Table 3). The K/DOQI stages of chronic kidney disease are shown in Table 4. Its modern congener, the BMT nephropathy syndrome, has been defined as azotemia (doubling of baseline serum creatinine level or a >50 % decrease in the GFR), hypertension and anemia after HSCT, in the absence of other identifiable cause of kidney dysfunction and in the absence of nephrotoxic medications (Cohen et al. 1993). It occurs at a median time of 8–12 months after the HSCT. Anemia is more severe in radiation nephropathy than it is in other causes of chronic renal failure. Features of hemolytic-uremic syndrome, with microangiopathic hemolytic anemia and thrombocytopenia, are not uncommon in the radiation nephropathy after TBI (Cruz et al. 1997), and less common in radiation nephropathy after non-TBI associated renal radiation (Tables 2, 3 and 4).

Radiation nephropathy can present in an acute and/or chronic form. The acute form may present with azotemia, hypertension, and anemia at several months after RT. In the chronic form, radiation nephropathy is generally subclinical within the first 6 months. Signs (e.g. decreased GFR, increased serum beta-2 microglobulin) and symptoms (e.g. edema) may develop in the sub-acute period (6–18 months). Chronic injury (>18 months following RT) is characterized by benign or malignant hypertension, elevated creatinine, anemia, and renal failure (Rubin and Casarett 1968; Verheij et al. 1994). Other signs and symptoms include dyspnea on exertion, headaches, fatigue, and papilledema. There are other causes of renal disease in subjects who have undergone

Table 2 Representative radiation-associated kidney toxicity endpoints segregated as shown

	Global		Imaging/regional
	Physiologic	Biochemical	
Subclinical	Elevated blood pressure Increased weight	Elevated serum creatinine Elevated cystatin C Elevated serum urea nitrogen Elevated serum beta2 microglobulin Elevated urine beta2 microglobulin Reduced glomerular filtration rate Decreased creatinine clearance Proteinuria Urine casts Hematuria Anemia	Reduced glomerular function, GFR ^{99m} Tc-diethylene-triamine-penta-acetic acid (^{99m} Tc- DTPA) renography Reduced tubular function ^{99m}Tc-dimercapto-succinyl acid (^{99m}Tc-DMSA) scintigraphy Perfusion deficits on scintigraphy I-131 radio-hippurate Asymmetric uptake of IV contrast on CT Kidney atrophy
Clinical	Malignant hypertension Headache Edema Dyspnea Fatigue Nausea Vomiting Confusion Coma Death	–	

TBI and HSCT. These include, for instance, membranous nephropathy, that occurs typically in association with graft versus host disease. It occurs at more than a year after HSCT, and there is generally more proteinuria in membranous nephropathy than there is in BMT nephropathy.

The long latency for clinical kidney toxicity was highlighted by Luxton in the 1950s (Luxton 1953). The time from bilateral kidney irradiation to clinical symptoms ranged from 1 to 9 months in the acute presentation and ranged from 18 to 62 months in the chronic presentation of radiation nephropathy. In another study, 67 patients with peptic ulcer disease, without preexisting hypertension, were treated with $\approx$20 Gy delivered over 3 weeks, to volumes that encompassed the left kidney (Thompson et al. 1971). Thirty-one patients (46 %) developed kidney toxicity 8–19 years following RT, including seven patients with fatal uremia (5) or malignant hypertension (2). The degree of shrinkage of the irradiated kidney relative to the spared kidney was related to the dose delivered. At autopsy, atrophy of the irradiated kidney with degenerative changes of the small and medium arteries was seen (Thompson et al. 1971). This long latency period may be due to radiation induced renal injury to the left kidney which resulted in hypertension, with resultant hypertension-induced renal injury to the right kidney. Hypertension-related renal injury is known to have a long latency. Latency may also be related to the radiation dose delivered, with a longer latency in patients receiving lower doses. Our ability to fully understand the effects of partial kidney irradiation is hindered by the long latency for RT-induced kidney injury and the high prevalence of factors other than radiation that may damage the kidneys.

4.1 Symptoms and Signs

Symptoms and signs of renal failure are related to the degree of impairment, and change in the GFR (Fig. 6) (Cohen and Robbins 2003). Changes on physical examination are usually not apparent until at least half of the normal kidney function is lost. Anemia is related to the serum creatinine level, but other factors can contribute. When the kidney function is less than 25 % of normal, hypocalcemia and muscle cramps can occur. Anorexia may occur when the GFR is less than 20 mL/min. Nausea and vomiting are later manifestations of renal failure, not usually occurring until the GFR is less than 10 mL/min.

For classic radiation nephropathy, if no changes in renal blood perfusion or GFR are observed within 2 years following RT to kidneys, then subsequent chronic injury is less likely (Cohen and Robbins 2003). However, fibrosis from radiation injury to the bladder or ureters may manifest as obstructive renal failure very late, e.g., more than 10 years after irradiation. Even if clinical symptoms do not occur following kidney RT, the patient's reserve for future renal insults, including chemotherapy or re-irradiation, may be reduced.

4.2 Renal Function Tests/Radiology

Tables 2 and 3 outline different serum markers and imaging tests that have been used to estimate or measure the GFR or other aspects of renal function (Tables 2 and 3). The LENT SOMA table provides an overview of the subjective symptoms, objective findings, the management required for both, and the analytic testing.

Table 3 LENT SOMA kidney

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Symptoms			Fatigue, headache	Obtundation, oliguria, edema
Objective				
Blood pressure		systolic ≤ 20 over normal diastolic ≤ 10 over normal	systolic > 20 over normal diastolic > 10 over normal	Malignant hypertension
Hematuria	Microscopic	Intermittent macroscopic	Persistent macroscopic	Refractory
Edema	None or transient	Pedal; 2+–3+	Pedal 4 + , edema of lower leg(s)	Uremic coma, anasarca
Specific gravity		Urine SpG decreased		
Management				
Blood pressure/renal failure	Diet	Antihypertension medication	Dialysis, unilateral nephrectomy	Permanent dialysis or renal transplant
Hematuria	Iron therapy	Occasional transfusion or single cauterization	Persistent transfusion or coagulation	Surgical intervention
Analytic				
Proteinuria	<3 gm/l	3–10 gm/l	>10 gm/l	Nephrotic syndrome
Creatinine clearance	5–10 % decrease	>10—30 % decrease	>30–60 % decrease	>60 % decrease
Creatinine	1.25 × normal–2.5 × normal	>2.5 × normal–5 × normal	>5 × normal–10 × normal	>10 × normal
B2 Microglob			>2 × normal–4 × normal	>4 × normal
Glomerular filtration rate	Quantification of filtration rate			
Renal scanning	Assessment of renal size and radioisotope clearance			

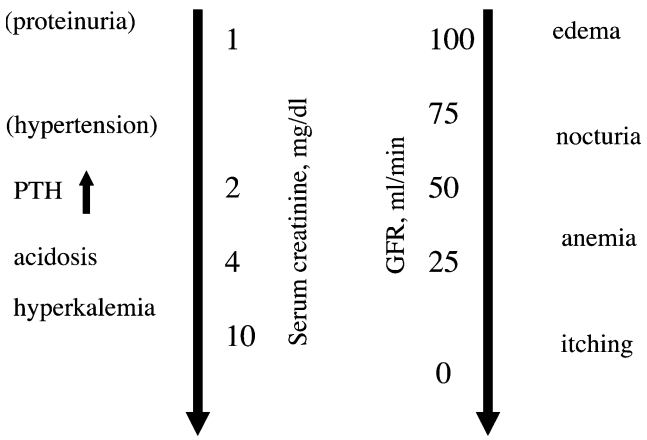

Fig. 6 Relationship between the level of kidney function and signs and symptoms. Features that may be absent are in parenthesis. Kidney function is shown as the serum or plasma creatinine in mg/dL and as the approximate corresponding glomerular filtration rate in mL/min (GFR). The downward directed arrows display the progressive nature of renal failure. Reproduced from Cohen et al. (2005) with permission

Table 4 K/DOQI stages of chronic kidney disease (kidney disease occurring for >3 months), from www.kidney.org

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies

5 Radiation Tolerance and Predicting Radiation Nephropathy

The existing literature on radiation nephropathy is largely derived from patients treated without CT-based planning, and with delivery techniques associated with substantial

dosimetric uncertainty, for instance the moving strip technique used for whole abdominal irradiation. Even with modern planning, kidney movements with breathing are not usually accounted for, introducing uncertainty in the delivered versus planned kidney doses (Moerland et al. 1994; Ahmad et al. 1997). Thus, breathing motion may increase the kidney doses compared to what was planned in large field abdominal radiation therapy (RT) plans in which kidney blocks or attenuators have been used to reduce the kidney doses.

5.1 Radiation Dose Time Fractionation

There is a dose–response effect for non-TBI whole kidney irradiation (Kunkler et al. 1952; Luxton 1953; Keane et al. 1976; Cohen and Creditor 1983; Markoe et al. 1989; Irwin et al. 1996; Schneider et al. 1999) (Fig. 7a). This is consistent with prior reviews (Emami et al. 1991; Cassady 1995) that have suggested a total dose associated with a 5 % risk of injury at 5 years, TD5/5, of 18–23 Gy and a total dose associated with a 50 % risk of injury at 5 years, TD50/5, of 28 Gy, in 0.5–1.25 Gy per fraction. Decreases in creatinine clearance have been observed following 10–20 Gy to both kidneys, in 0.8–1.25 Gy per fraction (Schneider et al. 1999). A summary of studies of bilateral whole kidney irradiation is shown in Table 5. For bilateral whole kidney irradiation, the recent QUANTEC review concluded that the risk of clinically relevant renal dysfunction will be <5 % if the mean dose is <15–18 Gy (Marks et al. 2010, Dawson et al. 2010).

5.2 Dose Volume (Partial Kidney Irradiation)

Nephrectomy may be associated with subclinical elevations in serum creatinine and late chronic kidney injury of the remaining kidney, as opposed to "nephron sparing" partial nephrectomy (Lau et al. 2000); (McKiernan et al. 2002). Similarly, partial kidney irradiation may cause less overall reduction of kidney function than would whole kidney irradiation. It is important to define the limits of irradiated kidney volume that may result in later injury. This analysis is complicated by the secondary effects of local kidney injury and scarring that may lead to hypertensive injury of the remaining kidney volume (Table 6).

There are many studies describing partial kidney tolerance to irradiation, using a variety of endpoints for kidney injury (ranging from subclinical to clinical renal failure) (Kunkler et al. 1952); (Thompson et al. 1971); (Jansen et al. 2007); (Willett et al. 1986); (Burman et al. 1991); (Nevinny-Stickel et al. 2007); (Kim et al. 1984); (Birkhead et al. 1979; Varlotto et al. 2006); (Dewit et al. 1993; Kost et al. 2002); (Flentje et al. 1993); (Kim et al. 1984; Welz et al. 2007); (Kim et al. 1980); (Avioli et al. 1963); (LeBourgeois et al. 1979). The dose/volume/outcome relationship, and resultant dose volume constraints are summarized in Table 6, and Figs. 7 and 8. The recent QUANTEC review concluded that the risk of clinically relevant renal dysfunction will be <5 % if the percent volume of kidney receiving ≥12 Gy (V12) is <55, percent volume of kidney receiving ≥20 Gy (V20) is <32 %, percent volume of kidney receiving ≥23 Gy (V23) is <30 %, and percent volume of kidney receiving ≥28 Gy (V28) is <20 % (Marks et al 2010, Dawson et al 2010).

Unilateral kidney irradiation may be followed by injury, as shown by Thompson et al. who observed a dose response for kidney atrophy and clinical kidney toxicity many years

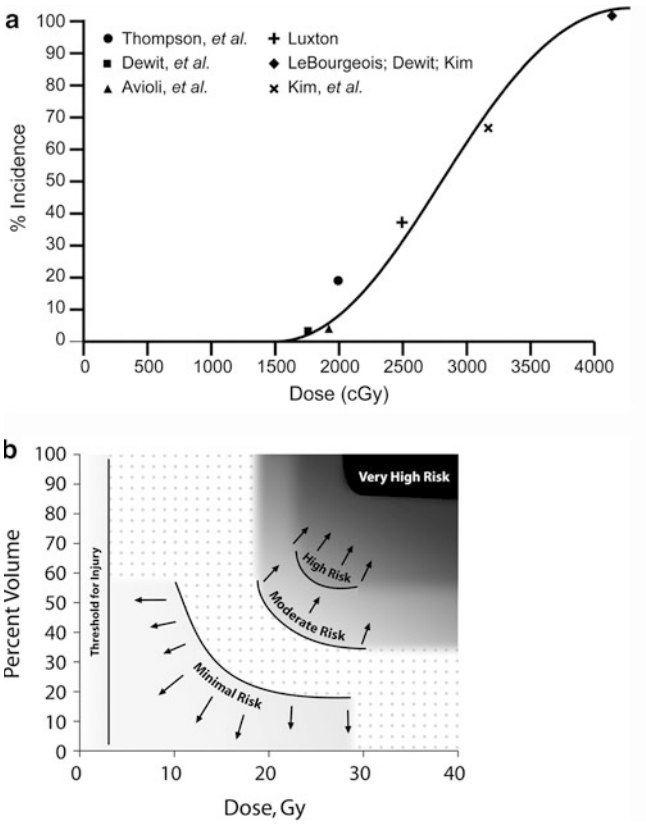

Fig. 7 **a** Correlation of doses associated with radiation nephropathy following bilateral kidney irradiation that is not part of TBI (excluding the series from Thompson, which is of unilateral kidney radiation), based on review of literature, modified from Cassady et al. with permission (Cassady 1995) (modified from Cassidy with permission) **b** Estimates of regions of a combined kidney dose–volume histogram (DVH) associated with minimal (<1 %), moderate (>5 %), high (>15 %) and very high (>50 %) risk of radiation nephropathy. The risk threshold curves were made from dose volume constraints used clinically, associated with various risks of renal injury. The actual risks associated within each region on its own or in combination are highly plan-specific and associated with substantial uncertainty. The risk in dotted region is undefined

Table 5 Selected studies of 10 or more patients treated with bilateral whole kidney irradiation (non-TBI)

Author	Number of patients	Disease	Chemotherapy	Dose (Gy)	Dose per fraction (Gy)	Incidence of injury	Endpoint
Kunkler (1952)	55	seminoma	–	23	0.92	2/18 (11 %)^	RF (sBP > 160 mm + albuminuria)
		ovarian cancer (5)	none	28	1.12	18/25 (51 %)^	RF (sBP > 160 mm + albuminuria)
Avioli (1963)	10	gynecologic cancer (8)	none	7.5–16.5	0.5–1.1	0/5	No change in GFR; no HTN or RF
		sarcoma (1), seminoma (1)	–	20–24	1.0–1.2	4/5	Reduced GFR (75-83 %), no HTN or RF
Irwin (1996)	60	ovarian cancer	none	7–23	1–1.25	5/60	New HTN
		NHL, carcinoid	–				No change in CrCl
Schneider (1999)	56	ovarian	Cisplatin (n = 25)	5–17	0.65–1.15	71–76 %	Reduced CrCl by > 2 mL/min/year

RF = renal failure; CrCl = creatinine clearance, GFR = glomerular filtration rate
^ denominator estimated from text

Table 6 Suggested dose–volume constraints (from Dawson et al. 2010, with permission)

Bilateral uniform kidney doses
TBI: Mean kidney doses ≤10 Gy (in 5–6 fractions), dose rate ≤10 cGy/min [a]
Other: Mean kidney doses <15–18 Gy (over 5 weeks) [b]
Non-uniform kidney recommendations (25 fractions)
Maximally spare as much of kidney volumes as possible (<6 Gy)
Each kidney mean dose <18 Gy (over 5 weeks)
If one kidney mean dose >18 Gy, maximally spare other kidney (V6 Gy <30 %)
Combined partial kidney irradiation (25 fractions)
V28 Gy < 20 % [c]
V23 Gy < 30 % [c]
V20 Gy < 32 % [d]
V12 Gy < 55 % [e]

VxGy = volume of bilateral kidneys receiving more than xGy
[a] estimated from Cheng (Cheng et al. 2008)
[b] estimated from Cassady (Cassady 1995)
[c] estimated from Nevinny-Stickel (Nevinny-Stickel et al. 2007)
[d] estimated from Jansen (Jansen et al. 2007)
[e] estimated from Welz (Welz et al. 2007); 62.5 % reduced to 55 % since 62.5 % is functional volume

following unilateral kidney RT (Thompson et al. 1971). Willet et al. reviewed renal complications in 86 patients surviving at least 1 year who had received at least 26 Gy in 1.5–1.8 Gy fractions to more than half of one kidney (Willett et al. 1986). A volume-dependent decrease in creatinine clearance was observed, with a 10 % decrease if 50 % of the kidney was irradiated, and a 24 % decrease if 90–100 % of the kidney was irradiated. Four of 14 patients with pre-existing hypertension required an increase in hypertension medications after RT, and two other patients developed hypertension after RT.

Renal function was assessed in 44 gastric cancer patients who were treated with 45 Gy in 25 fractions primarily using anterior–posterior beams with almost complete sparing of the right kidney. These subjects were also treated with capecitabine or weekly Cisplatin. The mean volume of left kidney receiving more than 20 Gy was 59 %. By isotope renography, there was a progressive decrease in left (versus right) renal function following chemo-RT, being an 11 % decline at 6 months and a 52 % decline at 18 months (Jansen et al. 2007). One patient developed renovascular hypertension. The volume of the left kidney receiving more than 20 Gy and the mean left kidney dose were associated with risk of renal injury. Another study in gastric cancer patients treated with adjuvant RT and Cisplatin suggested that if 38 % of the functional kidneys can be kept to 12 Gy or less, then the creatinine clearance can be preserved over a median follow-up of 2 years (Welz et al. 2007).

A study of 19 patients treated with four field conformal paraaortic node RT (50.4 Gy over 5 weeks) with a mean follow-up of 46 months (12–96 months) found that up to one-quarter of the bilateral kidney volume can receive doses >28 Gy, and up to one-third can receive >23 Gy with a low risk of toxicity. Three patients developed decreased renal blood flow following RT, and no clinical renal failure was observed (Nevinny-Stickel et al. 2007).

Another report included 142 patients with seminoma treated with paraaortic RT using predominantly rotational techniques, with a median follow-up of 8 years (Flentje et al. 1993). Renal toxicity was not observed in 100 patients in whom the median dose to the kidneys was 18 Gy or less, whereas 7 of 42 patients with a median kidney dose

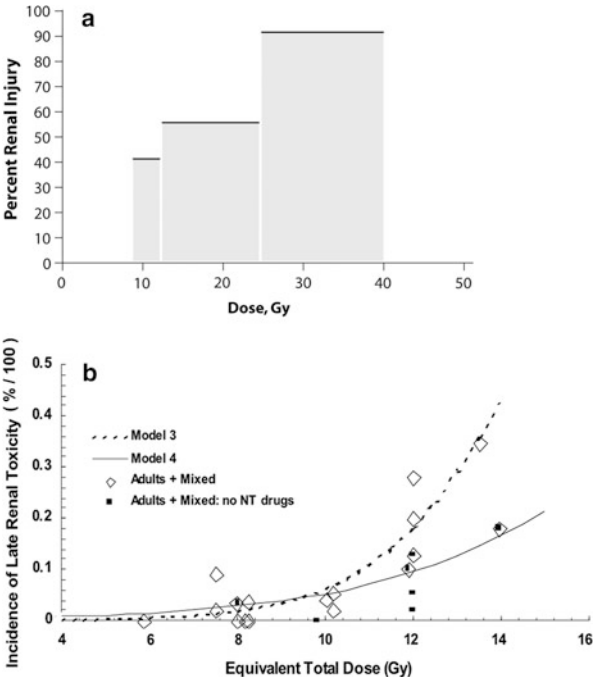

Fig. 8 **a** Dose-dependent loss of kidney function, from a study of 108 children who underwent nephrectomy, predominantly for Wilms' tumor, who received radiation therapy to the contralateral remaining entire or partial kidney, made from data from Mitus et al. published in 1969 (Mitus et al. 1969). The percent of patients with impaired creatinine clearance (CrCl) is shown, defined as <63 ml/min/m^2, relative to dose delivered. The width of the bars represents the range of doses delivered in each subgroup. 29 of 70 patients developed renal impairment following low doses (8–12 Gy); 15 of 27 patients developed renal injury following 12–24 Gy, and 10 of 11 patients who received more than 24 Gy developed renal injury. **b** Modified dose response curve for increased creatinine or hemolytic uremic syndrome following total body irradiation from Cheng et al. (2008), with permission. Open diamonds represent the fitted data points for studies that included adults alone or adult/pediatric mixed populations (with or without nephrotoxic (NT) drugs). The solid squares represent the fitted data points for the same population excluding those treated without NT drugs, cyclosporine, teniposide, or fludarabine. The fractionation schemes were converted into "equivalent" doses delivered in 6 fractions at a dose rate of 10 cGy/min, as described by Cheng et al. (2008). Model 3 includes all patients treated with or without NT drugs, while model 4 excludes patients treated with NT drugs (modified from Cheng et al. 2008 with permission)

between 18 Gy and 32 Gy (in ≈0.7–1 Gy per fraction) developed clinical renal toxicity 10–84 months following RT. In another study with a shorter median follow-up of only 11 months, 23 patients treated with IMRT (±cisplatin) to the paraaortic nodes developed an 18 % decrease in creatinine clearance, but without clinical nephropathy. For these plans, the kidney V16 (referring to the volume of bilateral kidneys receiving 16 Gy or more) had to be less than 35 % (Varlotto et al. 2006).

Regional kidney injury can be detected with scintigrams after low doses. In 91 patients with testicular cancer, renal cancers, or abdominal lymphoma treated with RT in 15–30 fractions, the effective dose associated with scintigraphic changes in 50 % of the patients (ED50) was 27 Gy when 10 % of the bilateral kidney volume was irradiated. The ED50 was only 7.6 Gy when 100 % of the bilateral kidney volume was irradiated. The effective dose associated with changes in 5 % of the patients (ED5) was 3–6 Gy, independent of irradiated volume. These scintigram changes improve over time, perhaps by compensation of the spared kidney tissue (Kost et al. 2002).

Taken together, these studies suggest that RT can cause subclinical regional injury to the kidney after low doses in the range of 6 Gy, although clinical manifestations of such low doses has not been demonstrated. Regional injuries can result in clinical kidney dysfunction, and a volume effect has been observed. In general, toxicity is more likely if median dose to the bilateral kidneys is more than 18 Gy.

5.3 Normal Tissue Complication Probability Models

Lyman-Burman-Kutcher normal tissue complication probability (NTCP) model parameters have been used to describe estimates of kidney tolerance (Burman et al. 1991). The NTCP model parameters that were fitted to these clinical estimates of renal toxicity are as follows: the 'TD50' parameter was 28 Gy, which is the total dose associated with a 50 % risk of injury; the '*n*' parameter, describing the volume effect of the tissue, was 0.70, and is consistent with more 'parallel' organ function; and the '*m*' parameter was 0.10, which is the steepness of the dose–outcome curve (Emami et al. 1991); (Burman et al. 1991). A synthetic analysis of bilateral whole kidney RT tolerance confirmed a threshold dose for whole-kidney RT injury of 15 Gy with a TD5/5 and TD50/5 of 18 and 28 Gy respectively, over 5 weeks (Cassady 1995) (Fig. 7a). Good quality quantitative data to support more refined models are not available.

In a literature review of renal injury following TBI, in which the median TBI dose was 12 Gy in six fractions over 3 days, Cheng et al. found that the dose associated with a 5 % risk of kidney toxicity was 9.8 Gy, irrespective of fractionation. The addition of nephrotoxic drugs increased the steepness of the dose–response curve (Fig. 8b).

5.4 Intensity Modulated Radiation Therapy

Few papers on kidney tolerance have focused on IMRT, and the effects of different spatial dose distributions are not well established. IMRT often leads to a low dose 'bath' delivered to a larger volume compared with simpler plans which usually completely spare RT to a portion of the kidneys.

This bath of low dose may impact the partial tolerance of the kidneys to RT, and it may reduce the possibility for a compensatory increase in function, although this has not specifically been studied. One study of 60 patients suggested that IMRT could be used following gastrectomy, without an increase in renal toxicity compared to conformal radiation therapy (Judit Boda-Heggemann et al. 2009). Clinical experience is required to test this hypothesis.

5.5 Stereotactic Body Radiation Therapy

The response of the kidney is highly dependent on the fraction size, so extrapolation of prior experience to different fraction sizes may be inaccurate. (Kavanagh et al. 2007; Wersall et al. 2005; Svedman et al. 2006; Beitler et al. 2004; Teh et al. 2007; Svedman et al. 2008). It is possible that near-complete sparing of a substantial volume of kidney should be associated with compensation by un-irradiated parenchyma and preservation of renal function, despite delivery of focally high doses. Symptomatic kidney injury has not been reported following SBRT, but follow-up is short. Asymptomatic elevated creatinine without reported symptoms was observed in two of seven patients with one functioning kidney treated with renal SBRT (10 Gy in 3 or 4 fractions) (Svedman et al. 2008). The first patient developed an increase in creatinine from ~120 μmol/L to 150–160 μmol/L 2 years after RT, with stability of the creatinine at 52 months. The second patient had recurrent renal cell cancer and received monthly bolus injections of bisphosphonates, which may have contributed to the peak creatinine level of 240 μmol/L at 55 months post SBRT. Follow-up of long-term survivors from SBRT series is required to learn about the kidney and the collecting system's tolerance to SBRT.

5.6 Compensatory Response

Following unilateral kidney irradiation, shrinkage of the irradiated kidney and hypertrophy of the spared kidney can be seen (Kim et al. 1984). A compensatory increase in kidney function of the spared kidney has also been observed on scintigraphy studies of glomerular and tubular function in gastric non-Hodgkin's lymphoma patients treated with radiation therapy (Dewit et al. 1993). Low dose RT to the "spared" kidney appeared to blunt this compensation. Six to 9 years following 40 Gy in 1.5 Gy fractions to the left kidney and 12–13 Gy in 1 Gy fractions to the right kidney, left kidney glomerular and tubular function, assessed with scintigraphy, decreased to 21 and 31 % of baseline respectively, with an associated decline in creatinine clearance. The compensatory response of the right kidney was reduced compared to patients who had complete sparing of at least 70 % of their right kidney (Dewit et al. 1993). It is possible that the compensatory recovery may be dependent on age, similar to the situation of compensatory recovery following nephrectomy, where less recovery is seen in older adults.

6 Chemotherapy Tolerance (Renal Toxicity)

Nephrotoxicity is an inherent adverse effect of many chemotherapeutic agents. Underlying renal impairment, combinations with other nephrotoxic drugs and urinary tract obstruction secondary to underlying tumor may all increase the risk of renal toxicity during administration of chemotherapy. The mechanisms involved in chemotherapy-induced renal dysfunction include prerenal perfusion deficits, damage to the vasculature or structures of the kidneys, crystal nephropathy, haemolytic uraemic syndrome, and thrombotic microangiopathy.

Before starting potentially nephrotoxic therapy, baseline renal function should be determined. A practical approach has been to follow serum creatinine concentrations. However, the most common renal functional abnormality related to cytotoxic therapy is a decline in GFR, with the most frequently used measure of GFR being the creatinine clearance. Creatinine clearance is less accurate than other measures of GFR but, for practical reasons, has been widely applied clinically, with a serial decline in creatinine clearance indicating worsening renal function. While estimates of the GFR from the serum creatinine concentration alone may have limitations, they are often used. These measurements at baseline, and routinely repeated during therapy, can help guide dose adjustments. Provided the drug-related nephrotoxicity is recognized early and the offending medication is discontinued, chemotherapy-induced renal impairment is generally reversible, although some toxicities may result in permanent renal impairment or renal failure requiring dialysis. Some of the most common chemotherapy-related renal toxicities are discussed here and summarized in Table 7. For a more extensive review and for strategies to reduce toxicities in patients with pre-existing renal failure, we refer the interested reader to Cohen et al. (2005) (Cohen and Moulder 2005).

6.1 Cytotoxic Therapy

Cisplatin is one of the most commonly used antineoplastic agents. The major dose limiting toxicity of cisplatin is cumulative nephrotoxicity, occurring in up to 36 % of patients treated with a single dose of 50 mg/m^2. It is associated with tubular necrosis of both proximal and distal

Table 7 Chemotherapy associated renal toxicity

Agents	Toxicity	Frequency	Comments/Recommendations
Tubular Damage			
Cisplatin	↓GFR, ARF HUS Electrolyte abnormality	Common, dose dependent. Unlikely at doses <50 mg/m^2 Rare. With combination therapy (bleomycin, gemcitabine) Hypomagnesemia common	IV hydration, mannitol ± amifostine
Carboplatin	Salt wasting, ATN	Low risk	IV hydration
Oxaliplatin	ATN	Low risk	IV hydration
Methotrexate	↓GFR, ARF	Increased risk with high dose therapy	Hydration, alkalinization, folinic acid, forced diuresis
Ifosfamide	Hemorrhagic cystitis Fanconi's Syndrome Nephrogenic Diabetes Insipidus ATN, RTA	Dose dependent Rare	IV hydration. Mesna
Streptozocin	RTA Proximal tubular dysfunction Proteinuria Fanconi Syndrome	Dose dependent Low risk for cumulative doses <1500 mg/m2	
Other			
Mitomycin C	TTP-HUS	Uncommon	Increased risk with high cumulative doses and long duration of therapy
Gemcitabine	Proteinuria Hemolytic Uremic Syndrome	Common Rare	
Cyclophosphamide	Hemorrhagic cystitis	Common	IV hydration. Mesna Renal toxicity rare
Targeted Agents			
Bevacizumab	Proteinuria/HTN Thrombotic microangiopathy	Common Uncommon	
Sunitinib	↑Creatinine	Common	
	Thrombotic microangiopathy	Rare	
Sorafenib Cetuximab/ Panitumumab	Proteinuria Magnesium wasting	Uncommon Common	

GFR: glomerular filtration rate; ARF: acute renal failure; HUS: hemolytic uremic syndrome; ATN: acute tubular necrosis; RTA: renal tubular acidosis; TTP: thrombotic thrombocytopenic purpura; HTN: hypertension

renal tubules (Yao et al. 2007). Cisplatin nephrotoxicity is dose dependent and can be permanent with high doses or prolonged treatment. Damage can be minimized or prevented, however, by intravenous hydration and mannitol diuresis. There is some evidence that amifostine, an organic thiophosphate, may also protect against cisplatin-induced toxicity (Kemp et al. 1996; Capizzi 1999). ARF due to hemolytic uremic syndrome has been reported with cisplatin combinations (Gardner et al. 1989); (Canpolat et al. 1994). Carboplatin is significantly less nephrotoxic than cisplatin with hypomagnesemia being the most common manifestation, although ARF has been reported. The importance of renal clearance to the metabolism and excretion of carboplatin is highlighted by its dosing, which is based upon an estimate of the GFR and the area under the concentration times time curve (AUC) rather that the more common dosing calculation based on body surface area. The risk of renal toxicity is low with oxaliplatin (Table 7).

Cyclophosphamide is typically associated with hemorrhagic cystitis, occurring in up to 40 % of patients on long term or high dose therapy, however, renal tubular necrosis can occur. Dose- and age-related proximal tubular damage is more commonly seen with ifosfamide, a synthetic analogue of cyclophosphamide. This manifests as glycosuria, renal tubular acidosis,

proteinuria, and renal wasting of electrolytes, with Fanconi's syndrome being an uncommon presentation (Skinner 2003). The tubular dysfunction is generally reversible.

Methotrexate, eliminated primarily by the kidneys, can precipitate in acidic and concentrated urine, causing a rapid rise is serum creatinine. Renal damage most frequently occurs with high-dose therapy and can be avoided by forced alkaline diuresis and administration of folinic acid. Streptozotocin, a nitrosourea, may cause proteinuria and renal tubular acidosis; progressive renal failure can be prevented by drug discontinuation. The most common form of nephrotoxicity associated with mitomycin is a syndrome of renal failure and microangiopathic hemolytic anemia termed thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP-HUS, which occurs in up to 10 % of patients receiving this agent (Kintzel 2001). TTP-HUS is related to the cumulative dose administered and the associated renal failure is usually delayed. A mortality rate of 50–100 % has been reported in patients developing mitomycin-induced HUS (de Jonge and Verweij 2006).

6.2 Targeted Molecular Agents

The use of molecular targeted therapies for the treatment of cancer has increased over the last decade. While typically associated with class-specific toxicities, renal toxicity has been reported with many agents. Proteinuria is a common side effect of bevacizumab, an anti-vascular endothelial growth factor (VEGF) humanized monoclonal antibody, occurring in 21–64 % of patients. Nephrotic range proteinuria, indicating structural damage to the glomerular filtration barrier occurs in 1–2 % of treated patients (Frangie et al. 2007); (Kelly et al. 2009). More recently, several cases of thrombotic micro-angiopathy, associated with arterial hypertension, acute renal insufficiency, and proteinuria, have been reported (Zhu et al. 2007). Sunitinib, a multikinase inhibitor, is associated with an increase in creatinine levels in 14–18 % of treated patients and thrombotic micro-angiopathy has also been reported (Motzer et al. 2007); (Bollee et al. 2009). In early studies, proteinuria occurred in 41 % of patients treated with sorafenib for hepatocellular carcinoma (Abou-Alfa et al. 2006), results not replicated in the large phase III SHARP trial (Llovet et al. 2008) or in the TARGET study in renal cell carcinoma (Escudier et al. 2007). The epidermal growth factor receptor (EGFR) inhibitors are typically not associated with renal toxicity, although cases of gefitinib-induced nephrotic syndrome and tubulointerstitial nephritis have been reported (Kumasaka et al. 2004); (Masutani et al. 2008). The monoclonal antibodies cetuximab and panitumumab are associated with magnesium-wasting and progressive hypomagnesemia.

7 Special Topics

7.1 TBI

Patients receiving TBI typically have substantial co-morbidities and have or will receive potentially-nephrotoxic chemotherapy. TBI dose appears to be related to risk of renal toxicity post HSCT. Miralbell et al. found that for patients treated with allogeneic BMT conditioned with 10, 12 and 13.5 Gy, the 18 month probabilities of renal toxicity free survival were 95, 74 and 55 % respectively (Miralbell et al. 1996). Renal dysfunction was also related to the development of graft-versus host disease. The importance of TBI dose was also shown by Lawton et al. who observed a significant reduction in kidney injury when renal shielding was used to reduce the kidney doses from 14 to 12 Gy. The actuarial incidence of renal injury at 18 months following HSCT was reduced from 26 % in 72 patients without renal shielding to 6 % in 71 patients treated with renal shielding ($p = 0.047$) (Lawton et al. 1991).

Cheng et al. conducted a comprehensive review of 12 reports (Tarbell et al. 1990; Rabinowe et al. 1991; Van Why et al. 1991; Chou et al. 1996; Miralbell et al. 1996; Lawton et al. 1997; Bradley et al. 1998; Borg et al. 2002; Frisk et al. 2002; Moreau et al. 2002; Igaki et al. 2005; Delgado et al. 2006) of kidney toxicity (defined as increased creatinine or HUS) following TBI (Fig. 8b) (Cheng et al. 2008). On multivariate analysis, for papers describing adult-only experience ($n = 479$), dose was the only significant factor associated with increased kidney toxicity. Neither dose rate, nor number of fractions was significant for this group. For the studies that included adult and pediatric mixed populations ($n = 437$), significant factors included dose, dose rate ($\leq$6, 6.1–9.9 versus $\geq$10 cGy/min), and use of fludarabine. When the studies of adults alone and the mixed adult and pediatric studies were combined ($n = 916$), the number of fractions became a significant factor in addition to total dose and dose rate ($p < 0.01$). For this group, the dose associated with a 5 % risk of kidney toxicity, was 9.8 Gy, regardless of fractionation (see Fig. 8b). For the pediatric group alone, at doses up to 13 Gy, the incidence of renal toxicity was less than 8 %. The linear quadratic model, describing fraction size sensitivity, did not fit these data well, and the authors suggest that other therapies used for HSCT or BMT may interfere with radiation repair and fraction size sensitivity.

7.1.1 TBI Combined with Chemotherapy (Clinical Parameters)

Chemotherapy can enhance RT-associated kidney injury in adults and pediatric populations treated with and without TBI (Donaldson et al. 1980) (Fig. 8b). A recent analysis of 12 articles, and 24 distinct TBI/chemotherapy conditioning

regimens, found that the risk of renal injury was significantly increased by use of fludarabine, cyclosporin, or teniposide following TBI (odds ratios of 6.2, 5.9, and 10.5 respectively). In this review, renal toxicity was defined as an increased serum creatinine level and/or elevated BUN and hemolytic-uremic syndrome. TBI dose rates of $\leq$ 6 cGy/min and 6.1–9.9 cGy/min were associated with odds ratios for renal toxicity of 0.0083 and 0.0046, respectively, compared to $\geq$10 cGy/min (Cheng et al. 2008).

Graft versus host disease following allogenic HSCT and TBI increases the risk of renal injury following RT, in addition to TBI dose (Miralbell et al. 1996).

Family history of kidney disease, underlying renal insufficiency, diabetes, hypertension, liver disease, heart disease, and smoking may reduce the kidney tolerance to RT, but the magnitude of these effects is not known.

The risk of radiation nephropathy depends on the use of whole volume or partial volume RT to one or both kidneys. In this section, whole kidney tolerance refers to bilateral uniform kidney RT, according to use of TBI or not. There is a large difference in the dose per fraction and the overall treatment time for TBI compared to the non-TBI experience. With TBI, there are often 1–6 RT fractions over 1–3 days, whereas in classical whole kidney irradiation, RT is delivered over 25 fractions over 30–40 days. Furthermore, in subjects undergoing TBI there is often use of nephrotoxic drugs. Thus, expectedly, the tolerance doses for the TBI and non-TBI experience are quite different. Partial kidney tolerance includes any partial volume RT, including uniform irradiation to one kidney.

7.2 Pediatrics

Neonates appear to have an increased sensitivity to RT. Doses of 12–14 Gy at 1.25–1.5 Gy per fraction to the entire neonate kidney have been associated with a decreased GFR (Peschel et al. 1981). Animal models of radiation nephropathy have shown that younger rats have an increased sensitivity to renal radiation as compared to adult rats (Moulder and Fish 1997); however, there is no convincing clinical evidence that the kidney radiation sensitivity is different in older children and adults. In a study of 100 children who underwent nephrectomy for Wilms's tumor ($n = 100$), neuroblastoma ($n = 6$) or renal cell carcinoma ($n = 2$), and RT to the contralateral remaining entire or partial kidney, subsequent loss of kidney function and severity of injury were dose dependent (Mitus et al. 1969). Abnormal creatinine clearance defined as <63 ml/min/m^2 was found in 41 % of children receiving less than 12 Gy, 56 % of those receiving 12–24 Gy and in 91 % of those receiving > 24 Gy to the remaining kidney ($p < 0.05$) (Fig. 8a). All five patients with creatinine clearance less than 24 ml/min/m^2 had hypertension and elevated BUN, and four died of kidney failure. In a different Wilms' study, nephropathy was seen in none of 17 children receiving 11 to 14 Gy to the remaining kidney and 1 of 4 (25 %) receiving 14 to 15 Gy (fraction size not reported) (Cassady 1995). In a third study, 1 of 38 children with bilateral Wilms' tumors developed kidney failure following 27 Gy in 21 fractions to the lower half and 12 Gy in 11 fractions to the upper half of the remaining kidney (Paulino et al. 1996). No kidney failure occurred in children receiving bilateral kidney doses of 10 to 12 Gy, in 1.5 to 2 Gy per fraction. In the National Wilms Tumor Study experience, kidney failure was more common in children with bilateral versus unilateral Wilms' tumor (Ritchey et al. 1996). For the three patients with unilateral tumors who developed kidney failure, the dose to the remaining kidney was 15, 18, and 20 Gy, in 1.5 to 2 Gy per fraction.

In Cheng's review of kidney toxicity following TBI in pediatric patients ($n = 192$), the use of cyclosporine and teniposide was associated with increased risk of kidney toxicity. When these drugs were excluded, at doses up to 13 Gy, the incidence of kidney toxicity was less than 8 % (Cheng et al. 2008).

Data on the pediatric kidney partial volume tolerance are not available.

7.3 Radionuclide Therapy

Radiolabeled monoclonal antibodies, antibody fragments, and low molecular weight peptides have been used to treat various cancers. The therapeutic efficacy of radiolabeled antibody fragments can be limited by renal toxicity, particularly when the kidney is the major route of extraction from the circulation. The radioisotopes deposit dose locally (with the range of dose deposition dependent on the energy) in a continuous low dose rate, which can lead to radiation nephropathy. The risk of toxicity depends on the characteristics of the molecule, including the molecular weight and the clearance pathways, as well as its chemical and physical characteristics. The kidney is the dose limiting organ for many targeted radionuclide therapies (Press and Rasey 2000).

In 1999, radiation nephropathy was reported in 4 of 29 patients treated with Yttrium-90 DOTA-d-Phe(1)-Tyr(3)-octreotide (DOTATOC) therapy (Otte et al. 1999). Renal biopsies of patients with toxicity confirmed thrombotic microangiopathy, consistent with radiation nephropathy. This was seen in patients treated with a cumulative dose exceeding 7400 MBq/m2. In another study, Holmium-166 1, 4, 7, 10-tetraazcyclododecane-1, 4, 7, 10-tetramethylene-phosphonate (166Ho-DOTMP) was delivered 6–10 days

prior to autologous HSCT in 83 patients with multiple myeloma (Giralt et al. 2003). A patient-specific therapeutic nominal dose was delivered to the bone marrow (20, 30, or 40 Gy). The median calculated dose to the kidney was 4.3 Gy (0.7–9.8 Gy). Thirty-six percent of patients developed grade 2 to 4 renal toxicity (elevation of creatinine by at least 1.5 times the upper normal limit). Seven patients developed severe thrombotic microangiopathy attributed to radiation, all who had received marrow doses of 30 Gy or more, with a median dose to the kidneys of 7.1 Gy, and all required dialysis. Survival was related to the delivered dose, with better survival in patients who received less than 30 Gy to their marrow.

Awareness of radiation nephropathy following a variety of radionuclide therapies is increasing. Different pharmaceuticals radiolabeled with the same isotope give different dose distributions, as might the same pharmaceutical labeled with different isotopes. Strategies to reduce radiation nephropathy include use of cationic compounds that can be co-infused with the radioisotope, but this has not been a feasible solution due to substantial side effects and potential toxicity from cationic infusions (Lambert et al. 2004). The mitigating therapies that have been studied in external beam radiation nephropathy (e.g. ACE inhibitors) are also being studied in radioisotope nephropathy.

The dose distributions in the kidney following radionuclide therapy are complex, as substantial temporal and spatial variability exists, and baseline renal function impacts retention of the radionuclide and the ultimate dose deposition to the kidneys. Positron emission tomography (PET) scans can be useful at measuring the dose distribution for some radionuclides, but further advances are required in order to better understand the partial volume tolerance of the kidney to radionuclide therapy.

7.4 Ureteric RT–Induced Toxicity

The renal calices, pelves, ureters, and urinary bladder have similar structure; their mucosa consists of transitional epithelium. “Early” radiation injury to the transitional epithelium of the ureters may not develop for 8 to 12 months after irradiation, which may be simultaneous with the onset of delayed complications produced by fibroblast and blood vessel injury. Early damage may lead to hematuria. Delayed toxicity includes ulcers and strictures.

Ureteric strictures following irradiation were first reported in 1934 following pelvic irradiation and radium brachytherapy for gynecological malignancies (Everett 1934). Ureteric strictures were more common in patients who developed serious bladder complications. These occurred 1–4 years following radiation therapy, but some strictures occurred more than 10 years following treatment.

The tolerance dose of the ureters is less well known than that of the kidneys or the bladder. Recently, SBRT has been used to treat kidney cancer near the collecting system or isolated sites of nodal metastases that may be adjacent to the ureters. There are no reports of toxicity following SBRT in this situation, but clinical experience is limited, as is follow-up. There is a need for prolonged follow-up of patients treated with high doses or SBRT to regions near the ureters, so that we may develop a better understanding of the tolerance doses for this structure.

8 Prevention and Management

8.1 Prevention

Animal models of BMT nephropathy have shown that angiotensin converting enzyme (ACE) inhibitors, dexamethasone or acetylsalicylic acid can prevent and treat chronic renal failure (Moulder et al. 2007) (Verheij et al. 1995; Cohen et al. 1997, 2007) (Moulder et al. 1987, Moulder et al. 1998a, b). Similarly, in a radioisotope model of radiation nephropathy, aldosterone or angiotensin II blockade mitigated renal failure (Jaggi et al. 2006). The benefits of ACE inhibitors in animal models are clear, even when the start of ACE inhibitors is delayed until 3 weeks after kidney irradiation (Moulder et al. 1997).

At the Medical College of Wisconsin, a randomized placebo controlled trial of the ACE inhibitor, Captopril, was conducted in 55 patients undergoing HSCT and TBI to study whether an ACE inhibitor could mitigate BMT nephropathy in patients (Cohen et al. 2008). TBI consisted of 14 Gy in 9 fractions over 3 days, 8–20 cGy/min with kidney shielding for a delivered kidney dose of 9.8 Gy. Following stem cell engraftment, patients were treated with Captopril (up to 25 mg t.i.d.) or placebo. The average time that patients were on captopril and placebo was 1.8 months and 2.4 months respectively. The use of Captopril was associated with a reduction in the cumulative incidence of nephropathy or HUS (3.7 versus 15 %, $p = 0.1$) and an improved 1-year survival rate (67 versus 48 %, $p = 0.09$). The lack of statistical significance in this study is likely due to a high type 2 error related to early closure of the study, in turn caused by declining accrual rates. The clinical benefit was high (a 50 % relative reduction in nephropathy), providing strong rationale for further trials of ACE inhibitors for the mitigation of radiation nephropathy.

8.2 Management of Radiation Toxicity

Once RT-induced renal injury has been detected, a referral to a nephrologist is recommended. Generally, in chronic kidney

disease, a reduction in renal workload by low protein diet, and salt restriction may delay the progression to renal failure. If anemia is present, erythropoietin is recommended.

In animal models, angiotensin-converting-enzyme (ACE) inhibitors have been shown to mitigate the severity of glomerular sclerosis compared to other anti-hypertensive medications (Juncos et al. 1993). ACE inhibitors are known to slow the progression of non-RT associated kidney failure (Lewis et al. 1993; Maschio et al. 1996); thus, they have been used to treat patients with radiation nephropathy (Cohen et al. 2003). An angiotensin II blocker, losartan, was used to treat radiation nephropathy that developed in a kidney transplant recipient whose kidney transplant had been irradiated with 7.5 Gy, 23 years previously. Stabilization of renal function followed (Cohen et al. 2003). Thus, angiotensin II blockers and ACE inhibitors should be considered in patients with radiation nephropathy. Although randomized trials of these interventions are desirable, they are not likely to be feasible, since the incidence of radiation nephropathy is low in most clinical settings.

Dialysis and renal transplantation may be needed if complete, end-stage renal failure develops. Unfortunately, in the setting of BMT nephropathy, outcomes of dialysis are poor (Cohen et al. 1998).

8.3 Management Chemotoxicity (Supportive Therapy)

The risk of renal damage is not restricted to cytotoxic agents. Many medications prescribed for complications of chemotherapy or for symptoms of the disease itself are potentially nephrotoxic. Aminoglycosides, commonly used for the management of febrile neutropenia, are associated with tubular cell toxicity, especially when duration of therapy is longer than 10 days or trough concentrations are greater than 2 μg/mL. Preventive strategies include extended-interval dosing, limiting duration of therapy, monitoring serum drug levels, and renal function 2–3 times weekly, and maintaining trough levels at 1 μg/mL or less. Reversible impairment in renal function is a common complication of Amphotericin B, occurring in up to 80 % of cases. Both tubular injury and renal vasoconstriction are potentially responsible for the nephrotoxic effect. The incidence and severity of renal damage can be reduced when a liposomal formulation is used. Bisphosphonates are widely used to treat skeletal complications and hypercalcemia of malignancy. Zoledronic acid and pamidronate are associated with a risk of renal toxicity, especially when given in high doses or over short infusion times. Appropriate hydration and dose adjustments made on the basis of renal function can decrease the risk. Non-steroidal anti-inflammatory drugs, frequently prescribed for pain control, can produce either acute, reversible, or permanent renal toxicity. With exposure to multiple computed tomography (CT) scans to assess treatment response and disease stage, patients are also at risk of contrast nephropathy, the reported incidence ranging from 5 to 38 %. This is usually a reversible form of ARF and preventative approaches include IV hydration and N-acetylcysteine for at-risk patients.

9 Future Direction and Research

The kidney partial tolerance to RT is largely unknown, and deserves more study. There is a need for collaborative prospective studies, with collection of dose–volume histograms and the spatial dose distribution, serial objective measures of kidney injury, and clinical kidney injury endpoints with long-term follow-up. This long-term aspect is important because cancer cures are now increasing, and long-term survival is becoming more common. Baseline clinical kidney function and comorbidities need to be documented, along with use of nephrotoxic or anti-hypertensive medications. Multi-center studies are desperately needed, and renal toxicity assessment should be an endpoint of cooperative group studies investigating novel RT approaches such as IMRT or SBRT. The partial volume tolerance models proposed here can be tested in new patient cohorts. Interventions to prevent and treat nephropathy (e.g. ACE inhibitors) should also be investigated in high risk populations. Sustained follow-up of patients on these trials will be required to document the clinical impact of renal injury. Proposed research topics of importance include:

a. Pathophysiology of RT-induced kidney injury
b. Interaction between clinical factors and kidney tolerance to RT
c. Mitigating factors and radioprotectors
d. Renal compensatory effects and how low dose RT alters the compensatory capacity
e. Spatial variation in radiation sensitivity (including functional imaging)
f. Surrogates for risk of clinical toxicity (e.g. proteomics)

10 Review of Literature and Landmarks

Kidney injury from ionizing radiation was observed shortly after the discovery of the X-ray (Edsall 1906). In 1927, the kidneys were described as “the abdominal organs most susceptible to radiation” (Doub et al. 1927). The sensitivity of the kidneys to bilateral whole organ irradiation was confirmed in the 1940–1960s, when large series of patients with testicular cancer and a smaller number of patients with gynecological cancers were treated with bilateral kidney irradiation (Luxton 1953); (Luxton and Kunkler 1964);

(Paterson 1952); (Avioli et al. 1963). A high incidence of hypertension was reported following whole kidney doses of 28 Gy, and approximately one in three patients developed hypertension following 23 Gy to both kidneys in 24–30 fractions (Luxton 1953). Presenting symptoms in these series included dyspnea on exertion, headache, leg edema, and fatigue. Albuminuria was a near-universal feature of radiation injury. Histological examination revealed findings similar to malignant nephrosclerosis.

Renal toxicity following bone marrow transplant (BMT) and total body irradiation (TBI) was described in 1978 in a child who received TBI, 10 Gy in one fraction (Kamil et al. 1978). In this case, at 6 months following TBI, microhematuria, proteinuria, azotemia, and hypertension developed followed by rapid death, emphasizing the unfavorable natural history and severity of renal toxicity that may occur following TBI and BMT. Subsequent animal and clinical series revealed that renal injury is a major normal tissue injury following TBI with BMT or hematopoietic stem cell transplant (HSCT) (Travis et al. 1985); (Moulder et al. 1987; Moulder and Fish 1989). Hemolytic uremic syndrome (HUS) may also be a feature of BMT-associated renal injury. An increased risk of renal injury was observed with increasing TBI doses, but renal toxicity has also been observed following HSCT without TBI as a preparative regimen.

The adverse experiences with kidney irradiation of the 1950s led to a reduction of the use of kidney irradiation for treatment of abdominal cancers, and an increase in the use of chemotherapy, instead. A similar evolution occurred 30 years later, once the link between TBI and renal failure was established. Lawton et al. observed a significant reduction in kidney injury following HSCT and TBI when renal shielding was used to reduce the kidney doses from 14 to 12 Gy. This resulted in a decline from 26 to 6 % in the incidence of injury at 18 months after HSCT and TBI ($p = 0.047$) (Lawton et al. 1991).

In the past few decades, three-dimensional conformal radiation therapy has enabled precise radiation delivery to tumors and defined portions of normal tissues. Computer aided optimized planning, breathing motion management, and image guidance at the time of radiation delivery improve the accuracy and precision of radiation delivery. Thus, there is a renewed interest in the kidney tolerance to irradiation, specifically the partial kidney tolerance; portions of the kidney(s) may be spared while irradiating smaller volumes to higher doses if required for cancer treatment. Radioisotope therapies are also being used more commonly for many cancers, and renal injury is dose limiting for many radioisotope therapies, again increasing the need for better understanding the kidney tolerance to irradiation (Moll et al. 2001); (Cohen et al. 2001).

Recommended Reading
Luxton (1953)
Lawton et al. (1997)
Cohen and Robbins (2003)
Lambert et al. (2004)
Cohen 2005 (Cohen and Moulder 2005)
Cohen et al. (2008)
Dawson (2010).

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Urinary Bladder

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Contents

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Abstract

- *Introduction* Radiation to the pelvis is used for several malignancies, including bladder, rectal, and anal cancer, prostate cancer in men, and gynecologic malignancies such as vaginal, vulvar, uterine, and cervical cancer in women. The treatment techniques for each malignancy vary significantly and imparts different risks for bladder injury and acute and late effects.
- *Anatomy* The bladder is a flexible organ; it is rounded when it contains urine, and pyramid-shaped when empty.
- *Histology* The superficial luminal cells of the bladder are large, umbrella-like, and connected by tight junctions, which contributes to the impermeability of the epithelial layer.
- *Physiology* Urine is maintained in the bladder by an intact voluntary external sphincter, involuntary internal sphincter, and a ureteral antireflux mechanism, until voiding occurs.
- *Pathophysiology* Vascular endothelial hyperplasia, perivascular fibrosis, and vascular occlusion occurs months to years after radiation therapy leading to bladder wall ischemia, remodeling, fibrosis, degeneration, and necrosis, which in turn results in clinical bladder dysfunction, loss of compliance, and contracture.
- *Clinical Syndromes* Symptoms of acute injury include cystitis and hematuria, and the reported incidence of acute bladder symptoms in patients receiving radiation for various primary tumors of the pelvis varies widely

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from 23 to 80 %. Late effects include fibrosis, bladder contracture, and chronic hematuria and cystitis, and symptoms typically appear 2–3 years after treatment, but there may be a long latency until the manifestation of symptoms.

- *Dose Tolerance* Side effects from bladder radiation may arise either from either whole organ radiation (global injury), such as in treatment to the male or female pelvis, or from focal injury. The risk of injury with radiation to the whole bladder occurs at a more limited dose (40–50 Gy), while focal injury occurs at higher doses from external beam dose escalation to a smaller field for bladder cancer (approximately 65 Gy) or prostate cancer (>70 Gy) or from brachytherapy for gynecological malignancies (cumulative point doses of ~90 Gy).
- *Dose Volume* The QUANTEC review failed to demonstrate a clear set of dose/volume/outcome data for the bladder, perhaps due to uncertainties in bladder volume and location.
- *Chemo/Radiation* As seen in RTOG bladder preservation studies, concurrent chemotherapy with whole bladder doses of 52.5–55 Gy in 1.5–1.8 Gy fractions, followed by a partial bladder boost dose of 12–15 Gy, resulted in ≥Grade 3 late GU toxicity in 6 % of patients.
- *Chemotherapy Rx* Cyclophosphamide use is independently associated with chronic hemorrhagic cystitis, incontinence, contractions, vesicoureteral reflux, and urothelial malignancies.
- *Management* For acute symptoms such as dysuria, nonsteroidal anti-inflammatories and topical agents such as phenazopyridine hydrochloride may be effective. Symptoms of urinary obstruction may be treated with alpha-blockers. Manifestation of late effects including hematuria, incontinence, or bladder contracture warrant prompt referral to an urologist for evaluation, and a broad differential including infection, bladder stones, and secondary malignancy should be considered.
- *Special Topics* The development of secondary malignancy of the bladder may have a very long latency period with bladder tumors observed as long as 10–20 years after radiation.

Abbreviations

BPH	Benign prostatic hypertrophy
CT	Computed tomography
DVH	Dose–volume histogram
EPIC	Expanded prostate cancer index composite
EBRT	External beam radiation therapy
GU	Genitourinary
GyE	Gray equivalent
HDR	High dose rate
ICRU	International commission on radiation units
IMRT	Intensity-modulated radiation therapy
IGRT	Image-guided radiation therapy
MRI	Magnetic resonance imaging
MBP	Maximum bladder point
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTCP	Normal tissue complication probability
OAR	Organs at risk
3DCRT	Three-dimensional conformal radiotherapy
TURBT	Transurethral resection of bladder tumor
TURP	Transurethral prostate resection

1 Introduction

The normal urinary bladder acts as a storage receptacle, holding urine excreted by the kidney. The muscular contraction of the bladder allows the passage of urine through the urethra, and continence is regulated by the external and internal urinary sphincter. The sphincters open in response to signaling from the spinal and cortical nerve control. The surface of the bladder is comprised of an epithelial cell layer, overlying a layer of smooth muscle.

Radiation to the pelvis is used for several malignancies, including bladder, rectal, and anal cancer, prostate cancer in men, and gynecologic malignancies such as vaginal, vulvar, uterine and cervical cancer in women. Treatment of primary bladder cancer typically targets the entire bladder, whereas radiation treatment of other intrapelvic diseases often results in incidental irradiation of only a portion of the bladder. For most gynecologic malignancies, brachytherapy follows external beam to the whole pelvis. Post-operative uterine cancer patients may receive vaginal cuff brachytherapy alone or whole pelvis radiation. The radiation dose contributions from intracavitary or interstitial brachytherapy remain difficult to quantify. Chemotherapy may also contribute to toxicity, since concurrent pelvic radiation and chemotherapy can play an important role in the treatment of many of these malignancies.

Injury to the bladder may occur in many ways. Patients undergoing oncologic surgery in proximity to the bladder, such as a radical hysterectomy for cervical cancer or a prostatectomy for prostate cancer, may experience bladder denervation from neurovascular injury. This may result in the need for long-term suprapubic catheterization. Radiation may also cause both early, reversible symptoms, and long-term toxicity. The pathophysiology of acute symptoms, including frequency, dysuria, and hematuria may be

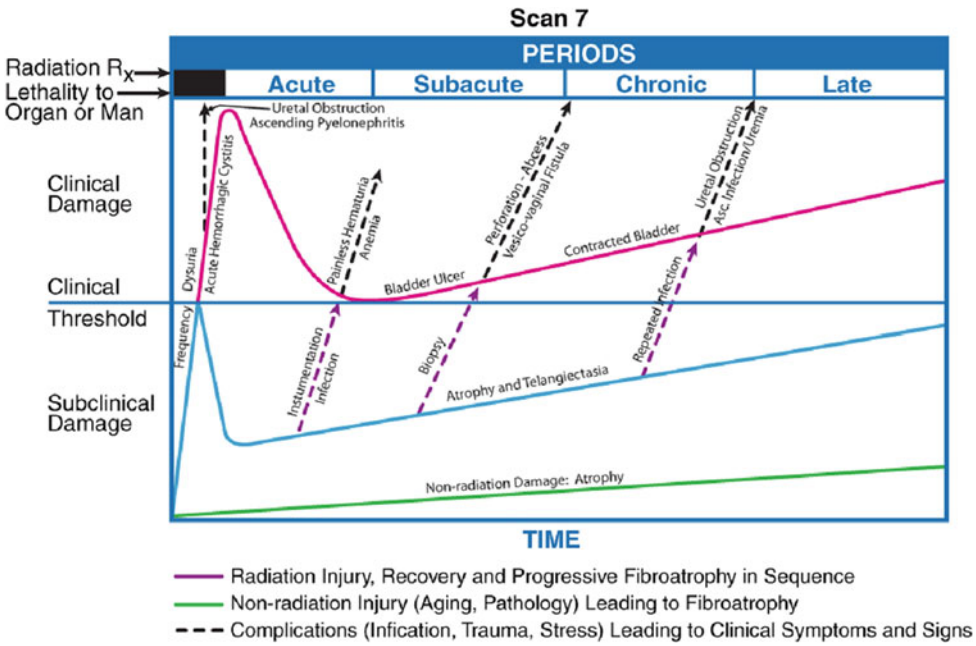

Fig. 1 Biocontinuum of adverse early and late bladder effects are shown (with permission from Rubin and Casarett 1968)

secondary to reparable damage to the epithelium and smooth muscle. Long-term complications from radiation include fibrosis and bladder contracture, which result in decreased bladder capacity and compliance. Fibrosis and remodeling of the bladder wall after radiation is likely due to underlying bladder wall ischemia from perivascular fibrosis and endothelial necrosis; the vascular endothelium is believed to be the major target tissue for long-term radiation-induced injury.

Severe late pelvic complications have been estimated to occur in up to 10 % of patients treated with radiation for bladder, prostate, and cervical cancer (Marks et al. 1995). Late effects may have a long latency period, and long follow-up is necessary to fully detect bladder injury and accurately report the incidence of side effects. The bladder is a relatively radio-resistant organ and is considered one of the least sensitive structures in the pelvis. Therefore, few studies have analyzed true dose limits to the bladder. The Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Normal Bladder Anatomy

The bladder consists of two main parts: (1) the body where urine is collected, and (2) the bladder neck, which is a 2–3 cm long, funnel-shaped extension of the body that traverses the urogenital diaphragm and connects with the urethra. The trigone region sits at the bladder base between the inlet of the two ureters and the urethral opening. The wall of the bladder is mainly composed of smooth muscle, called the detrusor muscle, and easily distends to allow passive bladder filling. At the neck of the bladder, the detrusor muscle fibers form the involuntary internal sphincter. These muscle fibers are in continuity with the muscle fibers of the wall of the prostatic urethra in males and the wall of the urethra in females. The muscular contraction of the bladder wall results in expulsion of urine through the urethra. Continence is regulated by the internal and external urinary sphincters, which respond to spinal signaling reflexes regulated by cortical control.

2.1.1 Anatomic Relationships

When empty, the urinary bladder sits in the true pelvis, posterior and slightly superior to the pubic symphysis, separated from the bone by the retropubic space. It rests on the pelvic floor and is bounded by the peritoneum superiorly. The uterus and ileum may also be superior to the bladder in females, and the colon and ileum may be superior in males. Condensations of the peritoneum provide loose attachments of the bladder to the lateral pelvic wall and anterior abdominal wall, including the median umbilical ligament, which attaches the bladder apex (dome) to the umbilicus. The bladder bed is formed by the pubic bones and obturator internus muscles anteriorly, the levator ani laterally, and posteriorly the vas deferentia, seminal vesicles, and rectum in males and the vagina and uterus in females (Fig. 2).

2.1.2 Bladder Structure

The bladder is a flexible organ; it is rounded when it contains urine, and pyramid-shaped when empty. The empty

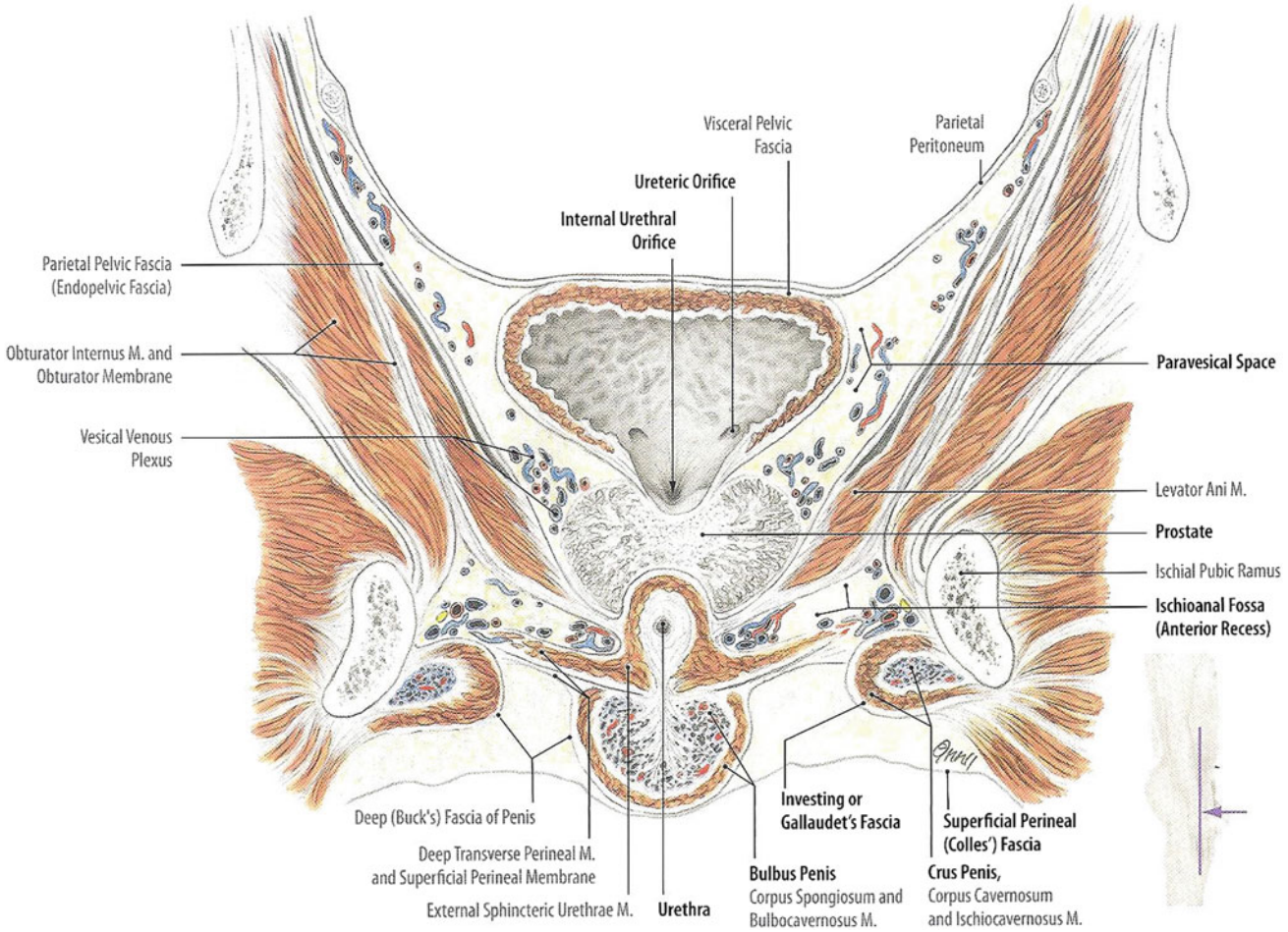

Fig. 2 Anatomy of the bladder (with permission from Tillman 2007)

pyramid-shaped bladder has four surfaces: the superior surface is bounded by the peritoneum; the two inferolateral surfaces are in contact with the fascia covering the levator ani; and the posterior–inferior surface is the fundus, which forms the base of the pyramid, and is adjacent to the anterior wall of the vagina in females and the anterior wall of the rectum in males. The apex (or dome) is the anterior portion of the bladder, which is located near the superior edge of the pubic bone, and ends as a fibrous cord, the median umbilical ligament, which is derived from the urachus, the original connection between the bladder and the allantois. The neck of the bladder is formed by the convergence of the fundus and the inferolateral surfaces, and is the most inferior part of the bladder. The neck of the bladder is continuous with the urethra, and is typically held in place by the pubovesical ligaments in females and the puboprostatic ligaments in males. The rest of the bladder is not fixed by connective tissue, and can be highly mobile. The ureters enter the bladder wall inferomedially on opposite sides at an oblique angle. The two ureteric orifices and the internal urethral orifice at the neck of the bladder form the three points of the bladder trigone.

2.1.3 Normal Bladder Innervation

Continence is regulated by the internal and external sphincters. The internal sphincter is derived from smooth muscle fibers, which are interconnected with the smooth muscle of the bladder wall. Sympathetic innervation from T11 to L2 maintains the smooth muscle tone of the internal sphincter and the trigone, which allows for involuntary continence. These sympathetic nerves arrive at the bladder via lumbar and pelvic splanchnic nerves. The external urinary sphincter is composed of voluntary, striated muscles surrounding the middle third of the urethra in females and the tip of the prostatic urethra in males, with contribution from the muscles of the pelvic floor such as the levator ani. Motor innervation to the external sphincter and pelvic floor muscles arises between the S2 and S3 levels and is delivered via the pudendal nerves.

Motor control of the detrusor muscles and inhibition of the internal sphincter occurs via parasympathetic fibers, which arise from the gray matter of the spinal cord (S2–S3) and travel to the bladder via the sacral and pelvic splanchnic nerves. Sensations of stretch and bladder fullness are carried along the pelvic parasympathetic nerves, while pain, touch,

and temperature sensory innervation travel via sympathetic pathways to the T11–L2 spinal cord level. These fibers transmit sensations of pain from over-distention or inflammation.

2.1.4 Bladder Vasculature

The bladder has a rich vasculature, and the major blood supply to the bladder is derived from branches of the internal iliac arteries. The anterior–superior portions of the bladder are supplied by the superior vesical arteries, while the fundus is supplied by the inferior vesical arteries in males and the vaginal arteries in females. Other minor blood suppliers include the obturator and inferior gluteal arteries. Venous drainage of the bladder occurs through the vesical venous plexus, the prostatic venous plexus in males, and the vaginal venous plexus in women. The vesical venous plexus predominantly drains to the internal iliac veins via the inferior vesical veins, but also may drain to the vertebral venous plexus via the sacral veins.

2.2 Histology and Functional Subunit

The surface of the bladder is comprised of an epithelial cell layer overlaying a muscle layer. The epithelial lining is composed of 3–7 layers of transitional cells, which rests on top of a basement membrane. The epithelial lining is continually repopulated by rapidly dividing cells in the basal epithelium. The superficial luminal cells are large, umbrella-like, and connected by tight junctions, which contributes to the impermeability of the epithelial layer. Overlying the epithelial lining is a sulfated polysaccharide layer (glycosaminoglycan), which prevents the attachment of small molecules, bacteria, protein, and ions found in urine. Radiation or inflammation may damage this superficial polysaccharide layer or disrupt the tight junctions of the luminal urothelium cells, resulting in the introduction of bacteria, ions, or small molecules to the underlying epithelium and leading to infection, cystitis, or other toxicity (Fig. 3).

Below the extracellular matrix of the basement membrane is the lamina propria, which is composed of loose connective tissue and a few smooth muscle fibers, and permits a significant amount of stretching of the mucosa. Beneath the lamina propria, lies the detrusor muscle layer. The detrusor smooth muscle is arranged in widely spaced bundles, infiltrated by a rich network of arterioles, venules, and small parasympathetic and sympathetic nerves. In the body of the bladder, the smooth muscle fibers are oriented in different directions and interweaving, but near the neck of the bladder, the smooth muscle bundles coalesce into three distinct layers: inner, outer, and medial. The inner and outer layers are oriented longitudinally, whereas the medial layer is oriented circularly. The inner layer extends into the urethra to form the longitudinal inner urethral muscle layer, while the medial layer condenses to form a dense circle that is most prominent anteriorly. The outer layer extends down into the urethra in females and to the end of the prostatic urethra in males, and constitutes the involuntary internal sphincter.

3 Physiology, Biology, and Pathophysiology

3.1 Physiology

No specific functional unit has been defined for the bladder. Different portions of the bladder such as the body and the neck have varying composition and architectural arrangements of smooth muscle, vessels, and nerves. However, all the structures listed in the prior section including the superficial polysaccharide layer, epithelium, bladder mucosa, detrusor muscle (muscularis propria), small blood vessels, and small nerves branches may all be considered to form part of a functional subunit (Fig. 4a) as described by Marks et al. (1995).

The bladder is a compliant structure that acts as a storage receptacle for urine, but also a dynamic muscular organ that allows for voluntary release of urine. Urine storage occurs by passive, compliant filling of the bladder with urine from the ureters. Urine is maintained in the bladder by an intact voluntary external sphincter, involuntary internal sphincter, and a ureteral antireflux mechanism, until voiding occurs. The antireflux mechanism, which is created by the oblique angle of entry of the ureters and basal detrusor muscle tone, ensures forward flow during micturition.

The normal bladder capacity is 400–500 ml in normal adults, although the bladder may expand significantly particularly in patients with atonic bladders. Table 1 describes the physiological parameters of the normal bladder. The normal bladder maintains low pressure (5–10 cm H_2O) filling until bladder capacity is reached, due to the compliance of the bladder wall (Fig. 4b). When the volume of urine in the bladder reaches beyond 300–400 ml, the intravesicular pressure rises rapidly. Once the bladder is filled to capacity, sensory stretch receptors in the bladder wall trigger the micturition reflex and lead to contraction of the detrusor muscle and relaxation of the internal sphincter. The spinal cord mediated micturition reflex is autonomic, but can be modulated by voluntary control from the cortex and inhibitory signals from the pons. Additionally, voluntary motor control of the external sphincter also allows control over micturition. Voluntary urination is initiated by voluntary contraction of the abdominal muscles which increases intra-abdominal pressure and forces more urine into the bladder neck, leading to increased distention of the bladder

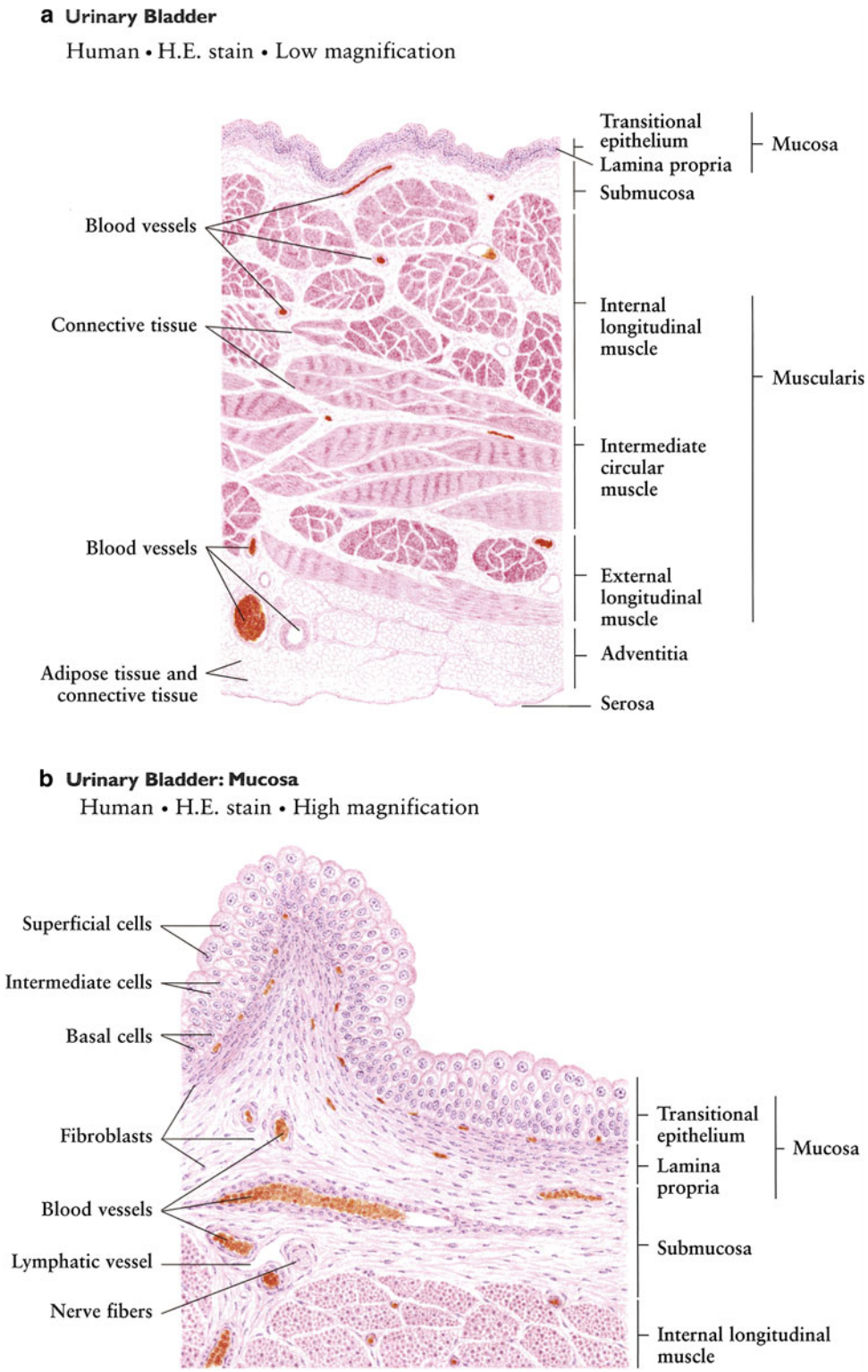

Fig. 3 Histology of the bladder: **a** low magnification, **b** high magnification (with permission from Zhang 1999)

neck, stimulation of the stretch receptors and triggers the micturition reflex. Once the spinal reflex is activated, a positive feedback loop occurs with detrusor muscle contractions raising intravesical pressure and activating stretch receptors, which rapidly increases the pressure in the bladder by 20–40 cm H_2O. Micturition then occurs with passive opening of the bladder neck, involuntary relaxation of the internal sphincter, and voluntary relaxation of the external sphincter. Once micturition occurs, the neural components of the micturition reflex enter an inhibited state for a period of minutes to an hour, which prevents further activation of the reflex. In a normal bladder, nearly all the urine will be emptied with approximately 5–10 ml left in the bladder.

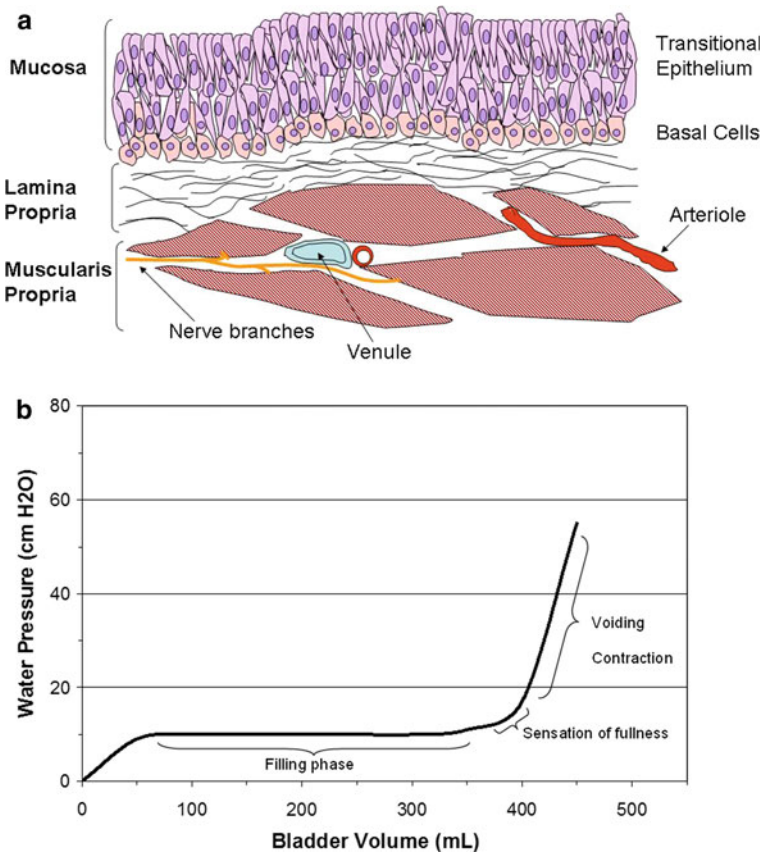

Fig. 4 **a** The functional subunit of the urinary bladder is illustrated. Normal function depends upon the successful interaction of the bladder wall mucosa, consisting of several layers of urothelium and a basement membrane, the lamina propria, detrusor smooth muscle layers, and supporting neurovascular structures. (Adapted from Marks et al. 1995). **b** A normal cystometrogram study showing a large capacity, compliant bladder. Little change in bladder pressure is produced with filling until capacity is reached. The pressure is high during voiding contraction as shown. (Adapted from Marks et al. 1995)

Table 1 Physiological parameters of the normal bladder

Functional parameter	
Bladder capacity	400–500 mL
Bladder wall volume	50–70 cm^3
Resting bladder pressure	5–10 cm H_2O
Contraction pressure	20–40 cm H_2O
Functional urethral length	6–7 cm (men)
	4 cm (women)
Urine flow rate	20–25 mL/s (men)
	25–30 mL/s (women)

3.2 Biology and Pathophysiology of Radiation-Induced Bladder Injury

Considering Marks' proposed functional subunit of the bladder, possible targets of radiation-induced damage include the epithelial cell layer, detrusor muscles, nerves, and microvasculature. The bladder responds to radiation injury and other stressors with inflammation, tissue reorganization, and cellular proliferation. The specific molecular mechanisms underlying the bladder response to injury have not been elucidated. Our limited understanding of the pathophysiology of radiation-induced bladder injury is derived largely from animal studies. The largest series of animal studies on the bladder were published by Stewart et al. at the Gray Laboratories in the 1980s (Stewart 1985, 1986; Stewart et al. 1978, 1980, 1981, 1984, 1990, 1991). These studies examined the histological changes and assessed bladder function via a urinary frequency assay in mice treated with radiation.

3.2.1 Urothelium

The urothelium's sensitivity to radiation has been observed in both mouse and rat models, and in the histology of bladder biopsy specimens from patient's treated with radiation (Stewart 1986; Antonakopoulos et al. 1982, 1984). Early changes and signs of damage including nuclear irregularity, cellular edema, and increased lysosomes and autophagic vacuoles in intermediate and basal urothelial cells, are seen approximately 3 months after irradiation. By 6–12 months, there is a dose-dependent increase in cellular proliferation and normal differentiation may be lost in many areas (Fig. 5a). Stewart looked at the proliferative response of mouse urothelium, using a thymidine incorporation assay and functional changes in the mouse bladder using urinary frequency and hematuria as endpoints, after treatment with radiation, cyclophosphamide, or both (Stewart 1985; Edrees et al. 1988). While cyclophosphamide-induced early increase in urinary frequency, hematuria, denuding of the urothelial layer, and rapid epithelial proliferation within

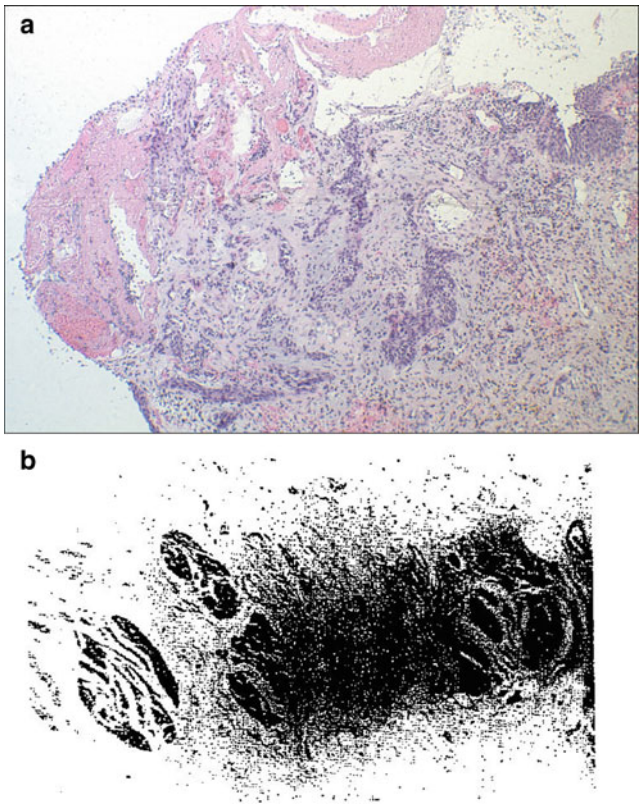

Fig. 5 **a** Histological image of radiation-induced bladder injury. Florid epithelial proliferation and reactive changes in the lamina propria in case of radiation cystitis. Images courtesy of Dr. Robert H. Young, Department of Pathology, Massachusetts General Hospital. **b** Photomicrograph of the muscularis propria of an irradiated bladder shows severe fibrosis of the bladder wall, which had a urine capacity of about 40–50 ml. This bladder was irradiated for a primary carcinoma that was eliminated by therapy. The patients subsequently died of metastases that were not apparent at the time of therapy (with permission from Fajardo 2001)

1 week of treatment, the effects of radiation alone were not seen until 4 months after treatment. These data suggest that early epithelial injury and turnover are not immediate precursors to late radiation-induced bladder toxicity. Edrees et al. demonstrated that there appears to be a synergistic effect between cyclophosphamide and radiation, since the combination led to early radiation dose-dependent damage within a week of treatment, and also more severe late radiation damage at 9–12 months compared to radiation alone (Edrees et al. 1988).

Disruption of the bladder epithelium may contribute to the development of early symptoms seen with bladder radiation. Radiation injury of the epithelium disrupts the normal tight junctions between urothelial cells and the protective polysaccharide layer, which allows hypertonic urine, toxins, ions, and bacteria to penetrate into the underlying tissue. The resultant damage and inflammation may lead to the onset of early radiation-induced symptoms including irritative voiding symptoms such as urinary frequency and urgency (Marks et al. 1995).

3.2.2 Microvasculature and Endothelium

Injury to the vascular endothelium also occurs early after radiation in mouse models. Endothelial cell edema is observed 3 months after radiation, and endothelial proliferation is identified ≥6 months after radiation, but does not occur to the same degree as seen in the urothelium (Stewart 1985). Further cell damage, including endothelial cell edema and necrosis, and perivascular fibrosis, occurs 6–12 months after radiation, and these findings have also been observed in human histological specimens (Antonakopoulos et al. 1984). Subsequently, vascular occlusion and focal bladder ischemia may occur months to years after radiation.

3.2.3 Detrusor Smooth Muscle

The smooth muscle can also be effected, and cellular edema occurs early and can be followed by cellular injury. Subsequent late tissue remodeling includes fibroblast proliferation, collagen disposition, and progressive fibrosis, which can lead to decreased bladder compliance, functional restriction of bladder capacity, and bladder contracture (Antonakopoulos et al. 1984). Extensive fibrosis can disrupt/replace the normal musculature. Experiments by Lundbeck et al. using cystometry to measure bladder pressure changes during bladder filling after radiation treatment in mice showed an acute dose-dependent decrease in bladder capacity by 14 days (Lundbeck et al. 1989a, b). The decreased compliance resolved over 14–28 days. Irreversible, late reduction in bladder compliance occurred at variable time intervals after treatment, and is consistent with clinical contracted bladder syndrome. Late loss of compliance was more commonly seen in animals treated with doses higher than 20 Gy (Stewart et al. 1991), and occurred after a latent period ranging between 35 and 401 days (Bentzen et al. 1992) (Fig. 5b).

3.2.4 Neural Tissue

While the bladder wall is richly innervated with sympathetic and parasympathetic nerves, the role of radiation-induced nerve injury in producing early and late symptoms has not been systematically studied and remains unclear. In some studies, early changes in bladder function after radiation do not appear to be caused by nerve injury (Stewart 1985, 1986; Antonakopoulos et al. 1982). Nevertheless, in patients treated with combined modality therapy, surgical procedures such as radical prostatectomy or radical hysterectomy may result in mechanical injury to the innervation of the bladder, leading to a spectrum of clinical outcomes from mild dysfunction to atonic

bladders. It remains unclear whether adjuvant radiation in these settings can exacerbate the underlying mechanical nerve injuries. The bladder wall does have stretch and pain receptors, and radiation-induced injury may lead to stimulation of these sensory nerves and result in pain, spasm, and incontinence.

3.2.5 Early Versus Late Functional Complications

Stewart et al. examined functional outcomes sequentially from 1 to 53 weeks after radiation with endpoints of urinary frequency and cystometric measurement of bladder volume (Stewart et al. 1991). Early signs of damage, including increase in urinary frequency and decrease in bladder volume, occurred 1–3 weeks after radiation, and typically lasted for less than 1 week. Late toxicity developed 16–40 weeks after fractionated treatment with total doses greater than or equal to 20 Gy, and was typically irreversible. Microscopically, the early, transient damage was not associated with changes in the epithelium or muscle layers of the bladder, but the irreversible late damage was accompanied by epithelial denudation, focal hyperplasia, fibrosis, and ulceration.

The exact mechanisms that cause the symptoms of early and transient bladder radiation-induced injury are unknown. As discussed above, disruption of the epithelial cell layer, tight junctions, and polysaccharide layer may result in permeation of urinary toxins into the bladder wall and subsequent tissue damage and inflammation (Marks et al. 1995). However, other investigators have proposed that smooth muscle damage as the underlying cause for early bladder toxicity, since mouse models have shown early smooth muscle cell edema and loss of bladder volume (Antonakopoulos et al. 1984).

Late injury is manifested mainly as bladder wall fibrosis, loss of bladder wall compliance and contraction. The existing evidence to date points toward vascular ischemia as the underlying pathophysiology behind these changes, and thus, the vascular endothelial cell has been proposed as the actual target for late radiation-induced bladder injury. As discussed above, endothelial cell injury and remodeling occur months to many years following radiation therapy, while acute epithelial cell injuries do not appear to be correlated with the development of late toxicity (Stewart 1985, 1986). Vascular endothelial hyperplasia, perivascular fibrosis, and vascular occlusion occur months to years after radiation therapy, leading to bladder wall ischemia, remodeling, fibrosis, degeneration, and necrosis, which in turn result in clinical bladder dysfunction, loss of compliance, and contracture.

3.2.6 Fractionation

There is evidence in animal models that suggest large fraction size is associated with higher complication rates (Stewart et al. 1981, 1984). Stewart et al. examined urinary frequency and bladder capacity in mice 10–14 months after irradiation to a range of doses using various fractionation regimens (1, 2, 5, 10, or 20 fractions), and observed increased late complications with high dose hypofractionation (>8 Gy). Based on these experiments, the authors estimated an α/β ratio in the range of 5–10 Gy, which is relatively higher than most other normal, slow dividing tissues.

3.2.7 Secondary Malignancy

Animal models have correlated bladder irradiation with secondary malignancies of the bladder. The development of transitional cell carcinomas in 10 of 20 F344 rats, 20 months after bladder radiation has been previously described (Antonakopoulos et al. 1982).

3.2.8 Reirradiation

Mouse models have also shown that retreatment of a previously radiated bladder (20–60 % tolerance dose with initial treatment) resulted in rapid development of functional damage within 2 weeks as manifested by increased urinary frequency and decreased compliance (Stewart et al. 1990). Reirradiation late bladder damage was inversely related to the dose given in the first treatment, but was independent of the interval between treatments. This suggests that there is minimal "slow repair."

3.3 Recovery/Regeneration

As discussed above, signs of early bladder damage including increase in urinary frequency and decrease in bladder volume occurred 1–3 weeks after radiation in mouse models, and typically lasted for less than 1 week (Stewart et al. 1991). Some investigators have found increased mitotic activity in epithelial cells after radiation treatment (Schreiber et al. 1969). Stewart et al. demonstrated that the bladder has the capacity for sublethal damage repair during fractionated radiation. Mice treated with fractionated radiation experienced bladder damage as manifested by increased urinary frequency and decreased volume, but sublethal repair occurred within 24 h and was greater than repair observed in mouse skin (Stewart et al. 1981). These data suggest that early bladder insults may be reparable and early bladder toxicity self-resolves as also seen clinically in patients treated with radiation to the bladder. After resolution of the symptoms of early bladder injury, there is a variable latent period lasting months to years before the development of late bladder injury. However, the connection between repair of early injury and development of late toxicity remains unclear. Late bladder wall fibrosis, loss of compliance, and contraction are typically irreversible.

Table 2 The subjective, objective and management components of the SOMA system for bladder

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dysuria	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Frequency	3–4 h intervals	2–3 h intervals	1–2 h intervals	Hourly
Hematuria	Occasional	Intermittent	Persistent with clot	Refractory
Incontinence	<weekly episodes	<daily episodes	≤2 pads/undergarments/day	Refractory
Decreased stream	Occasionally weak	Intermittent	Persistent but incomplete obstruction	Complete obstruction
Objective				
Hematuria	Microscopic, normal hemoglobin	Intermittent macroscopic, <10 % decrease in hemoglobin	Persistent macroscopic, 10–20 % decrease in hemoglobin	Refractory, >20 % decrease in hemoglobin
Endoscopy	Patchy atrophy or Telangiectasia without bleeding	Confluent atrophy or Telangiectasia with gross bleeding	Ulcerations into muscle	Perforation, fistula
Maximum volume	>300–400 cc	>200–300 cc	>100–200 cc	<100 cc
Residual volume	25 cc	>25–100 cc	>100 cc	
Management				
Dysuria	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Frequency	Alkalization	Occasional antispasmodic	Regular narcotic	Cystectomy
Hematuria/ Telangiectasia	Iron therapy	Occasional transfusion or single cauterization	Frequent transfusion or coagulation	Surgical intervention
Incontinence	Occasional use of incontinence pads	Intermittent use of incontinence pads	Regular use of pad or self-catheterization	Permanent catheter
Decreased stream		<Once-a-day self-catheterization	Dilatation, >once-a-day self-catheterization	Permanent catheter, surgical intervention

4 Clinical Syndromes (Endpoints)

The response of the bladder to radiation therapy can be divided into acute reactions that occur within 3 months of radiation, subacute reactions that occur 3–6 months after radiation, and late reactions that occur >6 months after radiation. As described above, acute symptoms such as hematuria or cystitis due to either radiation or chemotherapy may be secondary to reparable damage of the surface epithelium and smooth muscle of the bladder. These symptoms typically resolve spontaneously. Subacute effects often remain undetected. Long-term complications from radiation include fibrosis of the muscular wall of the bladder, with a resultant decrease in bladder capacity and compliance, and in severe cases, bladder contraction. Late hematuria may occur due to bladder mucosal telangiectasias, but may also be due to secondary bladder malignancy. LENT SOMA tables generated by RTOG/EORTC provide an overview and basis for grading toxicity (Tables 2 and 3).

4.1 Detection

4.1.1 Initial Evaluation

The initial evaluation should include a careful history of the patient's urinary complaints and a directed physical exam. Important questions include asking about the timing of onset of symptoms in relation to radiation therapy completion, distinguishing irritative (urinary frequency, urgency, dysuria) from obstructive symptoms (hesitancy, weak stream, dribbling), and identifying the presence of incontinence. If the patient is incontinent, the kind of incontinence should be distinguished, including urge incontinence (occurring after suddenly feeling the need or urge to urinate), stress incontinence (occurring when coughing, laughing, sneezing, or other movements that put pressure on the bladder), and overflow incontinence (occurring when there is unexpected leakage of small amounts of urine because of a full bladder). A broad differential for late bladder symptoms including tumor recurrence, urinary infection, bladder stones, and secondary malignancy should be considered in patients who

Table 3 Analytic (A) component of the SOMA system for bladder

Analytic	
Cystography	Assessment of mucosal surface
Volumetric analysis	Assessment of bladder capacity in milliliters
Contrast radiography	Assessment for ulcers, capacity and contractility
Ultrasound	Assessment of wall thickness, sinus and fistula formation
Electromyography	Assessment of sphincter activity using intralumenal pressure transducer, contraction pressure, and volume curves

Table 4 Representative acute and long-term toxicities to the bladder in patients treated with external beam radiation attributable to either focal or global therapy

Focal	Global
Hematuria	Dysuria
Fistula	Frequency
Obstruction	Urgency
Ulceration	Contracture
Necrosis	Spasm
	Reduced flow
	Incontinence

have received radiation therapy. In particular, secondary malignancy should be considered in patients with a late onset of irritative symptoms or hematuria after radiation therapy or cyclophosphamide.

The initial physical exam should include careful palpation and percussion of the abdomen and subrapubic region to assess for bladder tenderness and distention. The external genitalia should be inspected for inflammation and/or other lesions, and a rectal exam should be performed to assess for pelvic masses. In females, a pelvic exam is usually indicated, particularly if there are symptoms concerning for urinary tract fistula such as continuous incontinence. A clean catch urine specimen is often used to assess for infection and urine analysis. A urinary tract infection can mimic and/or exacerbate radiation injury, and thus the urine should be examined for red blood cells, white blood cells, and bacteria, a urine culture should be obtained, and any infection treated promptly. In patients with symptoms that may be indicative for a secondary cancer (e.g. irritative symptoms, gross hematuria and/or persistent microscopic hematuria on urine analysis without evidence of infection after radiation or cyclophosphamide), a urine cytology to assess for malignancy and referral to an urologist may be indicated (Tables 2 and 4).

4.2 Diagnosis

4.2.1 Imaging Evaluation

Initial radiographic work-up can include bladder ultrasound to assess for urinary retention, bladder wall thickness, masses, and bladder stones. Ultrasound of the upper tracts may be indicated if there are symptoms of flank pain, hematuria or renal dysfunction, and cystography may be indicated in patients with severe bladder dysfunction including incontinence (Fig. 6a, b).

4.2.2 Urodynamics

Referral to an urologist for urodynamic evaluation may be indicated in patients with severe symptoms of late effects of radiation including incontinence, inability to empty the bladder, and severe irritative voiding symptoms. Urodynamic evaluation includes simultaneous measurement during voiding of intraluminal pressure, sphincteric activity and flow rate, and cystometry provides a measure of bladder capacity and compliance (Fig. 4b). A voiding cystourethrogram, which allows visualization of the urethra in males and assessment for vesicoureteral reflux, may be helpful in patients with dysuria and persistent infections. Fluoroscopy can provided added information about bladder wall movement during voiding.

4.2.3 Acute Symptoms

Acute side effects during radiation therapy and up to 3 months after treatment typically manifest as symptoms of hematuria, dysuria, increase in urinary frequency and urgency, bladder spasm, and incontinence. These symptoms typically can be medically managed and resolve several weeks to months after therapy. Severe Grade 4 complications such as fistula or obstruction are rarely seen, and typically related to tumor location and changes rather than a direct radiation effect.

The reported incidence of acute bladder symptoms in patients receiving radiation for various primary tumors of the pelvis varies widely from 23 to 80 % (Amdur et al. 1990; Pilepich et al. 1987; Quilty et al. 1985; Shipley et al. 1985). In males, acute symptoms may be due to inflammation of the prostate and prostatic urethra, which can be difficult to distinguish from bladder toxicity. The wide range in incidence rates reflects the heterogeneity in dose and treatment technique for different tumors, but also likely underscores the inherent difficulty in collecting such subjective data. Since acute toxicity from radiation is typically not severe, subtle urinary symptoms may be under-reported by physicians and patients.

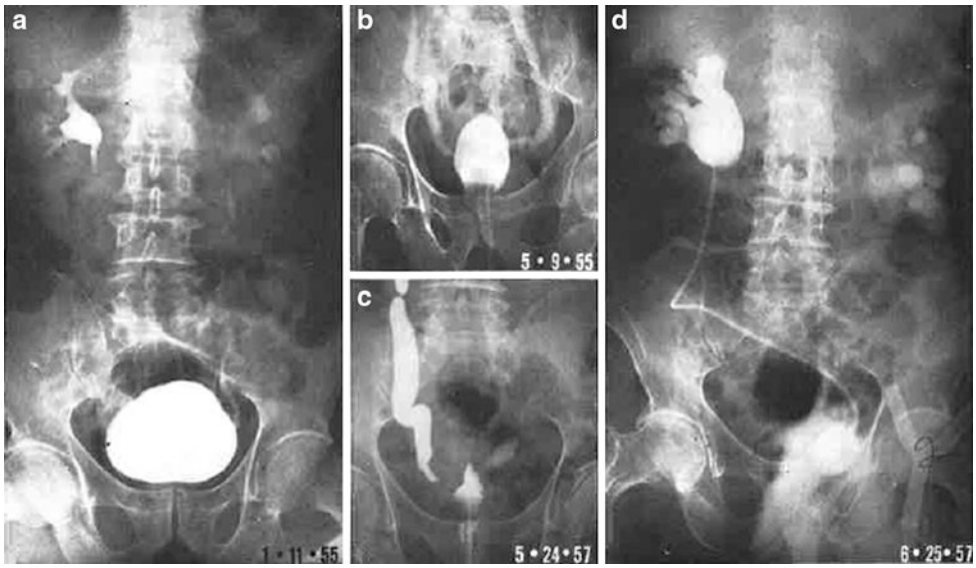

Fig. 6 **a** The patient presented with a Stage C, Grade IV carcinoma with adequate bladder capacity. **b** Two months after the completion of a 6 week course of 6,000 R irradiation, a decrease in bladder capacity and bilateral hydronephrosis were noted. **c** Severely contracted bladder with bilateral hydronephrosis. **d** Diversion required and performed via cutaneous ureterostomies (with permission from Rubin and Casarett 1968)

4.2.4 Late Toxicity Syndromes

Long-term toxicities, those occurring ≥6 months after radiation, include similar symptoms to those listed under short-term side effects, but can progress to permanent bladder contracture causing frequency, incontinence, fistula, and ureteral or urethral obstruction, and hematuria from chronic cystitis and telangiectasia. Necrosis and perforation of the bladder wall are extremely rare from radiation alone, unless directly related to tumor. Incontinence is an important potential side effect, but is clearly confounded by the natural aging process, as well as any surgical procedures that may have previously been performed. For example, women that have had many children, or those that have had a hysterectomy, may be more prone to incontinence, as are men that have had prior bladder or prostatic surgery (Fig. 7a).

Late low-grade complications may impact the patient's quality of life, and therefore should be consistently recorded and reported. Detecting long-term bladder complications requires at least 10 years of follow-up time and thus, bladder complications may be under-reported in the literature (Eifel et al. 1995). In general, the time to onset of late complications is several months to several years, but typically occurs 2–3 years after treatment with a median time of approximately 13–20 months, though the cumulative risk still rises at 4 years (Duncan and Quilty 1986; Duncan et al. 1986; Green et al. 1990; Greskovich et al. 1991; Lawton et al. 1991; Pilepich et al. 1981, 1987; Perez et al. 1984). The latency of several months before the onset of clinical symptoms in patients parallels the time of onset in mouse models, where a dose-dependent decrement of bladder capacity and increment in urinary frequency occurs only after 6 months (Stewart 1985; Stewart et al. 1978).

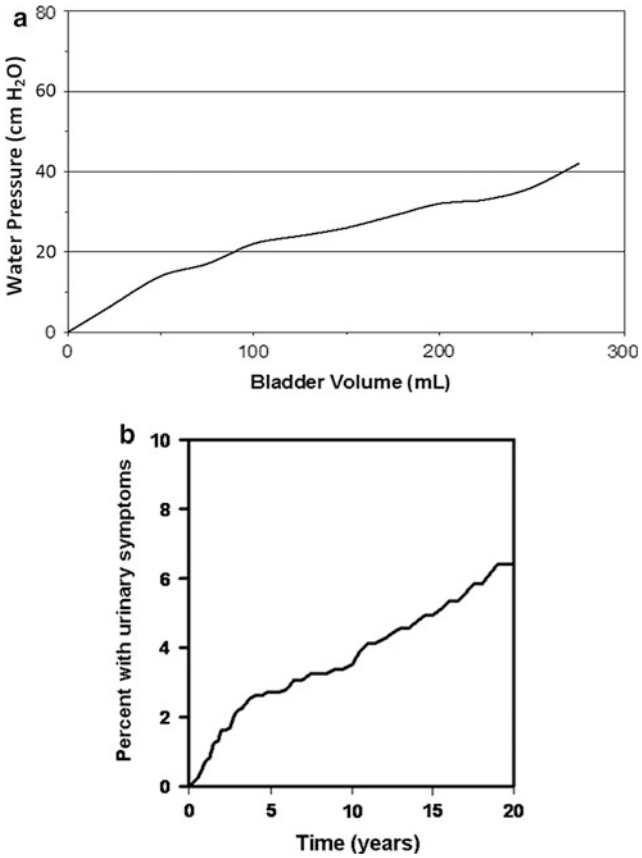

Fig. 7 **a** A cystometrogram performed 2 years after irradiation therapy for the management of cervical cancer. The bladder is reduced in capacity and shows a persistent rise in intravesical pressure with filling, which is consistent with loss of compliance due to fibrosis. (Adapted from Marks et al. 1995). **b** The cumulative frequency of developing "late" bladder complications, as a function of time in cervical cancer patients, persistently increases over decades. (Adapted from Eifel et al. 1995)

The long latency of late bladder symptoms was illustrated in a study of 1,784 patients with stage IB cervical cancer treated from 1960 to 1989 with approximately 45 Gy of external beam radiation therapy (EBRT) followed by tandem and ovoid brachytherapy (Eifel et al. 1995). Of these patients, 6.5 % developed hemorrhagic cystitis, a median of 3 years from the beginning of radiotherapy. The actuarial risk of hematuria was 6 % at 5 years, 7 % at 10 years, and 10 % at 20 years, with the risk of ≥ Grade 3 hematuria 1 , 1, and 2 %, respectively (Fig. 7b). Regression analysis controlling for confounders such as other medical conditions or type of radiation was not performed. Other series in patients treated with radiation therapy for cervical cancer have observed the first manifestation of bladder damage at an interval of 28 (Kottmeier 1964) and 39 (Zoubek et al. 1989) years after radiation treatment. While these are small case reports, long-term follow-up over decades may be necessary to accurately assess the risk of late bladder toxicity.

4.2.5 Grading Toxicity

Toxicity reporting has not been standardized. The methods used for toxicity scoring are not stated in many manuscripts. Timing criteria to distinguish between acute, subacute, and late complications are often not given and have not been standardized. In addition, complications are often only reported as crude numbers, rather than actuarial values, so one must be careful to exclude those patients no longer at risk for late bladder complications (e.g. those patients who underwent cystectomy for reasons other than complications).

Late damage may be assessed either symptomatically, radiographically, cystoscopically, cystometrically, or histologically. Symptoms can be quite varied (e.g. pain, bleeding, frequency, etc.) and the grading of toxicities based on treatment is subjective. Furthermore, it is difficult to classify some toxicities purely as bladder versus urethral in origin. Urethral symptoms such as hesitancy may be related to the amount of tumor present (for prostate cancer patients), or to the specific type of treatment (external beam only vs. brachytherapy only).

The vast majority of the available toxicity data is from retrospective chart reviews, which may underestimate the prevalence of complications. Patient-reported studies may provide a more accurate estimate of the prevalence of toxicity. For instance, Parkin et al., using a mailed questionnaire in patients treated with radiation for cervical cancer, noted 50 % of women reported urinary symptoms (Parkin et al. 1987). While a chart review likely underestimates the prevalence of symptoms, a mailed questionnaire may overestimate the problem since symptomatic patients may be more likely to respond to a questionnaire than asymptomatic patients. Additionally, scoring systems based on interventions directed by a physician may result in differences between institutions. A particular physician who is more likely to prescribe an intervention will note a higher rate of toxicity than would another physician who is less often prescribing an intervention. Toxicity scoring scales that require invasive procedure (e.g. cystoscopy) have fallen out of favor due to potential patient discomfort, inconvenience, and toxicity.

Several validated scoring systems exist for bladder toxicity including the RTOG-LENT/SOMA (Tables 2 and 3) criteria (Cox et al. 1995). In 2007, the most recent RTOG gynecologic group trials have incorporated the common toxicity criteria/adverse events (CTCAE) reporting version 3.0 which lists the following under renal/genitourinary toxicity: bladder spasms, cystitis, fistula, urinary incontinence, leak (including anastomotic, but without development of a fistula), obstruction, perforation, prolapse of stoma, renal failure, stricture/stenosis, urinary frequency/urgency, urinary retention, urine color change, and 'other', not distinguishing between acute or long-term effects. Further work is necessary to standardize the scoring of acute and late bladder toxicity.

In general, patient-reported toxicity data may be superior to physician reported data, although collection is more complex (Talcott et al. 1997; Litwin et al. 1995). Several patient-assessment scales exist, including the expanded prostate cancer index composite (EPIC) and Clark and Talcott scales, which continue to be developed and integrated into current clinical trials (Clark and Talcott 2001).

4.2.6 Differential Diagnosis of Radiation-Induced Bladder Toxicity

Urinary tract infections may frequently cause symptoms such as dysuria, urgency, and frequency that may mimic radiation injury. Further, radiation may cause mucosal changes, predisposing the patient to urinary tract infections. Therefore, it is imperative to be aware of the increased risk of infections and to appropriately diagnose a urinary tract infection with urinalysis and urinary cultures in patients presenting with dysuria and frequency.

In patients with symptoms suggestive of late bladder contraction and decreased compliance including increased frequency, incontinence, and pain, the differential diagnosis includes secondary malignancy, bladder neuromuscular dysfunction due to comorbidities such as diabetes mellitus, and underlying bladder pathology such as detrusor hypertrophy from outlet obstruction in men with benign prostatic hypertrophy (BPH). In patients with a history of transitional cell carcinoma or a long latent period after radiation (e.g. 10–20 years), the physician should have a particularly low index of suspicion for a secondary malignancy (See Sect. 4.2.7) and consider referral to a urologist (e.g. for cystoscopy).

4.2.7 Risk of Secondary Malignancy

Most of the data for secondary bladder malignancy after pelvic radiation therapy comes from retrospective series. Duncan et al. observed 8 secondary bladder malignancies in 2,674 patients treated with radiation for cervical cancer, which despite the low total number of cases, represents an incidence rate of 57.6 times that of the general female population (Duncan et al. 1977). In a case-controls series of 251 women with ovarian cancer, Kaldor et al. found a nearly 2-fold risk increase in secondary bladder malignancy for patients treated with radiation versus those treated with surgery alone (Kaldor et al. 1995). The addition of chemotherapy to radiation increased this risk. The use of cyclophosphamide increased the risk of secondary bladder malignancy 4-fold, regardless of the use of radiation or not.

The development of secondary malignancy of the bladder may have a very long latency period with bladder tumors observed as long as 10 years after radiation for ovarian cancer (Kaldor et al. 1995) and 20 years after radiation for cervical cancer (Duncan et al. 1977), which underscores the need for long-term follow-up and a high index of suspicion for secondary malignancy in patients presenting with hematuria after radiation therapy. Secondary bladder malignancies after radiation therapy are typically high grade, patients often present with locally advanced disease, and prognosis may be poor (Quilty and Kerr 1987).

An increased risk of secondary bladder malignancy after radiation exposure from the Chernobyl nuclear reactor meltdown has also been documented (Romanenko et al. 2002). In patients from the Ukraine undergoing cystoscopy for chronic cystitis or urinary retention, elevated urinary cesium-137 levels were detected in 156 patients residing in contaminated areas. In these patients, biopsies showed urothelial dysplasia in 139 (89 %), carcinoma in situ in 91 (58 %), and small transitional cell carcinoma in 10 (6.4 %). In a control group of 48 patients from noncontaminated areas of Ukraine, nine patients had dysplasia (19 %), but none had in situ or invasive carcinomas.

One analysis of secondary malignancy risk after brachytherapy and/or external beam radiation therapy for prostate cancer using Surveillance, Epidemiology, and End Results (SEER) data showed 11 cases of secondary bladder cancer in 448 patients at 5 years of follow-up. The incidence of secondary malignancy was 1.6 % in patients treated with brachytherapy alone versus 5.8 % in those receiving both brachytherapy and external beam radiotherapy ($p = 0.0623$). The relative risk of radiation therapy was 2.34 with a 95 % confidence interval of 0.96–3.72, and absolute excess risk of 35 cancers per 10,000 patients (Liauw et al. 2006). Similarly, in another SEER analysis, men with prostate cancer treated with external beam radiation therapy had an increased risk of secondary bladder cancer with an odds ratio of 1.63 with a 95 % confidence interval of 1.44–1.84 (Moon et al. 2006).

5 Radiation Tolerance: Predicting RT-Induced Injury

The different primary cancers originating in the pelvis have distinct treatment modalities, and thus radiation effects on the bladder are influenced by widely heterogeneous radiation techniques, dosing, proportion of the bladder irradiated, contribution from external beam versus brachytherapy, influence of chemotherapy and surgery in cases of combined modality, and underlying bladder pathology. Additionally, many patients may have underlying bladder pathology and dysfunction such as bladder muscle hypertrophy due to outlet obstruction in the case of men with benign prostatic hypertrophy, neurogenic bladders in patients with neuromuscular disorders, and chronic cystitis, which can confound the effects of radiation therapy and/or increase the risk of complications. Thus the correlation of radiation dose to late complications remains unclear, and the guidelines for the dose tolerance of the bladder have been revised upward since the 1990s.

5.1 Radiation Dose/Time Fractionation

Depending on the location of the primary tumor, anatomic variation of the bladder, and the type of radiation administered, the dose received by the bladder varies substantially. The incidence and type of bladder toxicity may be altered by radiation technique including: external beam radiation therapy versus brachytherapy, and low-dose whole bladder irradiation versus high dose partial bladder irradiation. To date, the ability to correlate 3-dimensional bladder dosimetry with the risk of complication has not been possible, since the bladder volume and location is highly variable. Additionally, the radiation-induced bladder toxicity profile for a specific patient will depend not only on the specifics of the treatment regimen, but also on the origin, stage, and the location of the primary tumor. For example, patients with bladder cancer may appear to have more acute radiation-induced symptoms than prostate cancer patients, but these symptoms may be related to the tumor response, the condition of the underlying and surrounding mucosa, the amount of bladder irradiated, and the daily motion of the bladder in and out of the field (Fig. 8).

Bladder volume and location uncertainties make measuring true dose–volume relationships and estimating bladder dose tolerances difficult. In this section, the incidence of bladder complications after radiation treatment for

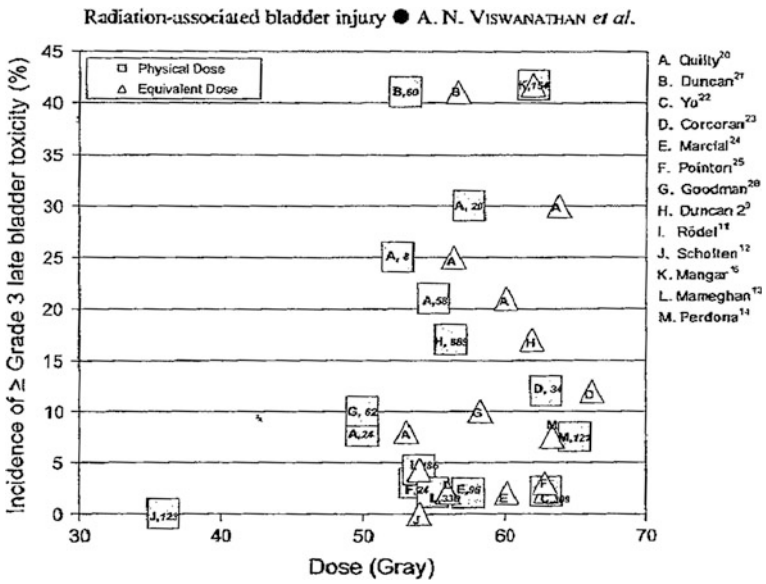

Fig. 8 Incidence of RTOG Grade 3 or greater later bladder toxicity in relation to average dose (*squares*) or linear-quadratic model equivalent dose (*triangles*) in 2 Gy fractions [From QUANTEC review, Viswanathan 2010]

bladder, prostate, and gynecological cancers will be reviewed, and the influence of radiation technique, bladder volume uncertainties, and contribution of brachytherapy dose will be discussed. The effects of whole bladder versus partial bladder irradiation on the risk of late complications will also be reviewed by cancer type.

5.1.1 Hypofractionation

Hypofractionation appears to increase the risk of late bladder toxicity (Marks et al. 1995). In prostate cancer patients treated with 5.17 Gy per fraction twice a week through AP-PA fields over 9 weeks with a 3-week break mid-way through therapy, there was a 19 % rate of serious bladder injury, including both global (cystitis and contracture) and focal (fistula) injury (Lindholt and Hansen 1986). Total dose with hypofractionation may also influence the risk of toxicity; another series found acceptable late bladder toxicity for patients receiving whole bladder treatment for bladder cancer in 20 fractions to 50 or 52.5 Gy, but a high toxicity rate with a total dose of 57.5 Gy (Quilty et al. 1985).

As with other normal tissues, the duration between treatments may be important. In one study of bladder cancer radiation therapy with 2D techniques, there was a 32 % risk of severe bladder injury with a split-course technique of 40 Gy to a large volume of the bladder (whole pelvic fields), followed by a boost dose to a small portion of the bladder to a dose of 20 Gy with both courses delivered at 2 Gy per fraction with 3 fractions per day and an interfraction interval of 4 h (Vanuytsel et al. 1986). However, in a randomized trial of 229 patients with muscle-invading bladder tumors treated without chemotherapy, there was no differences in acute and late bladder complications in patients treated with daily radiation therapy to 64 Gy in 32 fractions versus twice daily radiation therapy to 60.8 Gy in 32 fractions with a minimum 6 h gap between treatments (Horwich et al. 2005).

5.2 Dose–Volume Estimates (Focal vs. Global Bladder Radiation)

Side effects from bladder radiation may arise either from whole organ radiation (global injury), such as in treatment to the male or female pelvis, though this is usually to a more limited dose (40–50 Gy), or from higher doses to a small field resulting in focal injury, such as in cone down volumes for bladder cancer (approximately 65 Gy) or prostate cancer (>70 Gy). Brachytherapy results in significantly higher doses to the bladder than that administered by external beam alone (>75 Gy), but the volumes of bladder exposed to these high doses are much smaller (Fig. 9). Therefore, when discussing bladder toxicities in relationship to dose, it is important to acknowledge the heterogeneity of dose depending on whether the patient has received brachytherapy, external beam radiation, or both and the range of toxicities that may develop (Table 4). Unfortunately, no studies to date have comprehensively monitored true 3-dimensional bladder dosimetry in relation to toxicities. The 1991 publication by Emami et al. reported a bladder TD5/5 for whole and 2/3 volume irradiation of 65 and 80 Gy, respectively, based on initial series that did not utilize 3-dimensional imaging (Emami et al. 1991). The TD50/5 data point of 80 Gy was considered speculative. The endpoint for these estimates was "symptomatic bladder contracture and volume loss" ($n = 0.5$, $m = 0.11$).

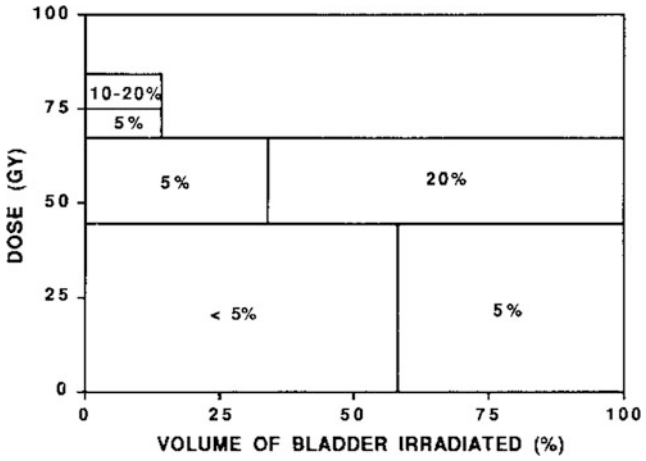

Fig. 9 Schematic diagram illustrating the relationship between dose–volume parameters and the complication rate shown. Adapted from Marks et al. 1995 with permission

Marks et al. in 1995 generated estimates of bladder toxicity based on complication rates seen on review of the existing literature of radiation treatment for prostate cancer, bladder cancer, and cervical cancer. Analyzing the incidence of Grade 3–4 toxicity and dose–volume relationships after external beam radiation therapy and/or brachytherapy, Marks et al. hypothesized that there were different dose tolerances for global and focal radiation-induced injury (Marks et al. 1995). Based on the published literature up to that point, Marks et al. estimated a clinical complication rate of ~5–10 % with a whole bladder dose of 50 Gy, and higher complication rates with doses of 50–65 Gy. Irradiation of approximately one-third to half of the bladder volume to a dose of 50–65 Gy resulted in ~5–10 % complication rates. Irradiation of smaller portions of the bladder (<20 %) to higher doses of 65–75 Gy resulted in late toxicity in ~5–10 % of patients. Additionally, the urethral tolerance dose was estimated to be greater than ~60–70 Gy; these doses resulted in urethral strictures in ~0–5 % of patients. Based on these data, Marks et al. estimated that whole bladder irradiation >50 Gy in 2 Gy fractions resulted in a significant risk of severe global bladder dysfunction, while partial bladder volume irradiation to doses greater than 75–80 Gy may be associated with a >10 % risk of serious bladder injury. However, these data are based on older studies and may overestimate the risk of bladder injury with current radiation techniques. Finally, Marks et al. estimated based on mice model data and the existing clinical data at that time that fraction sizes greater than 2.0 Gy increased the risk of bladder toxicity (Duncan et al. 1986; Quilty and Duncan 1986).

Recent advances in imaging and software over the past decade in 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT) have increased reporting of dose–volume histogram (DVH) calculations. This new dose–volume data generated by 3D imaging has shown that the Marks et al. data and estimates of toxicity using Lyman–Kutcher modeling likely overestimate the normal tissue complication probability (NTCP), and that the tolerance doses for whole bladder and partial bladder irradiation may be higher than previously reported (Dale et al. 2000; Cheung et al. 2007). One study used the data from the literature review of Marks et al. (1995) to produce a Lyman–Kutcher normal tissue complications probability model with an assumed $\alpha/\beta = 6$ for late complications (Dale et al. 2000). The model was fitted to the DVH data and the incidence of Grade 3–4 late toxicity in 14 patients with cervical cancer treated with external beam radiation therapy and high-dose-rate tandem and ring brachytherapy. The patients each underwent 3–6 planning computed tomography (CT) scans, the dose–volume histograms for each scan were summed, and the radiation doses were all converted to 2 Gy equivalents. With a prescribed dose of 89.2 Gy2, the calculated NTCP for Grade 3–4 late toxicity from the DVHs for the 14 patients was 61.9 %. The predicted n parameter was 0.13, (95 % CI 0.06, 0.19) and TD50 was 62 Gy, (95 % CI 57, 67). However, when compared to the observed Grade 3–4 late bladder complication rate of 14 % in 200 patients treated with the same technique and dose, the model significantly overestimated the complication probability. Uncertainties in bladder movement and measurement of dose to portions of the bladder may have contributed to the model's inaccuracy, and perhaps the bladder tolerance dose may be higher than the Marks data set predicts.

Another study used the incidence of ≥Grade 1 toxicity (*any* late bladder complication) in 128 patients with prostate cancer treated with two-phase 3DCRT to a total dose of 78 Gy and their DVH data to fit several models, including a Lyman model and a threshold dose model (Cheung et al. 2007). The bladder "hot-spot" was highly significant. The best fit Lyman parameters were $n = 0.00995$ (95 % CI: 0, 0.059), $m = 0.022$ (95 % CI: 0.013, 0.089), and TD50 = 77.6 Gy (95 % CI: 74.4 Gy, 80.3 Gy). These parameters would predict much higher bladder complications than are reported in a number of high dose prostate cancer series (Gardner et al. 2002; Kuban et al. 2008). Therefore, neither study reported reliable parameters which may be utilized in the future.

Both of these studies yielded much smaller n values and TD50s than previously predicted by Emami estimates (Emami et al.1991), and both models both predict very steep response curves with the highest dose portion of the DVH determining the complication rate. Additionally, both studies showed that existing models predict much higher complication rates than expected. Whether robust models can be constructed in the near future is uncertain. Bladder filling and volume variability poses a major hurdle to

accurately calculating dose–volume histograms, and different parameter sets may be necessary to describe complications in the setting of different radiation therapy techniques for prostate cancer, bladder cancer, and gynecological cancers. The 3D dose distribution is markedly different for each of these cancers, and caution must be taken when extrapolating data derived from one clinical scenario to another. Developing complication models for gynecological cancers involves the additional challenge of combining the external beam and brachytherapy components of treatment in a rational fashion. The recent QUANTEC review (Viswanathan et al. 2010) failed to demonstrate a clear set of dose/volume/outcome data for the bladder, perhaps due to uncertainties in bladder volume and location (see below). Future studies correlating accurate daily imaging of the bladder and dosimetry with long-term toxicities are needed.

5.2.1 Uncertainties in Bladder Volume and Location

The volume of the bladder changes from minute to minute due to continual filling. The bladder is a dynamic organ that has variable filling and is highly mobile; thus, attempts to standardize on-treatment bladder volume or position by instructing patients to empty or fill their bladders have still resulted in wide interfraction variation (Hellebust et al. 2001; Holloway et al. 2008; Jhingran et al. 2005; Turner et al. 1997; Muren et al. 2003; Lebesque et al. 1995; Roeske et al. 1995; Roof et al. 2004; Miralbell 1998). Though a patient may empty their bladder, the amount of residual urine may vary from day to day. Finally, patient movement from respiration or changes in bowel filling may shift the bladder position continually. Therefore, the true volume of any patient's bladder is never fully reproducible without mechanical drainage through a catheter. As a consequence of the bladder's dynamic distention and inherent mobility, studies with bladder DVH results based on a single static CT image cannot report truly representative values of bladder dose during a course of fractionated radiation. In addition, on CT it may be challenging to accurately delineate the trigone region of the bladder, which may have differing sensitivity than the bladder apex. The definition of the bladder volume at risk can also be variable; some reports define the bladder volume as the whole organ including the urine, while others use the volume of the bladder wall alone.

Two studies have presented data regarding bladder variation in patients with endometrial cancer after hysterectomy. One pilot study to evaluate bladder filling and movement was conducted at M.D. Anderson using a CT scan daily, while patients were on the radiotherapy linear accelerator couch. Approximately, 4 cm of bladder variation resulting in vaginal movement was detected daily (Jhingran et al. 2005). Another study from Brigham and Women's Hospital/Dana-Farber Cancer Institute assessed patients with a vaginal cylinder in place, and found that the variation of the D0.1 cc, an estimate of maximum point dose, for a given patient was approximately 14 % (Holloway et al. 2008).

Hellebust et al. studied 14 patients that underwent high-dose-rate (HDR) tandem and ovoid treatments for cervical cancer; 6 CT scans during fractionated HDR demonstrated an interfraction variation of bladder volume of 44 %, which was larger than the mean dose variation of 20 %. A linear regression showed a significant, negative relationship between time after treatment start and the whole bladder volume (Kirisits et al. 2007). An interfraction variation of 15–20 % in the dose, indicating that a CT examination should ideally be provided at every fraction or, alternatively, that the patient be treated with a standardized bladder volume. Another study showed that for tandem and ring brachytherapy, CT-based measurements of the bladder were equivalent to the volume measurements obtained on the gold standard MRI (Viswanathan et al. 2007).

To assess bladder motion in bladder cancer patients, one abstract analyzed interfraction motion as seen on CT scans obtained at weekly intervals (Roof et al. 2004). The authors found that after bladder emptying, at least a 2 cm margin was necessary to cover all aspects of the bladder. Similarly for prostate cancer, Lebesque et al. studied the effects of bladder movement on the bladder and bladder wall DVH (Lebesque et al. 1995). The 11 patients treated with conformal radiotherapy received 4 CT scans each over the course of treatment (at planning, week 2, week 4, and week 6). All were instructed to fill their bladders prior to scanning. No time trends were seen in bladder wall volume, but the total bladder volume, including the contents, decreased over time ($\sim$4 %/week). The authors concluded that the initial scan DVH can only be representative for the whole treatment if the bladder filling can be kept reasonably constant during treatment. The interfractional changes in the geometry of the bladder make the calculation of cumulative distributions nearly impossible with current techniques.

Dose–surface, instead of dose volume, histogram analysis may provide an alternative approach to consider bladder motion in dose/volume analyses. An algorithm for deformable structure registration of the bladder using three landmark points can describe the bladder surface as a triangular mesh closest to the area of dose; despite substantial variation in the bladder shape and volume, the deformable registration was accurate to 5 mm and the structure registration algorithm presents a means of calculating cumulative surface doses (Xiong et al. 2006).

Table 5 Risk of grade > 3 bladder complications following RT for bladder cancer (summary from Marks et al. 1995)

Author	Institution	Patient number	Total bladder dose (GY)*	Fraction size (Gy)	Total bladder dose, 2 Gy eq†	Risk grd ≥ 3 (%)
Shipley et al.	Mass. Gen. Hosp.	55	66	1.8	64.35	11
Quilty et al.	Western Gen. Hosp.	24	50	2.5	53.12	8
		8	52.5	2.6	56.43	25
		58	55	2.75	60.15	21
		20	57.5	2.88	63.82	30
Duncan et al.	Western Gen. Hosp.	60	53	2.56	56.71	41
Yu et al.	SUNY, Upstate	309	63	2	63	2.2
Goodman‡ et al.	Maxwell Evans, Canada	62	≥50	≥3.33	≥66.6	≈10
Corcoran et al.	Middlesex Hospital	34	63	2.4	69.3	12§
Marcial et al.	RTOG	96	55–60	2–2.75	60–65	2¶
Pointon et al.	Christie & Holt Radium	24	52.5–55	3.28–3.44	69–75	3
		20	49.5–51#	3.3–3.4	65.6–68.9	20
		20	54–55.5#	3.6–3.7	75.6–79	10
Studer** et al.	Univ. Bern & Swiss Inst.	19	45–54	2.25–2.7	47.8–63.5	47
Laramore et al.	RTOG	30	65–70#			17

* The total bladder dose, in most instances, represents the average dose delivered to the entire bladder. The bladder dose was usually uniform, because the entire bladder was usually included within the boost field. This was not the case for the Shipley series where care was taken to exclude part of the bladder from the boost field . The doses listed represent the approximate average dose delivered in the series of patients

† The calculation of the equivalent dose at 2 Gy was done using the linear quadratic model and by assuming an alpha/beta ratio of 6.0. See text

‡ Includes only those patients alive 10 years after irradiation. Four percent had cystectomy for contracted bladder and 6% had bladder contraction without cystectomy. See text

§ Requiring cystectomy

Some or all of the radiation given with neutrons. Doses are ≈ photon equivalent doses

¶ Rate among evaluable patients. They were randomized to receive either a continuous or split course

** Some or all of the radiation with pions. Doses are in photon equivalent doses. Nineteen evaluable patients with ≥ 9 months of follow-up

5.2.2 Bladder Cancer

Organ sparing combined modality therapy for bladder cancers consists of maximal transurethral resection of bladder tumor (TURBT), external beam radiation therapy, and concurrent chemotherapy. The risk of ≥Grade 3 toxicity in patients treated with combined modality therapy varies widely and likely reflects the heterogeneity of treatment and uncertainties in bladder volume (Marks et al. 1995; Viswanathan et al. 2010). Marks et al. summarized the late ≥Grade 3 toxicity rates in bladder preservation treatment studies prior to 1995 (Table 5) (Goodman et al. 1981; Laramore et al. 1984; Marcial et al. 1985; Pointon et al.1985; Studer et al. 1985; Yu et al. 1985), and Viswanathan et al. presented an update to that series (Table 6) (Marks et al. 1995; Viswanathan et al. 2010). A wide range of late ≥Grade 3 toxicity is seen after radiation therapy for bladder cancer, even within similar dose ranges. However, larger fraction sizes may result in increased toxicity, with two studies that treated patients with hypofractionated treatment (Duncan et al. 1986; Quilty and Duncan 1986) and a third study that treated to a dose of 62 Gy in 2 Gy fractions (Mangar et al. 2006) reporting late toxicity rates ≥25 %. The large variation in reported severe late bladder toxicity rates even within the same dose range, suggests that increasing dose not account for all toxicity. Confounding factors include different treatment techniques (e.g. surgery, chemotherapy), small patient numbers in some studies, variation in patient-reporting and/or physician-recording of symptoms, and differences in how complications are defined.

Some centers use whole bladder radiation throughout the treatment course, while others utilize a boost volume to the portion of the bladder involved by tumor. The Massachusetts General Hospital and the current RTOG trial regimen consists of whole bladder radiation to 52.5–55 Gy in 1.5–1.8 Gy fractions, followed by a partial bladder dose of 12–15 Gy, and results in a cumulative tumor dose of 64–65 Gy (Shipley et al. 2002; Logue and McBain 2005).

Table 6 Dose/volume: The risk of late ≥Grade 3 bladder toxicity in patients treated for bladder cancer in selected series not included in Marks et al. (1995) (Reproduced with permission from Viswanathan et al. 2010)

	#	Simulationimaging	Total dose	Whole bladder dose	Partial bladder dose	Fraction size (Gy)	Fraction #	EQD2 (Gy)	Late Grade ≥3 toxicity (%)
Duncan and Quilty (1986)[a]	889	2D	55–57.5	55–57.5	–	2.75–2.88	20	60.2–63.8	17
Moonen et al. (1997)[a]	15	3D	66	66	–	2	Last 8 BID	66	0
	25	–	66	66	–	2	Last 13 BID	–	31
Rodel et al. (2002)[a]	186[a]	2D	45–69.4	45–69.4	–	1.8–2	25–33	45–69.4	4[c]
Scholten et al. (1997)[a]	123	2D	36	36	–	6	6 (2×/ week)	54	0
Mameghan et al. (1992)[a]	330	2D	65	45–65	–	1.8–2.5	25–30	43.9–69	2[c]
Perdona et al. (2008)[a,b]	121	3D	65	65	–	1.8	35	63.4	4[c]
Mangar et al. (2006)[a]	154	3D	60–64	60–64	–	2	30–32	60–64	42
(C D)	75	–	60–64	48–52	12	2	24–26	52/60–64	23
Cowan et al. (2004)[a,d]	25	3D	52.5	52	–	2.63	20	56.3	4
(P B)	22	–	57.5	–	57.5	2.88	20	56.3–63.8	18
(P B)	16	–	55	–	55	3.44	16	57.1–64.9	6
Yavuz et al. (2003) (CD)	87	3D	45/67.5	45	22.5	1.8/1.5 CB	35	43.9–65	1
Pos et al. (2003)	47	3D	55	55	–	2/2.75 CB	20	40/55	9
(C D)		–	40	40	15	–	–	–	–
Efstathiou et al. (2009) (C D)	157	2D	64–65	52–55	12–15	1.8/ 1.5–1.8	36–42	60.9–62.2	6

2D conventional simulation, *3D* CT-based 3-dimensional planning, *CD* first phase includes whole bladder followed by cone down to partial bladder with CT-based planning, *CB* concomitant boost, *PB* all treatment fields include only part of bladder, as determined by site of primary tumor with CT-based planning, *BID* twice daily, *EQD2* equivalent dose in 2 Gy fractions, assuming $\alpha/\beta = 6$

[a] Treatment to the whole bladder as localized with contrast or CT

[b] Bladder in treatment fields; cone down from pelvic fields at median dose of 45 Gy

[c] Concurrent with chemotherapy

[d] Grade 2+ toxicity reported

Serious late complications occur in less than 25 % of patients for treatment to the whole bladder followed by partial bladder boost as listed in Tables 5 and 6, (Mangar et al. 2006; Cowan et al. 2004; Pos et al. 2003). The 2008 presentation of the RTOG trials of TURBT, chemotherapy, and radiation documents a late ≥Grade 3 genitourinary (GU) toxicity rate of 6 % (Efstathiou et al. 2009; Shipley et al. 2007).

Initial concerns that high dose bladder irradiation would have long-term effects on bladder function have not been borne out; quality of life data from multiple trials have shown preservation of good bladder function after bladder preservation therapy. In an MGH series of 49 patients treated with TURBT and chemoradiation followed for a median of 6.3 years after treatment, urodynamics study including cystometrograms showed that 75 % of the patients (with a median age of 71) had compliant bladders with normal capacity and flow parameters (Zietman et al. 2003). In a quality of life questionnaire, 85 % of patients reported no or only mild bladder symptoms. Additionally, severe complications are relatively rare, and few patients need cystectomy for management of complications. With long term follow-up, none of 190 patients and 3 of 186 patients required cystectomy for relief of severe bladder contracture in the MGH and Erlangen bladder preservation series (Shipley et al. 2002; Rodel et al. 2002). Although

some studies suggest that larger fraction size or accelerated fractionation may increase late complications, (Quilty et al. 1985; Scholten et al. 1997; Moonen et al. 1997) there are insufficient data to accurately determine late bladder tolerance for the range of techniques, doses, and fractionation schemes encountered in external beam treatments for bladder cancer.

There is wide variability in late bladder complication rates in the published bladder preserving therapy literature. Accurate estimates of the risk of complications from radiation are confounded by the presence of tumor in the organ at risk itself, bladder motion, the effects of surgery and chemotherapy, and patient comorbidities. However, a review of the available studies suggests that limiting whole bladder or partial bladder doses to 64–65 Gy in 36 daily fractions or in 40–42 twice daily fractions results in late bladder complication rates equivalent to RTOG Grade 3 toxicity in $\leq$6 % of patients.

5.2.3 Prostate Cancer

Given that the bladder neck lies close to the prostatic urethra and within the treated volume during radiation therapy, the distinction of bladder versus urethral symptoms in the prostate cancer literature is not feasible, as a physician cannot easily distinguish these symptoms. It is important to understand that studies can only report GU toxicity and not bladder toxicity specifically. Furthermore, the day-to-day variability of bladder size over the treatment course is a problem in interpreting planning scan dosimetry, even if the patients are treated (or repeat imaged) with a full or empty bladder. Prior to the standardized use of 3D imaging, treatments consisted of 45–50 Gy to a whole pelvic field via a 4-field approach followed by a boost to the prostate with margin, resulting in the inferior part of the bladder receiving full dose. More recently, dose escalation and the use of conformal techniques, including IMRT and proton radiation therapy, have delivered high doses ($\geq$70 Gy) to the prostate and hence the inferior portion of the bladder, but excluded the superior portions of the bladder (Kuban et al. 2008; Chism et al. 2003; Peeters et al. 2006; Karlsdottir et al. 2008; Zelefsky et al. 2006; Cahlon et al. 2008; Skala et al. 2007). Overall, the incidence of acute and late serious (equivalent of $\geq$RTOG Grade 3) GU complications from external beam prostate treatments is relatively low despite a decade of dose escalation (Zelefsky et al. 2008; Al-Mamgani et al. 2008).

In a prospective study from MGH, patients treated for prostate cancer with 50.4 Gy to the prostate and seminal vesicles, using 3D conformal photon therapy followed by randomization to either a 19.8 Gray equivalent (GyE) or 28.8 GyE prostate boost with protons to a total dose of 70.2 GyE or 79.2 GyE. There was an actuarial incidence of late GU complications of 41 % at 10 years, which was most commonly transient Grade 1 or 2 hematuria; there was one ureteral diversion and three Grade 3 urethral strictures. Whether the hematuria was due to either bladder or urethral toxicity was not clear (Gardner et al. 2002). A subset of these patients received a quality of life questionnaire, and a preliminary report with long-term follow-up suggests that there is no significant difference in patient-reported symptoms between the high dose and conventional dose arms (Talcott et al. 2008).

In another randomized dose escalation trial of 78 Gy versus 70 Gy with photons for prostate cancer, Kuban et al. reported no significant difference in the 10 year incidence of GU toxicity; Grade 2 or greater toxicity was 8 % for the 70 Gy arm and 13 % for the 78 Gy arm, whereas Grade 3 GU toxicity was 5 % versus 4 %, respectively. There were no Grade 4 or 5 GU complications (Kuban et al. 2008). As described above, Cheung et al. correlated the dose–volume histogram relationships with the late bladder toxicity results for a subset of 128 patients from the above trial prescribed 78 Gy. In 11 of the 19 patients who experienced late toxicities ($\geq$Grade 1) at 10 years, the dose to the 2.9 % of the bladder receiving the highest dose was $\geq$78 Gy. If the dose to 2.9 % of the volume of the bladder receiving the highest dose was $<$77.3 Gy, no patients experienced bladder symptoms (Cheung et al. 2007).

The dose response for late GU toxicity in prostate cancer treatment remains unclear. In a Dutch dose escalation randomized trial of 669 prostate cancer patients treated with 3DCRT, there was no significant difference in late GU toxicity between the 68-Gy and 78-Gy treatment arms (Al-Mamgani et al. 2008). With a median follow-up of 7 years, cumulative $\geq$Grade 2 toxicity was 40 % in the high dose and 41 % in the low-dose arms, and cumulative Grade 3 or higher toxicity was 13 and 12 %, respectively. While no dose–response relationship was seen in the above studies, a study by Zelefsky et al. demonstrated an overall dose response for Grade 2 or higher GU toxicity in a single-institution study of 1,571 patients treated with high dose IMRT versus lower dose non-IMRT. There was a cumulative 20 % incidence of Grade 2 or higher GU toxicity at 10 years after 81 Gy IMRT to the prostate, compared with 12 % for non-IMRT patients treated to lower doses. However, in all patients, only 3 % developed Grade 3 GU toxicity and no patient experienced Grade 4 GU toxicity. The median time to development of symptoms was 30 months, and $<$1 % developed late GU toxicity after 10 years. The authors did not report DVH values (Zelefsky et al. 2008). However, based on the reported dose escalation studies to date, as much as 20–30 % of the bladder or bladder wall (as determined from the simulation CT scan DVH) can be treated to over 70 Gy in conventionally fractionated prostate treatment with similar bladder toxicity to that observed at lower treatment doses.

A study from Princess Margaret Hospital also attempted to correlate patient-reported symptoms to dose (Skala et al. 2007). A total of 437 men treated for localized prostate cancer with 75.6–79.8 Gy of 3DCRT or IMRT between 1997 and 2003 filled out a toxicity questionnaire based on the RTOG-LENT scoring system. Bladder toxicity was categorized as $<$ or ≥ 2 and correlated with dosimetry and the first three principal components of bladder DVHs. Principal component analysis is a tool capable of quantifying the variability in a dataset of DVHs and segregating DVHs with similar morphology (i.e., comparable doses to similar relative volumes). This allows comparison between groups of similar DVHs with respect to complication risk. Patients were simulated with a comfortably full bladder. Dose constraints were set for 50 % of the bladder to receive ≤ 50 Gy. Median follow-up was 37 months. The patient-reported Grade 0, 1, 2, and 3 late urinary toxicity was 74, 16.5, 8.8, and 0.9 %. These results are comparable to those reported by others (Storey et al. 2000; Zelefsky et al. 2001; Michalski et al. 2000), reflecting the difficulty of excluding the base of the bladder from the planning target volume. Four patients had Grade 3 urinary toxicity, three reported persistent use of incontinence pads, one experienced clinically significant hematuria (but had also had a prior superficial bladder cancer treated), and one experienced hourly nocturia. There were no significant relationships between dose delivered to the bladder wall and patient-reported late urinary toxicity. The strengths of this article are its patient-base approach to toxicity reporting, the homogeneity of treatment approaches in a modern era using 3DCRT or IMRT, and the analysis of variability through the component statistical approach. Similar to other retrospective reviews, future studies must address concerns regarding methods to estimate the daily variation in bladder position, in order to more accurately calculate a true DVH. Other centers have reported that chronic toxicity may be independent of dose, when normal tissue dose constraints are met (Vargas et al. 2005).

In the post-prostatectomy setting, a series from Memorial Sloan Kettering of 42 patients treated with 3DCRT to a median dose of 64.8 Gy (prescribed to minimum PTV dose), and with a median follow-up of 2 years, experienced a 7 % incidence of acute Grade 2 GU toxicity (no higher acute toxicity), and a 5 % actuarial risk of Grade 2 late GU complications. One patient developed late Grade 3 (urethral) GU toxicity. The authors noted that the GU toxicity rate was much lower than that for patients treated with definitive RT (same dose range, up to 30 % toxicity) and hypothesize that Grade 2 GU toxicity for patients with intact prostate is, in part, caused by prostate edema and inflammation of the prostatic urethra rather than by the bladder itself (Zelefsky et al. 1997). A larger multi-institutional retrospective series of 959 men treated with either post-prostatectomy salvage (81 %) or adjuvant (19 %) 3DCRT also showed a very low rate of GU toxicity with a median follow-up of 55 months. At 5 years, only 10 % of patients had Grade 2 late GU toxicity and 1 % had Grade 3 late GU toxicity (Feng et al. 2007). The much lower rates of long-term GU toxicity seen with post-prostatectomy radiation therapy compared to radiation to the intact prostate suggests again that GU symptoms observed in the latter group suggests that much of the toxicity is attributable to effects on the prostatic urethra.

For conventional four- and six-field 3DCRT treatment of the prostate and seminal vesicles with an approximately 1 cm margin, the volume of the empty bladder or bladder wall receiving approximately prescription dose should be less than 30 %. For prostate IMRT planning, optimization constraints that keep regions of dose higher than prescription out of the bladder wall or the urethra may be considered, though none of the previously published bladder constraint parameters are known to be associated with a decrease in potential toxicity (Cahlon et al. 2008; Skala et al. 2007; Vora et al. 2007; Jani et al. 2007). Daily image-guidance with ultrasound or radiographic imaging of implanted fiducial markers for prostate localization has become increasing popular. In the future, imaging may allow clinicians to decrease the prescribed margin, and may improve our knowledge of bladder location and estimates of delivered dose.

5.2.4 Gynecologic Cancers

No studies to date have adequately correlated bladder volumes with toxicity in gynecologic cancers. Historic data does indicate that locally advanced cervical cancer treated with high doses (>60 Gy) of external beam radiation alone results in a high incidence of late genitourinary toxicities and poor outcome (Logsdon and Eifel 1999). Therefore, patients preferentially receive a combination of external beam and brachytherapy. The dose to the entire bladder with external beam typically ranges from 40 to 50 Gy, whereas the total dose with brachytherapy to the region closest to the implant ranges on average from 70 to 90 Gy and can reach maximum dose levels above 100 Gy. When calculating the maximum dose delivered to the bladder, the contributions from the external beam and intracavitary therapy have historically often been simply added, although the radiobiological validity of this assumption has been appropriately questioned. This mathematical exercise is further confounded with the growing popularity of high dose rate brachytherapy. Additionally, many dosimetry programs do not account for the shielding present in many standard implant devices, such as Fletcher Suit ovoids.

The most common system in gynecologic brachytherapy for reporting the bladder dose, as described by the International Commission on Radiation Units and Measurements

(ICRU 38), assigns a point intersecting the Foley balloon at the level of the on ovoids as seen orthogonal radiographs. This method has several limitations (ICRU 1985). The ICRU bladder point is not representative of the CT or ultrasound-based (Barillot et al. 1994) volumetric dose and surface area of normal tissue irradiated (Fellner et al. 2001; Pelloski et al. 2005; Schoeppel et al. 1994; Ling et al. 1987). Nevertheless, several studies have utilized ICRU bladder point information to correlate dose with toxicity (Crook et al. 1987; Pourquier et al. 1987).

The dose delivered to the bladder during each fraction of brachytherapy may be measured non-invasively with 3-dimensional image-based contouring of the organs at risk (OAR). Although MRI is considered the gold standard (Mitchell et al. 2006), CT may be utilized instead of MRI for OAR contouring (Viswanathan et al. 2007). Practice patterns vary widely, but techniques to standardize the estimated bladder volume at risk include emptying the bladder prior to scanning and instilling approximately 50 mL of contrast, which allows improved delineation between the posterior bladder wall and anterior portion of the cervix.

In vaginal cylinder brachytherapy, the maximum bladder point (MBP) provided an efficient and accurate estimate of the bladder dose in 20 patients with either a full or empty bladder; and may be used as a surrogate for complex dosimetry (Stewart et al. 2008). More recently, guidelines describing a consistent method for reporting DVH values for brachytherapy included values of D0.1 cc (minimum dose to hottest 0.1 cc) and D2 cc (minimum dose to the hottest 2 cc of the bladder). The D2 cc has gained acceptance as an important dose parameter because the maximum point dose may be sensitive to positioning, and is less likely to remain consistent between brachytherapy fractions (Potter et al. 2007).

In one study of 141 patients with locally advanced cervical cancer treated with tandem and ring brachytherapy, a 4 % 3-year actuarial rate of Grade 3–4 late bladder toxicity was noted for a mean D2 cc bladder dose of 95.3 ± 21 Gy ($\alpha/\beta = 3$). There was no significant difference between those treated with a bladder D2 cc < or >95 Gy; 13 % (11/87) developed Grade 1–4 late toxicity with D2 cc ≤95 Gy compared to 17 % (9/54) if the D2 cc dose exceeded 95 Gy, indicating that the focal dose threshold is not clear from the available data (Kirisits et al. 2005; Potter et al. 2006). In another study of patients treated with MR-guided interstitial gynecologic brachytherapy with a median D2 cc bladder dose of 69 Gy, no Grade 3 or 4 genitourinary toxicities were reported after a 2-year median follow-up (Potter et al. 2007; Viswanathan et al. 2006). Other studies have shown a 30 % incidence of acute Grade 1 bladder toxicity with interstitial brachytherapy (Viswanathan et al. 2007). Even with the above limitations, increased dose to the bladder is clearly associated with an increased incidence in severity of late urinary complications.

In general, the dose to the pelvis given via external beam to the pelvis ranges from 40 to 50 Gy, which is well within the tolerance dose to the whole bladder and severe long-term sequelae are rare. Brachytherapy with either a vaginal cylinder, tandem, and ovoid, interstitial and other applicator treatments increases the dose to a focal region of the bladder in closest proximity to the applicator. In cervical cancer brachytherapy with CT or MRI-guided imaging for each fraction, limiting the D2 cc bladder dose to <90 Gy_3 results in a 3 % Grade 3–4 late bladder toxicity rate (Kirisits et al. 2005, 2007; Potter et al. 2007). Modern studies with image-guided brachytherapy have observed relatively low complication rates at doses that are significantly higher than previously estimated dose tolerance limits (Marks et al. 1995). However, long-term follow-up with these approaches have not matured to assess for late toxicity, and further work is needed to accurately measure 3D dosimetry and correlate to the risk of late bladder complications.

6 Chemotherapy

Chemotherapy administered concurrently with radiation is intended to enhance the effects of radiation and may sensitize the normal tissue to radiation-associated effects. However, there is no evidence of increased risk of long-term bladder complications in patients treated with concurrent chemoradiation for cervical cancer (Eifel et al. 2004; Stehman et al. 2007; Whitney et al. 1999) or bladder cancer (Marks et al. 1995; Eapen et al. 1989; Farah et al. 1991; Jakse et al. 1989; Kubota et al. 1984; Rotman et al. 1990; Russell et al. 1990; Sauer et al. 1990; Shipley et al. 1987; Raghavan et al. 1989). With 8 years of follow-up of chemoradiation for cervical cancer patients, 3 % developed late bladder side effects (Eifel et al. 2004). Over the last several decades, bladder preserving approaches for patients with muscle-invasive bladder cancers have included EBRT with different chemotherapy regimens (Eapen et al. 1989; Farah et al. 1991; Jakse et al. 1989; Rotman et al. 1990; Russell et al. 1990; Sauer et al. 1990; Shipley et al. 1987). As described above, combined modality therapy with radiation doses to the whole bladder of 64–65 Gy given with cisplatin-based chemotherapy are well tolerated (Zietman et al. 2003; Shipley et al. 2007) (Table 7).

Chemotherapy alone may cause toxicity, for example when active metabolites accumulate in the bladder. Cyclophosphamide use is independently associated with chronic hemorrhagic cystitis, incontinence, contractions, vesicoureteral reflux, and urothelial malignancies (Levine and Richie 1989). Hemorrhagic cystitis may occur at any time after treatment, and there is a spectrum of clinical severity

Table 7 Chemotherapy that has been used for cancer of the bladder

Doses and schedules
Methotrexate 30 mg/m^2 IV on day 1
Vinblastine 3 mg/m^2 IV on day 2
Doxorubicin 30 mg/m^2 IV on day 2
Cisplatin 70 mg/m^2 IV on day 2 (with adequate pre- and post-hydration)
Repeat methotrexate and vinblastine on day 15 and 22 if white blood cell count >2,000/μL and platelet count >50,000/μL
Cycles should he repeated every 28 days
Gemcitabine 1,000 mg/m^2 day 1
Cisplatin 70 mg/m^2 on day 2
Repeat gemcitabine on day 8 and 15 if white blood cell count >2,000/μL and platelet count >50,000/μL
Cycles should be repeated every 28 days
Carboplatin AUC 5 day 1
Gamcitabine 1,000 mg/m^2 day 1 and day 8
Cycles repeated every 21 days
Carboplatin AUC 6
Paclitaxel 225 mg/m^2
Cycles repeated every 21 days
250 mg/m^2 IV over 24 h every 21 days

AUC area under the curve; *IV* intravenously

and duration from transient to chronic. Conventional dose and high-dose cyclophosphamide have been observed to cause chronic hemorrhagic cystitis in up to 40 and 70 % of patients, respectively (Levine and Richie 1989; Stillwell and Benson 1988; Stillwell et al. 1988; Klein and Smith 1983). The addition of doxorubicin to cyclophosphamide with radiation therapy to the bladder may further increase the risk of toxicity (Klein and Smith 1983).

7 Special Topics

7.1 Surgery

Any kind of procedure or surgery before radiation treatment including transurethral resection of bladder tumor (TURBT), prostatectomy, hysterectomy, or biopsy may increase the risk of bladder complications. Wounds from a bladder biopsy or TURBT may heal slowly or result in long-term ulceration after radiation therapy, while hysterectomy and prostatectomy may denervate the bladder and result in urinary hesitancy, retention and/or overflow incontinence. The development of incontinence is likely related to surgical manipulations of the bladder neck and urethra. In a study designed specifically to address this issue, post-radiation incontinence was seen in 5.4 % (7/130) of patients who had had a prior transurethral prostate resection (TURP), compared to 1 % (1/105) of patients who had not (Green et al. 1990). The rate of urethral stricture after EBRT for prostate cancer is estimated to be 2–5 % in patients without prior TURP, and 6–16 % with TURP prior to radiation treatment (Marks et al. 1995; Klein and Smith 1983). A hysterectomy may also affect innervation of the urethral sphincter. Bladder dysfunction post-radical hysterectomy is common with approximately 5 % of patients requiring chronic suprapubic catheterization, and 38–50 % may develop detrusor instability, impairment of bladder sensation, altered bladder compliance, and decreased maximum urethral pressure (Axelsen et al. 2007).

7.2 Patient-Related Risk Factors

Patient-related risk factors for bladder injury include a history of chronic urinary infections, incontinence, or cystitis. A history of diabetes can exacerbate bladder infections, result in poor wound healing, and increase the likelihood of chronic infections. Patients with portal hypertension may have a high rate of hematuria as do patients medicated with warfarin or other anticoagulation medication. Many patients develop incontinence with aging, and the effects of radiation amplify symptoms, although incontinence is a rare event due to radiation alone (Marks et al. 1995). Secondary factors may cause subclinical radiation damage to become symptomatic. For instance, patients with diabetes mellitus may be prone to develop late onset fistula, chronic bladder infection, and incontinence, particularly as they age (Kucera et al. 1987).

In a series of 3,489 patients treated for gynecologic cancers at MD Anderson with 10 years follow-up, late bladder complications were recorded in 115 patients (Eifel et al. 2002). On multivariate analysis, black race (HR 1.89, $p = 0.003$), tobacco use (≥1 pack per day) (HR 1.81, $p = 0.006$), body mass index (HR 1.55, $p = 0.05$), and central dose of external beam radiation >50 Gy (HR 3.34, $p = 0.002$) were significantly associated with late bladder complications. In this series, age, diabetes, and hypertension were not correlated with risk of complications. Few centers have such thorough and comprehensive follow-up data. In prostate cancer patients with pretreatment GU symptoms, there is a significantly higher risk of late GU toxicity after definitive radiation therapy compared to patients without preradiation symptoms (Karlsdottir et al. 2008; Cahlon et al. 2008; Peeters et al. 2005; Schultheiss et al. 1997). Other risk factors for late toxicity in patients with prostate cancer include acute toxicity, older age, and the use of hormonal therapy (Karlsdottir et al. 2008; Zelefsky et al. 2008; Peeters et al. 2005; Schultheiss et al. 1997). The use of hormonal therapy resulted in an actuarial rate of ≥Grade 2 toxicity of

40 % versus 25 % with no hormonal therapy (Peeters et al. 2005; Schultheiss et al. 1997).

7.3 Psychosocial, Familial, and Genetic

Quality of life assessments tools attempt to address the psychosocial implications of bladder toxicity, but further systematic study may be necessary. No clear correlation between specific genetic syndromes and bladder toxicity has been reported.

8 Prevention and Management

8.1 Prevention and Predictive Assays

There are currently no preventative approaches or predictive assays for radiation-induced bladder complications.

8.2 Management of Symptoms of Acute Bladder Toxicity

Acute symptoms typically are self-limited and resolve several weeks after the completion of radiation therapy. Medical therapy to ameliorate these acute symptoms includes nonsteroidal anti-inflammatory drugs (NSAIDs) to decrease cystitis and urethritis and provide analgesia. For patients with dysuria, phenazopyridine hydrochloride (200 mg by mouth, 3 times a day) is an effective local analgesic as the majority of the drug enters the urine unchanged and acts as a topical anesthetic in the bladder. This medication turns the patient's urine orange, so it is important that patients be alerted to this so that they not become alarmed. More severe symptoms of dysuria can be managed with oral narcotics. As noted above, the symptoms of acute bladder toxicity are similar to those of a urinary tract infection. Urine analysis and urine culture are appropriate in patients with acute symptoms that are refractory to medical management. In female patients with a complaint of dysuria, bacterial vaginitis and/or vaginal yeast infections should also be considered. Genitourinary and gynecological infections should be treated promptly with an appropriate course of antibiotics, as an untreated infection may exacerbate the symptoms associated with radiation injury (Table 8).

Symptoms of urinary frequency and urgency may be due to outlet obstruction and/or bladder detrusor muscle spasms. Outlet obstruction seen in external beam radiation therapy or brachytherapy for prostate cancer can be managed with alpha-adrenergic antagonists such as terazosin and doxazosin. In severe cases, catheterization may be necessary for symptomatic relief. In patients with bladder wall spasm, anticholinergics such as oxybutynin (5 mg, 2–3 times a day), propantheline, or imipramine may relax the bladder wall by inhibiting smooth muscle muscarinic receptors.

Table 8 Pharmacotherapy for urinary complications

To increase bladder storage	
Propantheline bromide	15–30 mg Q 4–6 h
Oxybutynin chloride	5 mg TID
Imipramine hydrochloride	25 mg QID
To increase outlet resistance	
Ephedrine hydrochloride	25–50 mg QID
Pseudoephedrine hydrochloride	30–60 mg QID
Phenylpropanolamine	50 mg TID

8.3 Management of Symptoms of Late Bladder Toxicity

8.3.1 Management of Late Effects

Overview

As described above, dysuria may be managed by NSAIDs, phenazopyridine hydrochloride, and narcotics. Symptoms caused by bladder wall spasm may be treated by antimuscarinic agents such as oxybutynin, propantheline, or imipramine (Wein 1987). Patients with persistent symptoms should be promptly referred to an urologist for consideration of cystoscopy, particularly those presenting with late onset of hematuria after radiation therapy or cyclophosphamide, and/or history of bladder cancer, may require cystoscopy to evaluate for a secondary bladder malignancy.

Management of Hemorrhagic Cystitis

Patients with mild hemorrhagic cystitis can be managed with increased hydration, while persistent bleeding may be medically managed with hyperbaric oxygen, medications such as conjugated estrogens, sodium pentosan polysulfate, or recombinant factor VII. In patients who do not respond to medical management, or with severe hemorrhage resulting in urinary retention, cystoscopy with clot removal, and selective cauterization of bleeding vessels or instillation of alum, silver nitrate or dilute formalin may be helpful. In the relatively rare patients with persistent, recurrent, or severe hemorrhage, more invasive procedures including vesical artery embolization, bladder diversion, or cystectomy and reconstruction may be necessary. Although there has historically been a concern that high dose pelvic radiation is a contraindication to orthotopic lower urinary tract reconstruction, more recent studies have shown that orthotopic

urinary reconstruction is feasible with minimal complications (Bochner et al. 1998; Gschwend et al. 1996). Nevertheless, these procedures should be performed by skilled urologists with experience in dealing with post-radiation complications.

Management of Bladder Dysfunction

Decreased bladder compliance and capacity as a result of fibrosis may eventually cause hydronephrosis and kidney damage, and requires intervention. Initial medical management includes antimuscarinic medications, which may improve bladder compliance via smooth muscle relaxation. Repeated urodynamics should be performed after initiation of these medications to document improvement of bladder compliance. As described above, patients with severe bladder dysfunction may eventually need surgical management including bladder diversion or cystectomy and reconstruction.

Severe complications such as a vesicovaginal or vesicorectal fistula are typically uncommon. In a series of 2,248 patients treated with radiation therapy for cervical cancer, Alert et al. reported an incidence of fistulas of 1.6 % (Alert et al. 1980). Perez et al. reported a similar incidence of 0.6–2.0 % in a cohort of 1,456 patients receiving external beam radiation therapy and LDR brachytherapy to a dose of 70–90 Gy to point A for stage I–III cervical cancer, and there appeared to be a dose response (Perez et al. 1999). In a patient presenting with a post-treatment fistula, local recurrence should be on the differential, and a biopsy of the fistula tract should be considered. However, if the clinical suspicion for recurrence is low, it might be better to avoid a biopsy as the trauma from the biopsy itself may aggravate the situation. Surgical repair of a vesicovaginal or vesicorectal fistula requires meticulous excision of the fistula, multilayer closure with well-vascularized tissue, and the interposition of flaps or grafts such as omentum, muscle, fat, or peritoneum to prevent recurrence.

9 Future Research

The upper limit of bladder dose tolerance is not known. Future studies detailing the dose–volume data, accounting for organ motion and distension, and having long-term clinical follow-up data are needed. In addition, reports in the future should attempt to address some of the issues listed below.

The use of 3D imaging during conformal RT will facilitate studies that relate the actual dose–volume parameters to the clinical outcomes.

An improved understanding of the physiology of bladder distention might allow construction of deformable models that could facilitate estimates of bladder dose distribution according to the bladder volume and surface area. Statistical methods might also be useful to understand the likely degree of bladder motion during a course of RT and to better estimate the delivered 3D doses.

All regions of the bladder might not be equally important for different functions. Studies that estimate the physiologic effect of doses to different regions of the bladder could be helpful.

Statistical approaches such as Cox regression proportional hazard models should be used to adjust for the potential confounding effects of medical comorbidities and other treatments. Patients with recurrent disease should not be included in such studies because the symptoms from recurrence and repeated treatment could be confounding.

Better determination of the linear-quadratic model parameters describing bladder injury is needed. The radiobiologic determinants of the α/β and the biologic model used to calculate a normalized total dose in 2-Gy fractions (EQD2) for high dose rate brachytherapy should be analyzed to determine whether they are valid for the high doses administered during cervical cancer treatment. An increased understanding of the applicability of the model to bladder injury, especially in the setting of brachytherapy, is needed.

Patient-based, rather than physician-derived, toxicity scoring must be reported to better reflect the true symptomatic incidence of bladder injury (Viswanathan et al. 2010).

10 Review of Literature and Landmarks

As described above, the literature indicates no specific bladder DVH relationships to date. Important readings in this regard include:

1920 Schmitz: Reported the first case of ureteral stricture attributed to scar formation in the parametrium due to radiation-induced fibrosis.

1927 Dean: Gave the initial careful documentation of ulceration of the urinary bladder as a prominent effect of radium applications.

1939 Everett: Made the first attempt to relate pre and post irradiation findings in the urologic tract in cervical carcinoma. Fifty of the cured patients showed changes, of which 15–20 % were of serious significance.

1947 Watson, Herger, and Sauer: Presented a fine documentation of radiation reactions in the bladder: their course, development and reasons for occurring in female pelvic cancer.

1953 Kottmeier: Documented a 3.8 % incidence of bladder injuries in 2,756 cases of carcinoma of the cervix treated by irradiation over 10 years.

1960 Gowing: Documented the pathologic changes in the bladder after irradiation by internal and external sources

on the basis of specimens after 50 total cystectomies. Mentioned the intractability of some bladder ulcers.

1968 Rubin and Casarett: Correlated the Biocontinuum spectrum induced by radiation histopathologically and clinically.

1981 Stewart, Michael, and Denekamp: Late radiation damage in mouse bladder as a function of fractionation.

1984 Shipley et al.: Report of tolerability of cisplatin and full dose radiation in bladder cancer.

1995 Marks et al.: Introduced Global/Focal injury and bladder toxicity as a function of dose/volume paradigm and LENT-SOMA Toxicity Grading Program.

2003 Trotti and Rubin: Incorporate radiation, chemotherapy, and surgery early/late effect in CTC V.3.0.

Recommended Reading

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2. Viswanathan, A.N., et al. *Radiation dose volume effects of the urinary bladder.* Int J Radiat Oncol Biol Phys, 2010.**76**:S116–S122	Recent review of the literature on bladder toxicity and provides guidelines based on modern techniques including IMRT and image-guided brachytherapy.
3. Cox, J.D., J. Stetz, and T.F. Pajak, *Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).* Int J Radiat Oncol Biol Phys, 1995. **31**(5): p. 1341–6	LENT-SOMA scale

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Prostate, Seminal Vesicle, Penis, and Urethra

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Contents

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Abstract

- Late histologic changes in irradiated benign prostate ducts include variable ductal atrophic change, cytologic and nuclear atypia, basal cell hyperplasia, increased foreign body giant cell reaction to corpora amylacea, nuclear pleomorphism, nuclear vacuolation, hyperchromatic DNA, and presence of prominent nucleoli.
- In the later phases of fibrosis, TGF-beta and PDGF, among others, simulate the proliferation of fibroblasts and the synthesis or extracellular matrix constituents and MMPs.
- Irradiated urothelial cells demonstrate changes including nuclear pleomorphism, swollen cytoplasm, and altered labeling indices as compared to non-irradiated urothelial cells.
- The most common acute urinary morbidities during external beam radiation therapy for pelvic malignancies are classified as irritative and are caused by acute

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inflammation and epithelial denudation of the urethra and possibly the bladder neck.
- In patients treated for prostate cancer, brachytherapy is associated with more late GU toxicity, but less late GI toxicity, than external beam RT.
- The main sexual side effects of radiation therapy to the pelvis are impotence, decreased libido, decreased ejaculate, and painful ejaculation.
- Late genitourinary toxicities of radiation therapy to the pelvis include chronic cystitis, chronic urethritis, bladder neck contracture, urethral strictures, hematuria, and urinary incontinence.
- Rectal complications are the main late toxicities that limit dose escalation in prostate cancer.
- Modern highly conformal techniques can be used to minimize dose to the penile bulb and cavernosa whenever possible, and MRI identification of the apex of the prostate may be helpful in this regard.
- For erectile dysfunction in the post-treatment setting, first-line phosphodiesterase inhibitors such as sildenafil 25–100 mg po prn, tadalafil 10 mg po prn, vardenafil 5–20 mg po can be considered.

Abbreviations

BPH	Benign prostatic hyperplasia
CTGF	Connective tissue growth factor
PSA	Prostate-specific antigen
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
NVB	Neurovascular bundle
3D-CRT	Three-dimensional conformal radiation therapy

1 Introduction

In men, malignancies of the bladder, rectum, and prostate account for approximately one-third of all new cancer diagnoses. Radiation therapy is often used in the treatment of these and other pelvic and lower extremity malignancies, exposing the distal male urogenital tract, including the prostate, seminal vesicles, penis, and urethra, to potential toxicity. Toxicities to these organs can negatively affect genitourinary, gastrointestinal, and sexual quality of life. It is essential that the treating oncologist has an understanding of the treatment-related toxicities of these tissues, their management, and the radiation dose-volume constraints that guide treatment planning. It is further essential that these radiation planning parameters are properly integrated with increasingly common clinical scenarios such as the use of concurrent chemotherapy, biologic agents, and altered fractionation radiation regimes which can influence further the potential for normal tissue complications.

This chapter will first briefly highlight the landmark events in the history of radiotherapy for the distal male GU tract and assess the current state of the field. A detailed review of the gross anatomy, histology, and radiation histopathology of the organs of the distal male GU tract then follows. A description of each organ-related radiation toxicity is then reviewed along with the appropriate dose–volume constraints that should guide treatment planning. Finally, guidelines for the clinical management of common radiation-related toxicities are offered. Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The distal male urogenital tract extends from the lower pelvis to the ventral portion of the body and includes the prostate gland, seminal vesicles, urethra, and penis. The testicles, which are also a part of the distal male urogenital tract, are addressed in a separate chapter. The primary roles of the distal urogenital tract are to generate components of the seminal fluid, serve as a conduit for urine and semen, and facilitate sexual intercourse. Highly detailed anatomic descriptions and atlases are available in both textbook (Gray 1995; McAninch 2008) and publication (Meyers 2001; Walz et al. 2010) form. It is increasingly clear that there can be significant variations between individuals in terms of the form and structure of the prostate gland, neurovascular bundles, external urethral sphincter, prostatic ligaments, and vascular supply to these structures.

2.1.1 Prostate Gland

The prostate gland lies within the lower pelvis immediately superior to the musculofascial floor. It is the largest accessory gland of the male reproductive tract, weighing approximately 30 grams in men without prostatic pathology. A fibrous capsule surrounds the gland, which is continuous with the surrounding connective tissue stroma, but is not present at the apex of the prostate. The fascia surrounding the prostate gland is variably adherent to the capsule. Shaped like an inverted tapered cylinder, the prostate base is immediately caudad to the bladder and its tapered apex cephalad to the urogenital diaphragm. The apex contains muscle fibers continuous with the urogenital diaphragm. The prostate lies posterior to the symphysis pubis, connected via the puboprostatic ligaments, and anterior to the rectum, separated from it by the anterior portion of Denonvilliers fascia (rectovesical septum), a thin

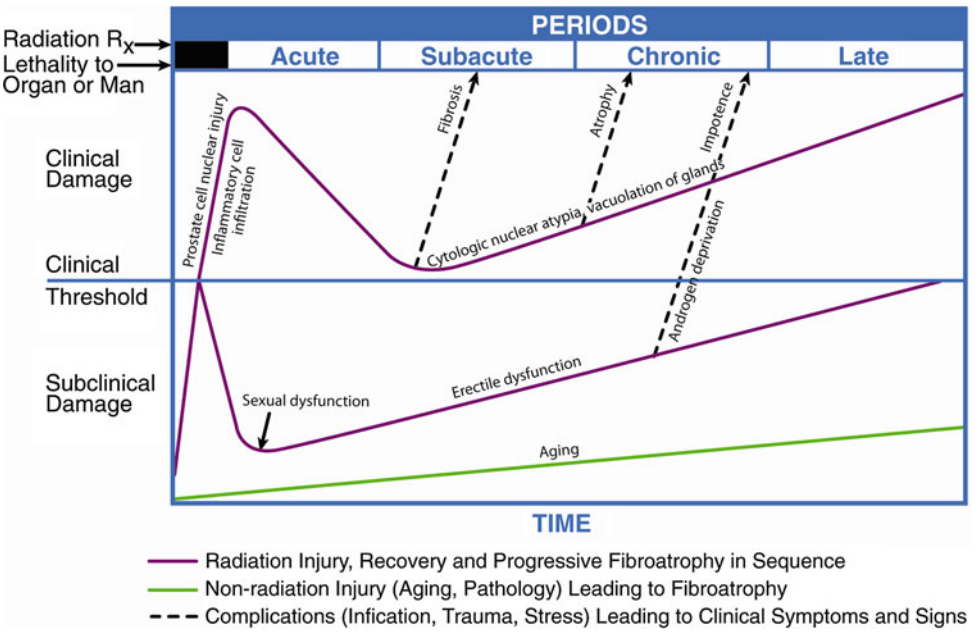


Fig. 1 Clinical pathologic course: prostate gland, seminal vesicles, and penis (with permissions from Rubin and Casarett 1968)

layer of connective tissue that separates the prostate and seminal vesicles from the anterior rectal wall. The prostatic urethra passes through the gland from the base of the bladder to the membranous urethra. The ejaculatory ducts course from the convergence of the ducti deferens and the seminal vesicles obliquely, anteriorly and caudally, through the posterior prostate to communicate to join with the prostatic utricle to open into the prostatic urethra.

The blood supply of the prostate gland is from the prostatic branches of the inferior vesicle, pudendal, and middle rectal arteries. Venous drainage is shared with the penis, urethra, and lateral pelvic organs via the dorsal venous plexus (Santorini's plexus) to the internal iliac vein. The predominant course of lymphatic drainage is to the internal iliac nodes, but alternative drainage routes to the obturator, external iliac, sacral, vesicle, and rarely the periaortic lymph nodes are common. The prostate gland has dual autonomic innervation from the prostatic nerve plexus. Parasympathetic innervation is provided by the pelvic splanchnic nerve (S2-4) and sympathetic innervation is provided by the inferior hypogastric plexus (T10-L2). The neurovascular bundle (NVB) courses between fascial layers on the posterior lateral surfaces of the prostate gland and is intimately related to the dorsal surfaces of the seminal vesicles.

The prostate has been anatomically described in terms of both lobes and zones (McNeal 1981). There are four lobes of the prostate: anterior, posterior, median, and lateral. The anterior lobe is located anterior to the urethra and contains no glandular tissue, just fibromuscular stroma. The median lobe lies in the center of the gland, with the urethra anteriorly and the ejaculatory ducts posteriorly. The paired right and left lateral lobes are the largest lobes and contain the bulk of glandular tissue, being separated into halves by the prostatic urethra. The posterior lobe lies at the dorsal portion of the gland and can be palpated via a digital rectal examination.

The zonal anatomy of the prostate (Fig. 2) was first described by McNeal in 1981 and is used more commonly. This system is based on embryonic development patterns and includes four prostatic zones described relative to the urethra: the peripheral zone, the central zone, the transition zone, and the anterior fibromuscular stroma. The peripheral zone is a horseshoe-shaped structure extending posteriorly and laterally around the inner regions of the prostate gland and contains approximately 70 % of the prostatic glandular tissue. It is embryologically derived from a double row of developing prostatic ducts that extend posterolaterally from the distal urethra. The central zone contains approximately 25 % of the glandular tissue and is formed from developing ducts that grow cephalad, posteriorly and laterally into the mesenchyme surrounding the ejaculatory ducts. It is a cone-shaped volume extending from the bladder base to the verumontanum, encompassing the ejaculatory ducts. The transition zone lays anteromedial to the central zone and surrounds the mid-prostatic urethra. Benign prostatic hypertrophy occurs most commonly in the transition zone. The fibromuscular stroma is the anterior part of the prostate and contains little to no glandular tissue but does account for one-third of the total bulk of tissue within the prostatic capsule.

2.1.2 Seminal Vesicles

The seminal vesicles consist of two lobulated glands posterior to the bladder and prostate gland that converge medially. They are inferior and lateral to the ampulla of the ductus deferens and lie against the fundus of the bladder.

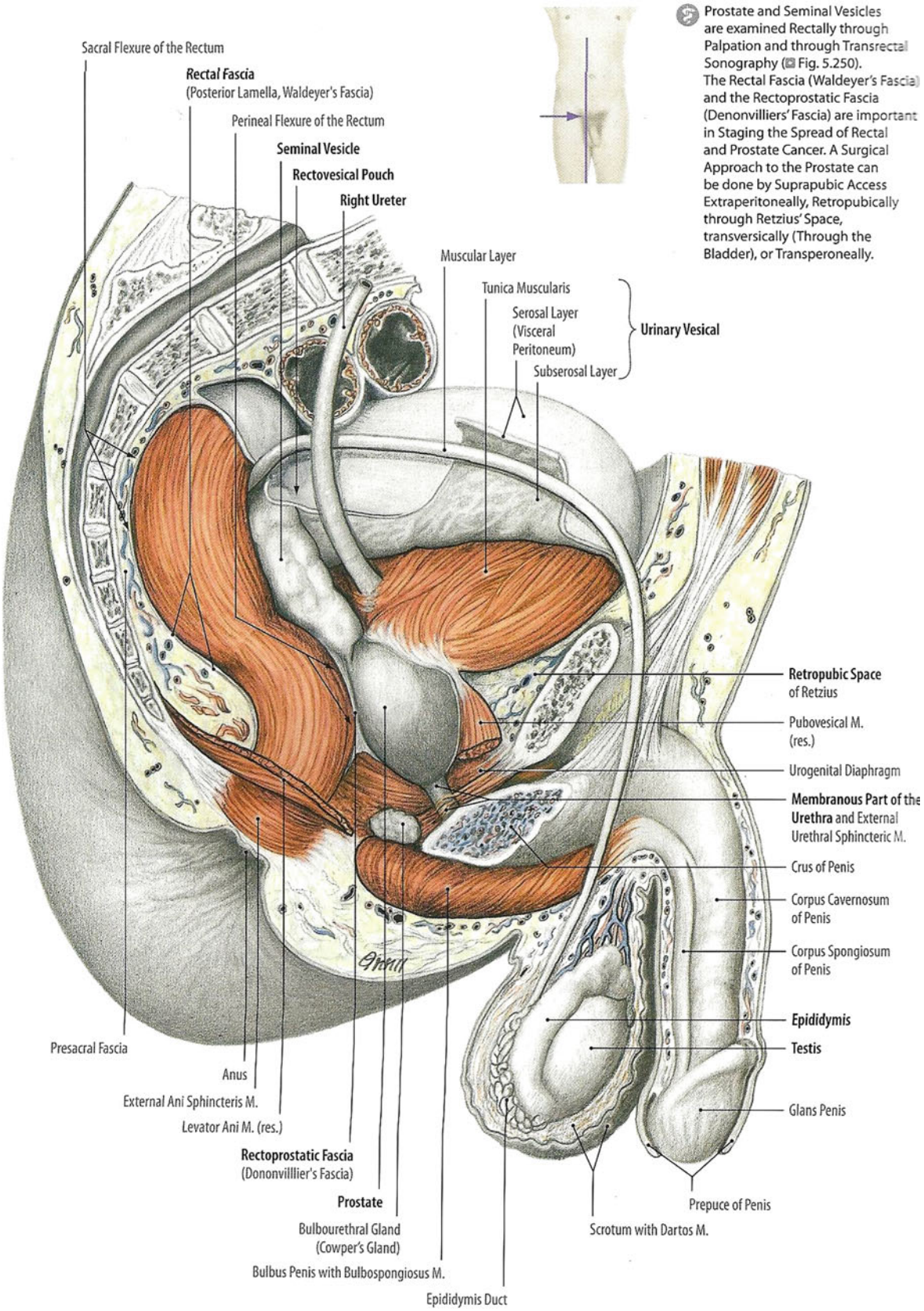


Fig. 2 Anatomy of the prostate (with permissions from Tillman 2007)

The majority of these glands lie in the retroperitoneum and are enclosed by dense fascia, except for the most cephalad portion, which is intraperitoneal. Their cephalad surface abuts the posterior bladder and their caudad surface interfaces with the anterior rectum at the rectovesical (Denonvilliers') fascia. The ureters lie medial to each seminal vesicle. The seminal vesicles converge with the vas deferens to form the ejaculatory ducts which enter the prostate gland. They produce alkaline secretions that are added to the semen. Their blood supply is from the inferior vesicle artery and vein and middle rectal artery and vein. Their main lymphatic drainage is to the internal iliac lymph nodes. Sympathetic innervation is via the superior lumbar and hypogastric nerve, which regulates rapid contraction of smooth muscle cells during ejaculation. Parasympathetic innervation is from the pelvic splanchnic nerve and from the inferior hypogastric plexus.

2.1.3 Male Urethra

The male urethra courses from the base of the bladder to the tip of the penis and is subdivided into prostatic, membranous, and spongy portions. It provides a conduit for urine and semen to be excreted from the body. The prostatic portion enters the anterior portion of the prostate gland and travels with slight anterior concavity so that it courses posteriorly toward the mid gland before resuming an anterior position at the prostatic apex. The change from the posterior to anterior course happens at a sharp, approximately 35-degree angle, at the level of the verumontanum, a midline protrusion along the posterior urethra where the ejaculatory ducts enter the prostatic urethra. The prostatic urethra is about 3-cm long and is the widest and most compliant portion of the urethra. The membranous urethra is approximately 1-cm long and extends through the urogenital diaphragm from the apex of the prostate gland to the bulb of the corpus spongiosum. The external urethral is a complex anatomic and physiologic structure closely related to the urogenital diaphragm. The innervation for the external sphincter travels near the apex of the prostate. The external sphincter is a circular muscle under partial voluntary control (innervated by the somatic nervous system) in the urogenital diaphragm and regulates the passage of urine through the urogenital diaphragm. Once the urethra enters the penile bulb, it becomes the spongy (penile) urethra which extends to the navicular fossa at the tip of the penis. The spongy urethra is about 6-cm long and is contained in the corpus spongiosum.

2.1.4 Penis

The penis is subdivided into three portions: the root, the body, and the glans. The root is anchored to the os pubis, symphysis pubis, and ischium by the crura and suspensory ligaments. The body of the penis extends between the root and the glans, a dome-shaped extension of the corpus spongiosum. The penis contains three erectile bodies, each encased in a fascial cover: two paired corpora cavernosa and the corpus spongiosum. All corpora are further encased together by the fibrous Buck's fascia. The spongy urethra courses within the corpus spongiosum after entering this structure at the penile bulb, the most proximal portion of the spongiosum. The penile skin rests upon Colles' fascia, which is continuous with Scarpa's fascia of the abdominal wall.

The arterial supply of the penis and urethra is from the internal pudendal arteries which branch into the deep penile artery, the bulbourethral artery, and the dorsal artery of the penis. The deep artery supplies the corpora cavernosa, while the others supply the remainder of these organs, including the urethra and corpus spongiosum. There are multiple routes of venous drainage of the penis. The superficial dorsal vein is external to Buck's fascia, while the deep dorsal vein lies deep into this thick fascial layer between the paired dorsal arteries. The dorsal veins join the pudendal plexus and eventually the internal pudendal vein. The penile skin and superficial fascia's main route of lymphatic drainage is to the superficial inguinal lymph nodes. The predominant lymphatic pathway for the glans penis is through the external iliac nodes. The urethra drains to the internal and common iliac lymph nodes.

The anatomy of the pelvic floor is challenging to visualize on CT or MRI, and hence definition of the penile bulb varies. This may contribute to inconsistent reports (5–15). The penile bulb appears as an oval-shaped, hyperintense midline structure on T2-weighted MR images; on axial CT imaging it is bounded by the crura, corpora spongiosum, and the levator ani muscle. At University of California-San Francisco, the bulb is defined as the most proximal portion of the penis sitting immediately caudal to the prostate.

2.2 Histology

2.2.1 Prostate Gland

Many excellent textbook references are available with detailed descriptions of the histology of the organs of the distal male genitourinary tract (McAninch 2008; Bostwick 1998). Several cellular subtypes are evident upon histologic examination of the prostate, including basal, secretory, neuroendocrine, urothelial, and ejaculatory duct cells (Fig. 3a, b). Under the thin fibrous capsule of the prostate are smooth muscle layers and layers of collagen which also surround the prostatic urethra, forming the involuntary sphincter. Deeper to this layer is the prostatic stroma, which encases the glandular compound tubuloacinar secretory units, numbering 30–50. These units are arranged concentrically into three groups based on their relationship to the

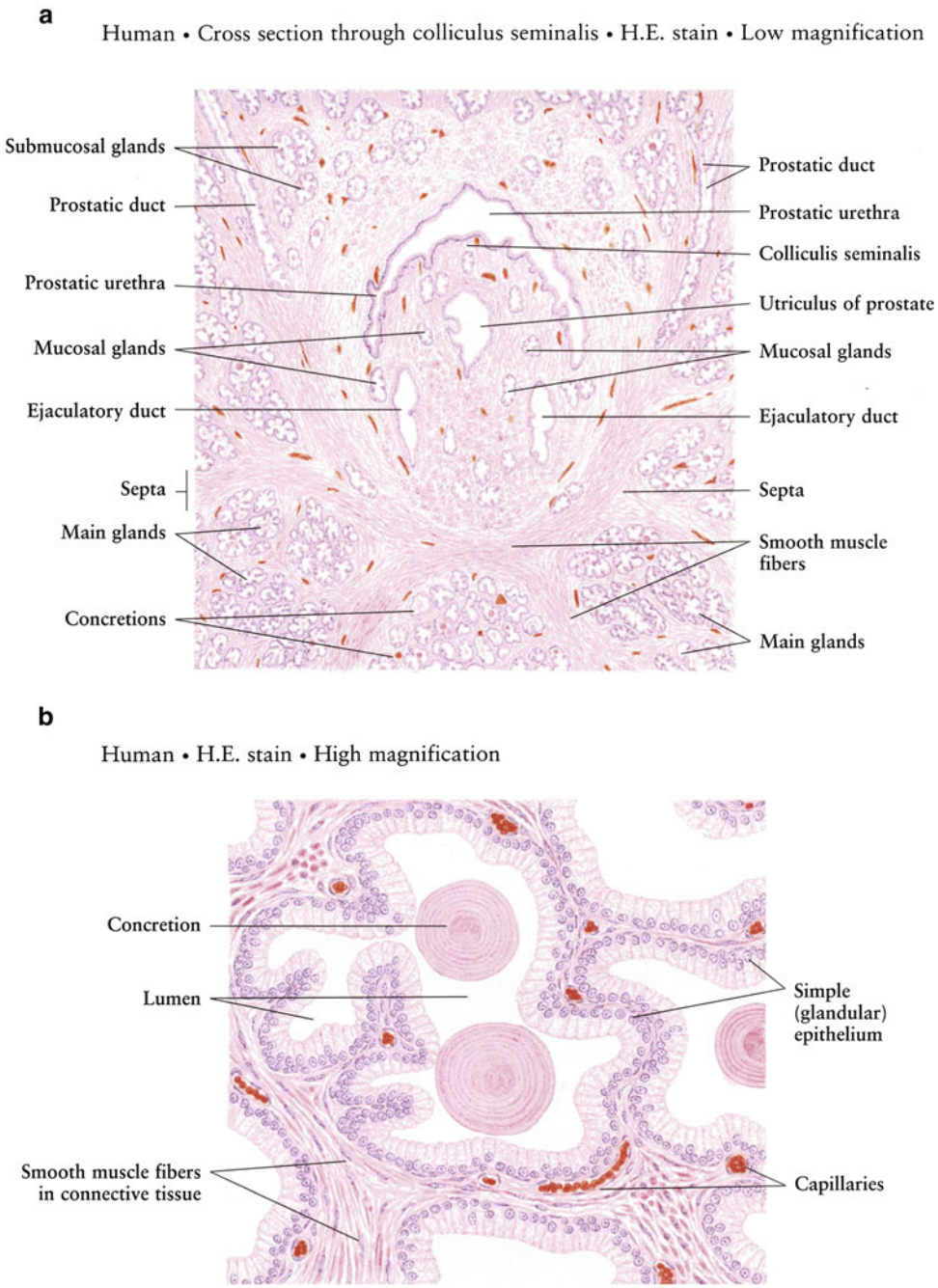


Fig. 3 Histology **a** Prostate gland. **b** Prostate gland: Acini **c** Penis **d** Penis corpus cavernosum (with permissions from Zhang 1999)

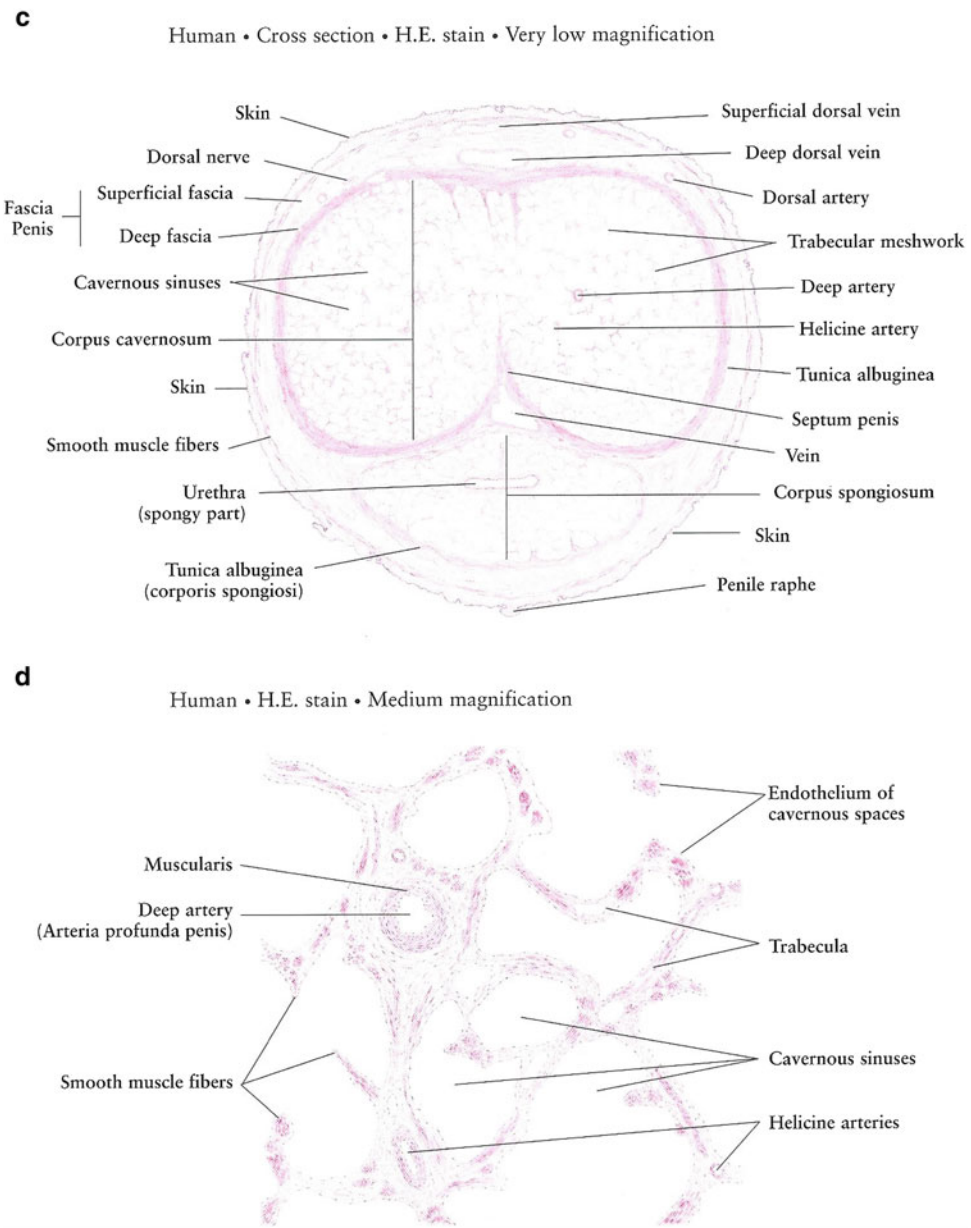
urethra. The majority of these ducts open on the floor of the prostatic urethra near the verumontanum. The main group is farthest from the urethra and constitutes the largest in number. The mucosal and submucosal glands, along with their adjacent stroma, undergo hyperplastic change with age, leading to compression of the urethra and symptoms consistent with benign prostatic hyperplasia (BPH).

The glandular acini are highly redundant and are lined by two layers of cells: a luminal layer of tall columnar cells and a layer of cuboidal cells adherent to the underlying basement membrane. Between prostatic glands is fibromuscular stroma containing smooth muscle, collagen, and elastic fibers. In parenchymal portion, glands consist of a simple high cuboidal/low columnar epithelium.

2.2.2 Seminal Vesicles

Histologically, each seminal vesicle consists of a single coiled tubular structure that forms a large irregular lumen with many mucosal folds. The epithelium is composed of mixed columnar and pseudostratified columnar cells with mucosal crypts generated by infoldings of the mucosa. It is surrounded by two muscular layers that contract to create

Fig. 3 (continued)



positive pressure to move secretions through the lumen and into the ejaculatory duct. The duct of each seminal vesicle combines with the ductus deferens to form the ejaculatory duct.

2.2.3 Urethra

Deep into the superficial urethral mucosa is the submucosa which contains smooth muscle, elastic tissue, and other stromal elements. The superficial histology of the urethra is dependent on its anatomic subsection. In the prostatic portion, it is lined with transitional epithelium. In the spongy portion, it contains stratified columnar epithelium until the navicular fossa, where a transition to non-keratinizing stratified squamous epithelium is seen. The lamina propria of the spongy portion of the urethra merges with the surrounding corpus spongiosum.

2.2.4 Penis

In the penis, cavernous bodies are irregular and lined with simple squamous endothelium and contain venous blood. The cavernous spaces of the cavernosa are larger than those of the spongiosum and have thinner stromal trabeculae, allowing the cavernosa to become more turgid than the corpus spongiosa when the penis is tumescent. (Fig. 3c, d).

2.2.5 Penile Bulb

The penile bulb consists of corpus cavernosum and responds during sexual arousal becoming distended, and is the base of the penis when erect.

3 Physiology and Biology

3.1 Physiology

The actively secreting prostate ductal areas contain pseudostratified columnar epithelium, while ducts with less secretory activity demonstrate simple columnar or high cuboidal epithelial cells. Within some ductal lumens are prostatic concretions, also called corpora amylacea, which are of uncertain physiologic significance. These concretions become more numerous with age and often calcify.

3.1.1 Prostate

The prostate gland is arranged in three concentric groups: 1. Main, one-half glandular; 2. Submucosal, one-fourth fibrous tissue; 3. Mucosal, one-fourth involuntary muscle (Fig. 4).

The prostate gland is influenced by the male sex hormones, i.e., testosterone and adrenal androgens which are converted into dihydrotestosterone (DHT) which is 30 × more potent that testosterone. The DHT stimulates growth of the normal prostate glandular epithelium. The prostate gland secretes prostate acid phosphatase and prostate-specific antigen (PSA) which are incorporated into seminal fluid of which only a small fraction enters circulating blood (i.e. 4 Ng/ml). As the prostate enlarges and undergoes malignant transformation, PSA increases to >4 Ng/ml and serves as a biomarker for cancer increasing to 4.0–10.0 Ng/ml. In addition the prostate gland secretes prostatic acid phosphatase (PAP), an enzyme that regulates prostate cell growth and metabolism of the glandular epithelium. The fibronolysin in the secretions liquefies semen.

3.1.2 Seminal Vesicles

Seminal vesicle secretions consist largely of prostaglandins (accounts for the name of prostate gland) which during ejaculation discharges its secretions and assists in flushing out the semen through the urethra.

3.1.3 Urethra and Penis

During its erectile stage due to filling of its vascular spaces, allows for penetration of the vagina and its ejaculate of semen via the urethra, initiates the fertilization of the ovum (Fig. 4).

3.1.4 Penile Crura: Sexual Performance

Male sexual performance consists of specific sequence of events (Fig. 4):

Sexual arousal → libidinous desire → erection → ejaculation → orgasm → detumescence

- Sexual arousal and libido are multifactorial and depend on the sex partner and level of testosterone. Arousal sensation via pudendal nerve S_2–S_4 somatic fibers).
- Erection occurs with pelvis splanchnic (S_2–S_4 parasympathetic) innervations, penile vasodilatation of corpora cavernosum, and spongiosum-dependent patent inferior vesicle arteries and arterioles and mediate veno-occlusion, entrapping blood in penis to allow for vaginal penetration.
- Ejaculation and orgasm via sympathetic via nerves.
- Detumescence results with vasoconstriction of arterioles, diverting blood from corpora cavernosum and spongiosum into the periprostatic venous plexus via dorsal vein of the penis, via alpha-adrenergic receptor activation.

3.2 Biology

3.2.1 Prostate

The ducts of the prostate functional units empty into the prostatic urethra. The secretory elements (ducts) are surrounded by smooth muscle and connective tissue that separate the secretory units. Prostatic secretions are expelled into the urethra and join other components of the seminal fluid when these smooth muscle units contract. Prostatic secretions are alkaline (pH 6.5) and serous, containing acid phosphatase, carbohydrates, lipids, lipofuscin, hormones, citric acid, amylase, and fibrolysin, which act to liquefy the seminal fluid.

Late histologic changes in irradiated benign prostate ducts include variable ductal atrophic change, cytologic and nuclear atypia, basal cell hyperplasia, increased foreign body giant cell reaction to corpora amylacea, nuclear pleomorphism, nuclear vacuolation, hyperchromatic DNA, and presence of prominent nucleoli. Several metaplastic changes have been noted, including mucinous metaplasia, squamous metaplasia, and Paneth-like cell change. There is no significant difference in the histologic appearance of irradiated benign glands when the patients are treated with androgen deprivation therapy (Gaudin et al. 1999; Magi-Galluzzi et al. 2003). The surrounding stromal cells also undergo chronic inflammatory processes. The molecular and cellular mechanisms underlying this chronic inflammatory change are well described. Briefly, after the initial insult of radiation therapy, a cascade of inflammatory mediators is initiated including TNF-alpha, interleukin-1, and interleukin-6 (Haase 2004; Bentzen 2006). In the later phases of fibrosis, TGF-beta and PDGF, among others, simulate the proliferation of fibroblasts and the synthesis or extracellular matrix constituents and MMPs. Connective

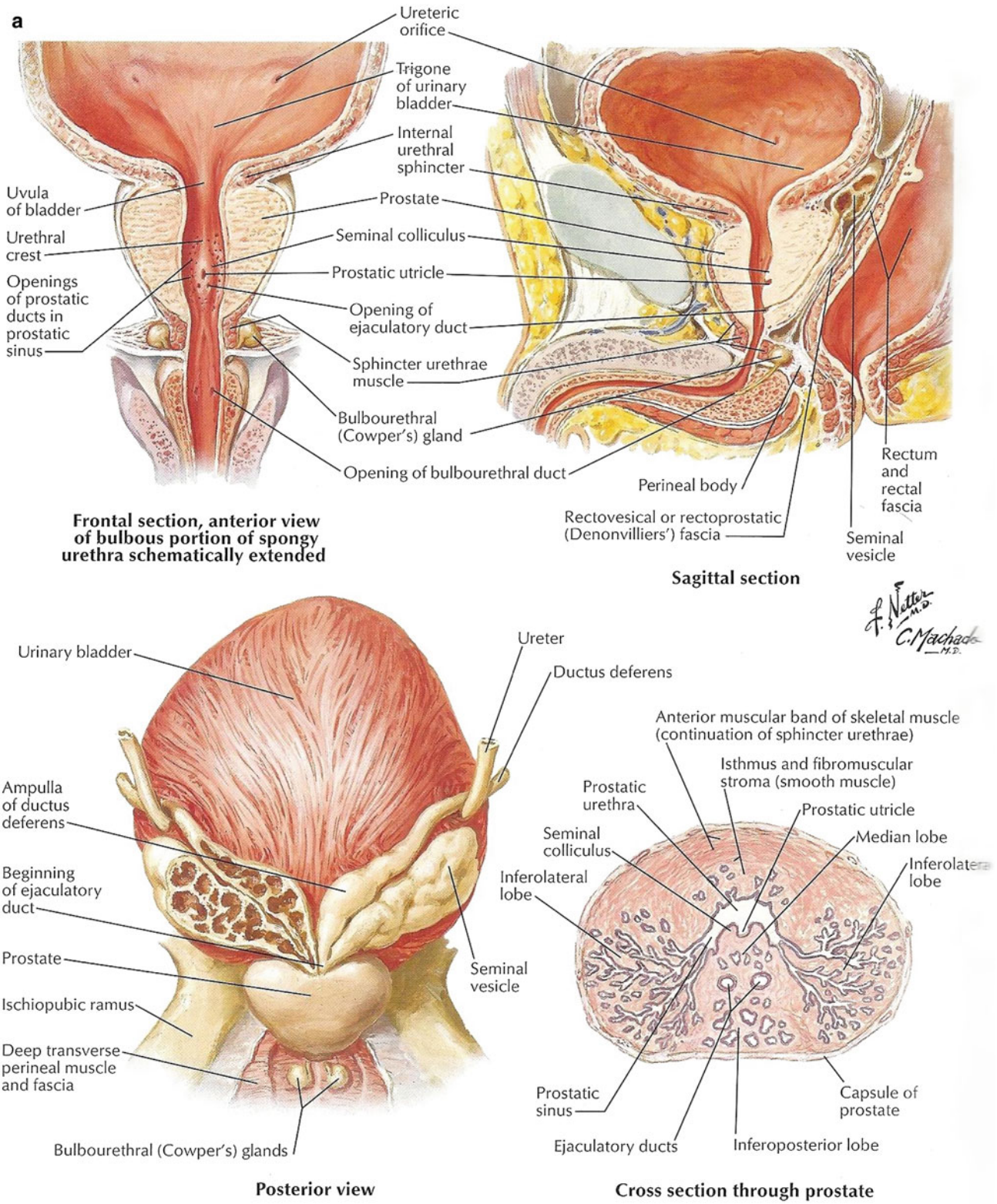


Fig. 4 Physiology of prostate (**a**) Urethra and penis (**b**) Penile Crura: sexual performance (**c**) (with permission from Netterimages.com)

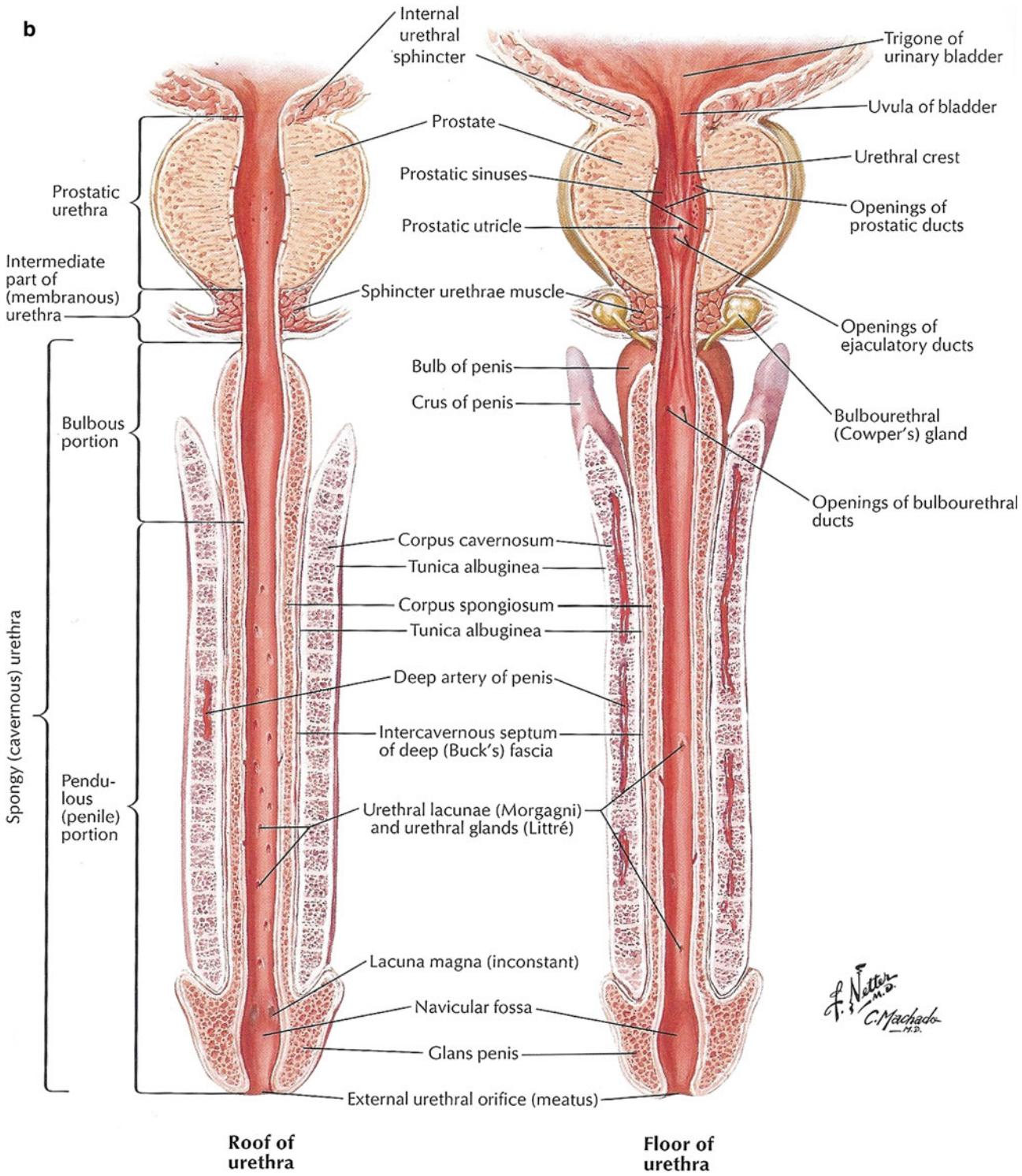


Fig. 4 (continued)

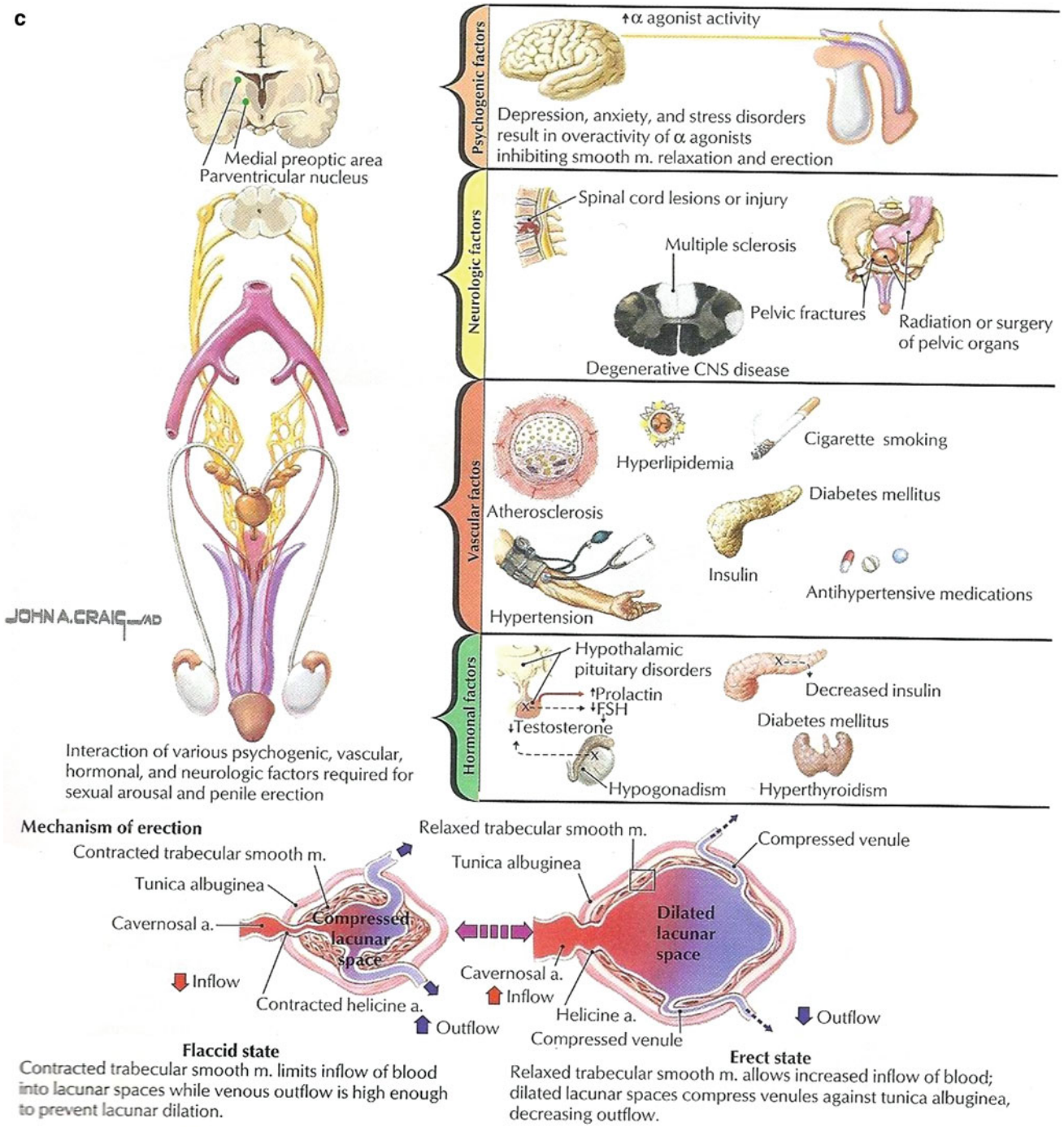


Fig. 4 (continued)

tissue growth factor (CTGF) further promotes fibrotic change (Vozenin-Brotons et al. 2003).

3.2.2 Seminal Vesicles

The seminal vesicles produce a viscous fluid containing high amount of fructose that nourishes the sperm. Other components include simple sugars, amino acids, ascorbic acids, and prostaglandins.

4 Pathophysiology

4.1 Prostate Gland

Several publications have documented the effects of various modalities of radiation therapy on prostatic tissues (Bostwick et al. 1982; Gaudin et al. 1999; Sheaff and Baithun 1997). In general, radiation changes are similar in patients receiving external beam radiation and brachytherapy, although the brachytherapy-associated changes may be more marked (Magi-Galluzzi et al. 2003).

Early histologic changes in the irradiated prostate, seen after several weeks, include nuclear contraction, signs of cytoplasmic injury, and small areas of early necrosis. These areas of injury and necrosis initiate the well described processes of acute inflammation, where polymorphonuclear cells, macrophages, and lymphocytes are recruited in a characteristic chronological pattern. As treatment progresses, a mixed acute-late inflammatory histology appearance predominates that gradually gives way to fibrotic change once radiation treatment has been completed.

Recruitment of cells typically involved in the chronic inflammatory process is also evident. Specifically, macrophages are seen in the early phase of fibrosis, which chemically recruit fibroblasts, which in turn transform to fibrocytes. Additionally, vascular changes are noted, including endothelial cell damage, intimal hyperplasia, marked arterial luminal narrowing, arterial medial thickening, cytoplasmic swelling, hyaloid changes of the capillary wall, and thinning of the capillary network (Sheaff and Baithun 1997; Herrmann 2006).

Prostate cancer cells respond differently than benign prostate cells after radiation therapy has been administered. This response, although characteristic, is quite variable, ranging from significant treatment-related changes to no apparent change after radiation therapy (Gaudin et al. 1999). Prostate cancer cells with no evident effect had an appearance similar to pre-treatment specimens. Prostate cancers with profound radiation changes demonstrated several characteristic morphologic changes including a decrease in the number of neoplastic glands, with residual glands in a more irregular morphology and some individual scattered cells not associated with glands. The cells demonstrated abundant cytoplasm with vacuolated and reticulated changes but little nuclear pleomorphism. In contrast to radiation changes in benign prostate tissues, radiation changes in prostate cancer cells were not associated with nuclear pleomorphism or prominent nucleoli. Furthermore, benign glands with radiation changes were extremely reactive to immunohistochemical stains for cytokeratin 34[beta]E12 and had a variable staining pattern to antibodies specific for prostate-specific antigen (PSA), while cancerous glands with radiation changes were not reactive to cytokeratin 34[beta]E12 were intensely immunoreactive for PSA. Additionally, while benign glands tended to maintain a lobular architecture, cancerous areas are arranged in a random, infiltrative morphology.

Part of the issue in determining the effects of irradiation of the prostate gland is the presence of a prostate cancer, which is the most common reason to treat the gland. Initially, following 60–70 Gy doses, necrosis of the cancer cells occur. Months to years later, the glandular epithelium are reduced in size and becomes atrophic and are replaced by fibrosis. The residual glands appear as "pale ghosts," the columnar epithelium changes to cuboidal with pyrokinetic nuclear squamous metaplasia form irregular islands surrounded by dense fibrosis, foreign body giant cell reactions around corpora amylacea. Vascular changes are quite severe with obliteration of arterioles with internal forming cells.

Despite these characteristic changes, histopathologic interpretation of biopsies of a patient treated with radiation therapy is fraught with difficulty (Bostwick 1982). The risk of misinterpretation is that benign radiation changes will be mistaken for prostate cancer. In general, rebiopsy after radiation treatment (Fig. 5a–d) is reserved for the setting of a rising PSA after treatment when an isolated local recurrence is suspected and salvage brachytherapy or surgery is being considered. The presence of malignant cells in the biopsy specimen after radiation therapy should not be automatically interpreted as treatment failure. Prostate cancer cell death is a post mitotic event in a cancer with a long potential doubling time, meaning that regression of viable cancer is evident to at least 3 years after treatment (Crook et al. 2000). Furthermore, nearly 50 % of men with positive biopsies after brachytherapy and a short course of external beam treatment had viable cancer cells on planned repeat biopsy. Interestingly, only 27 % of these men experienced a biochemical failure (Goldstein 1998). Prestidge et al. reported serial post-treatment biopsies have demonstrated that a higher number of indeterminate biopsies after treatment eventually become negative after brachytherapy treatment (Prestidge et al. 1997). In general, if radiation biopsies show profound treatment effect in the adenocarcinoma, these patients are unlikely to fail therapy.

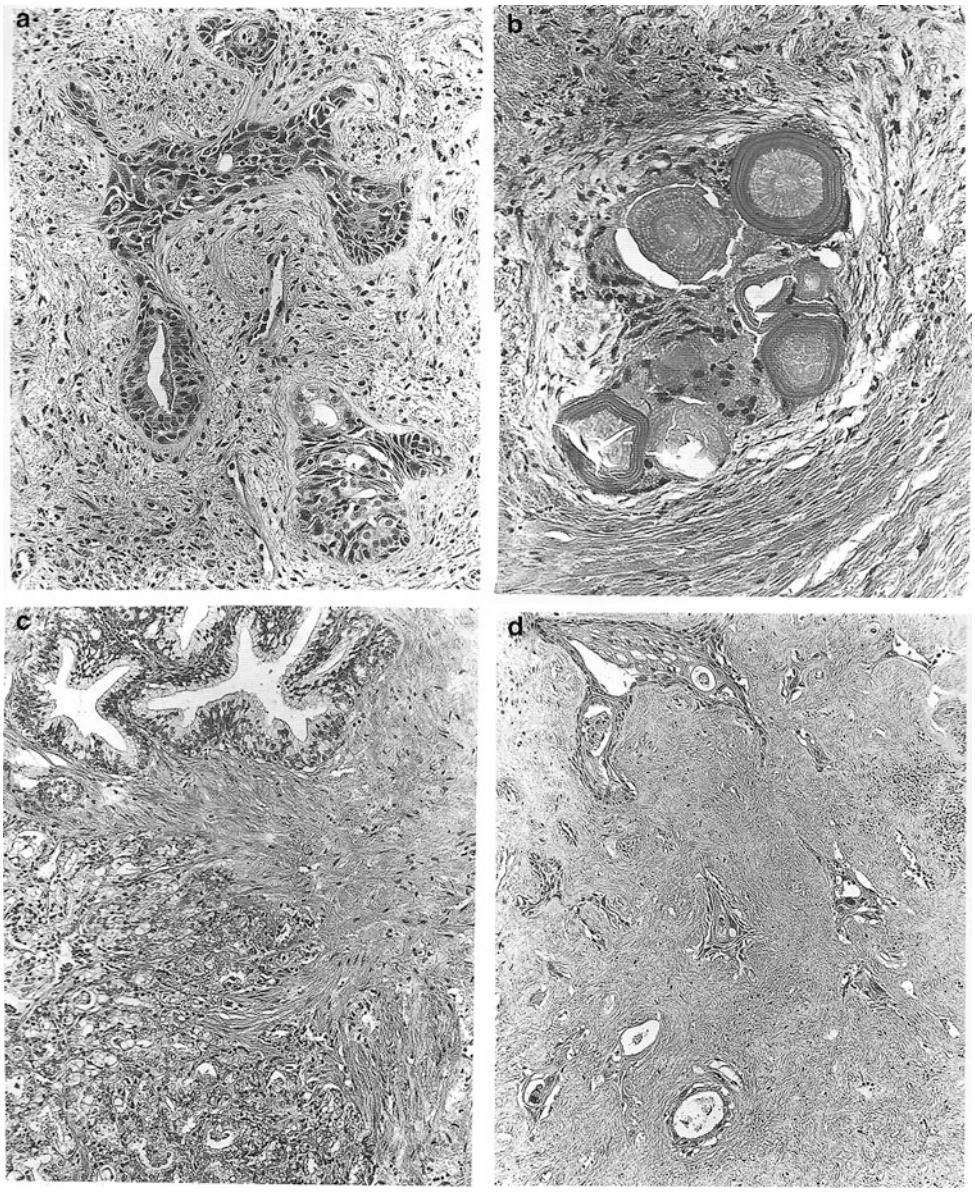


Fig. 5 Post-RT histologic changes in the prostate gland. **a** Postradiation (~7000 cGy) squamous metaplasia in non-neoplasic prostatic glands with mild cytologic atypia. H&E, ×192. **b** Foreign body giant cell reaction around corpora amylacea 26 months after irradiation. No resudial epithelium can be recognized. H&E, ×192. **c** Well-differentiated adenocarcinoma in the lower field contrasting with normal glands in the upper field prior to radiation. Compare with (**d**), obtained 30 months after irradiation with ~7000 cGy (same magnification): there is no residual carcinoma, and the field displays extensive stromal fibrosis. The remaining, nonneoplastic glands show atrophy and extensive squamous metaplasa. H&E, ×192 (with permission from Fajardo 2001)

There are also histological changes from the use of androgen deprivation therapy alone. Androgen stimulation is an important component of normal prostate metabolism. 90–95 % of circulating testosterone is made by the testes, with the remainder produced by the adrenal glands. In the prostate gland, testosterone is converted into dihydrotestosterone by alpha-5-reductase. Dihydrotestosterone stimulates growth of both normal prostate tissue and prostate adenocarcinoma cells. When androgen deprivation is administered, consistent effects can be seen regardless if combined androgen blockade (LHRH agonist and peripheral androgen receptor blocker) or anti-androgen monotherapy (LHRH agonist alone) is used. Degenerative phenotypes are noted, including nuclear pyknosis, and vacuolization of the cytoplasm (Tetu 1991; Armas 1994). Furthermore, androgen deprivation also suppresses the histological changes commonly used to diagnose adenocarcinoma, such as increased nuclear size, nuclear pleomorphism, and prominent nucleoli. Therefore, care must be taken in the histological evaluation of patients who have received androgen deprivation therapy prior to prostate biopsy because there is a risk of underestimating both tumor extent and Gleason score. Rigorous examination of the specimen for scant individual malignant cells and special immunohistochemical stains are essential in this clinical situation (Vernon 1983).

In addition to the above commonly used strategies of androgen blockade, other agents, such as estrogens and 5-alpha reductase inhibitors also cause histological changes in normal and malignant prostate cells. The effect of

estrogen administration on prostate histology is mainly of historical interest, as estrogens are not commonly used in contemporary treatment algorithms. However, estrogens induce the above changes seen with modern anti-androgen regimens and further cause a unique effect of squamous metaplasia in benign and malignant prostate cells (Schenken 1942; Franks 1960). Finasteride and dutasteride block the conversion of testosterone to dihydrotestosterone in the prostate gland by inhibiting 5-alpha reductase and are used in a variety of clinical situations including BPH and androgenetic alopecia. Their use has been found to have minimal influence on prostate cancer cells and does not typically interfere with pathologic diagnosis or the prognosis of Gleason grade (Yang et al. 1999; Carver et al. 2005; Iczkowski et al. 2005). These agents do reduce PSA values by approximately 50 % (Etzioniet al. 2005) and prostate size by about 25 % (Thompson et al. 2003). Furthermore, 5-alpha reductase inhibitors do appear to have the ability to affect the incidence and grade of prostate cancers in men who use them (Andrioleet al. 2005). The most compelling argument for this comes from the Prostate Cancer Prevention Trial, which demonstrated that healthy men treated with 5-alpha-reductase inhibitors had a 24.8 % reduction in the risk of developing prostate cancer. In this cohort, certain risk factors while on finasteride were predictive of Gleason score $\geq$7 disease, including higher absolute PSA values, increasing PSA values, an abnormal digital rectal examination, and older age (Thompson et al. 2003, 2007).

4.2 Seminal Vesicles

Radiation effects on the seminal vesicles are more obvious than in the prostate gland. The normal complex arborizing glands are reduced to narrow cavities with a few branches embedded in dense collagen scoring.

Radiation also causes changes in the urothelium (Antonakopoulos et al. 1982, 1984; Stewart 1986). Irradiated urothelial cells demonstrate changes including nuclear pleomorphism, swollen cytoplasm, and altered labeling indices as compared to non-irradiated urothelial cells. Loss of tight junctions is noted, allowing hypertonic urine access to the interstitial area, leading to chemical fibrotic injury and increasing the probability of bacterial infection and subsequent inflammatory damage. These morphological changes correlate clinically with the onset of irritative urinary symptoms encountered after a course of radiation therapy (Marks et al. 1995). When bulbomembranous urethral strictures are examined histologically, there is an initial ulceration of the urothelium that develops into proliferative changes of stratified squamous epithelium with interposed elongated myofibroblasts and multinucleated giant cells that produce abundant collagen (Baskin et al. 1993). The myofibroblasts are thought to be a primary causative factor for stricture formation. The ubiquitous stromal changes of radiation therapy are also noted, including obliterative endarteritis, ischemia, and fibrosis.

4.3 Penis and Urethra

Penis and urethra are incidentally irradiated in treating prostate gland cancers. In laboratory rats after single fraction doses of 1,000 and 2,000 cGy, after 5 months, the animals had impaired responses to central and peripheral stimulation, at both doses, increased with the higher dose; the number of nerve fibers positive for nitric oxide synthase.

In each penile segment decreased significantly by approximately 25 % compared to control. The mechanism for radiation-induced erectile dysfunction was attributed to defective vascularity of penile tissues as well as peroneal nerves and smooth muscle.

5 Clinical Syndromes (Endpoints)

Patients undergoing radiation to the distal male GU tract are at risk for developing both acute and late genitourinary, gastrointestinal, and sexual toxicities. Acute toxicities are attributable to effects from acute inflammation, while late toxicities are usually attributable to radiation-induced fibrosis, vascular damage, and altered patterns of vasculature. Late effects of radiation are particularly multifactorial, being affected by comorbidities, genetic factors, and other cancer treatments in addition to radiation-related variables such as total dose, dose per fraction, fractionation schedule, and dose–volume parameters. With modern teletherapy techniques such as intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), in addition to improvements in brachytherapy, the overall morbidity of external beam radiation therapy has been significantly reduced despite higher contemporary prescription doses. The addition of systemic agents, such as cytotoxic chemotherapy or androgen deprivation therapy, may alter the risk of these toxicities (Zelefsky et al. 2000; Valicenti et al. 2003; Liu et al. 2004; Feigenberg et al. 2005; Zapatero et al. 2005; Lawton et al. 2008).

5.1 Sexual Dysfunction after Radiation Therapy

The main sexual side effects of radiation therapy to the pelvis are impotence, decreased libido, decreased ejaculate, and painful ejaculation. Recent reports demonstrate the rate

of radiation-related erectile dysfunction is of the order of 35–55 % (Cahlon et al. 2008; Mantz et al. 1997; Potosky et al. 2000; Hamilton et al. 2001). The process of tumescence is a complex process, depending on afferent cavernous nerves supplying the penis with nitric oxide. Relaxation of the afferent internal pudendal and accessory pudendal arterioles and cavernosal smooth muscle occurs, which allows for filling of the trabecular space. Increased venous resistance prevents outflow, causing trapping of blood, and contraction of the bulbocavernosus and bulbospongiosus muscles further increase intratrabecular space pressure. In general, radiation-induced impotence is thought to manifest within the first 2 years after treatment (van der Wielen 2007). The decline in ability to obtain and maintain erections after therapy has historically been thought to be caused by radiation exposure of tissues involved in the process of tumescence, including the afferent neurovascular bundles, the penile bulb, and the corpora cavernosa (Fisch et al. 2001; Roach et al. 2004; Wernicke 2004). However, a recent publication has demonstrated that radiation-induced erectile dysfunction is mainly due to afferent arterial insufficiency, with only a small percentage of cases due to changes in veno-occlusive capacity (Zelefsky and Eid 1998). Additionally, several publications suggest that doses to structures such as the penile bulb are not predictive of post-therapy impotence (van der Wielen et al. 2007; Hoogeman et al. 2008; Solan 2009). Regardless, modern radiation techniques are able to minimize radiation dose to these tissues that are at risk, including the penile bulb and base of the penis, possibly decreasing the rates of radiation-related erectile dysfunction (Sethi et al. 2003; Buyyounouski et al. 2004). However, sparing the neurovascular bundle with external beam techniques is not yet achievable, given its close proximity to the prostate, need for the appropriate PTV margins to account for interfraction and intrafraction motion, and continuing trends of dose escalation.

5.2 Erectile Dysfunction

The evaluation of radiation-related erectile dysfunction is complex, depending on the method of assessment, toxicity scale used, time since radiation, and radiation technique used for treatment (Rosen et al. 1997; Litwin 1998; Talcott et al. 1998). Additionally, a multitude of other factors can exacerbate post-treatment erectile dysfunction, including existing peripheral vascular disease, diabetes mellitus, smoking history, hypertension, hypercholesterolemia, administration of androgen deprivation therapy, and other medications (Hollenbeck et al. 2004; Goldstein et al. 1984). Androgen deprivation contributes to erectile dysfunction because physiologic amounts of testosterone contribute to sexual desire (O'Carroll 1984), homeostasis of the erectile apparatus and nerves (Saad et al. 2007), and cavernous vasodilation (Aversa et al. 2000).

The social situation of the patient also has a significant role on sexual function, including the presence or absence of a willing partner and the physiological and emotional impact of cancer diagnosis and treatment on the patient (Goldstein et al. 1984; Fiorino et al. 2009). Furthermore, independent of a diagnosis of cancer, loss of erectile function is common in men between 40- and 69-years old, with up to 26 out of every 1,000 men developing ED each year (Johannes et al. 2000). It is therefore difficult, if not impossible, to define the radiation parameters clearly causing sexual dysfunction and the time frame in which they manifest after treatment.

It is recommended by Quantec authors that patients undergo pre- and post-RT assessment of ED using the IIEF. Patients can be grouped into five groups according to their scores; for example, in none (D'Amico et al. 2004; Chen et al. 2001; van der Wielen et al. 2007; Goldstein et al. 1984), mild (Macdonald et al. 2005; Merrick et al. 2002; Zelefsky et al. 1999; Weber et al. 1999; Rosen et al. 1999), mild to moderate (Wallner et al. 2002; Zelefsky et al. 2006; Wernicke et al. 2004; van der Wielen et al. 2008; Skala et al. 2007), moderate (Selek et al. 2004; Roach et al. 2004; Pinkawa et al. 2009a, b; Mangar et al. 2006), and severe (Fisch et al. 2001; Cahlon et al. 2008; Brown et al. 2007). It is important that the evaluation of ED is performed with a detailed history including sexual, medical, and psychosocial status and other laboratory tests (Rosen et al. 1997, 1999; Kratzik et al. 2005; Rosenberg 2007). Further clinical studies may be needed to validate the IIEF for the assessment of ED after RT.

5.3 Acute and Late Effects from Penile Radiation

The main acute toxicity of irradiation of the penis is the skin reaction (see "Thyroid"). However, some relevant radiation-specific literature is available on this topic and merits discussion (Crook et al. 2009, 2010). After interstitial penile brachytherapy, moist desquamation appears to be the only significant acute toxicity, peaking 2–3 weeks after treatment and taking several months to heal. Patients are also at risk for acute post-treatment adhesions which usually present with a split or deviated urine flow from the meatus. Common late complications include penile soft tissue necrosis and urethral stenosis, which occurs in about 10 % of men treated with interstitial penile brachytherapy for squamous cell carcinoma (Crook et al. 2009). Soft tissue necrosis usually appears as an area of progressive ulceration that typically takes place 6–18 months after brachytherapy (Delannes et al. 1992). Ulcerations leading to necrosis can

be exacerbated by thermal injury or traumatic episodes to the penis, including biopsy. Radiation-induced penile urethral strictures occur between 1 and 3 years after treatment and can present with altered urodynamics, divergent stream, pain, or hematuria. The skin can also undergo chronic atrophic change after treatment, including thinning of the dermis and epidermis, formation of irregular pigmentation patterns with gain or loss of natural pigment, increased skin sensitivity or pain, and formation of teleangectatic vessels.

5.4 Radiation-Induced Urinary Incontinence

Following RT for prostate cancer, the rate of RT-induced urinary incontinence is of the order of 1–4 % in men who have no history of invasive prostatic procedures (Talcott et al. 1998; Potosky et al. 2000; Hamilton et al. 2001). This rate increases when the patient undergoes surgical procedures to the prostate gland before or after radiation treatment. Furthermore, a history of intercurrent illness, especially diabetes mellitus, increases the risk of late GU toxicity. Investigators at Fox Chase Cancer Center found that diabetics treated with three-dimensional conformal radiation therapy for prostate cancer had increased rates of late Grade 2 GU toxicity (Herold et al. 1999). Additionally, they reported that diabetics had an early onset of late toxicity (median 10 months versus 20 months for non-diabetics).

In limited circumstances, radiation therapy can cause chronic improvement in urinary function. Specifically, reports of improved urinary function and quality of life have been noted in patients with significant pre-treatment irritative or obstructive symptoms (Chen et al. 2009). The proposed mechanism for these improvements is a radiation-induced reduction in prostate volume (Coia et al. 1995).

5.5 Fecal Incontinence

Although rare, radiation-induced fecal incontinence profoundly effects quality of life. Two large, modern studies have demonstrated that the chance of using pads of fecal incontinence at any time after treatment is approximately 10 % and the probability of needing regular use of pads after 2 years of treatment is approximately 3 % (Peeters et al. 2006c; Fiorino et al. 2008). Profound incontinence is even rarer, with the chance of needing multiple pads per week years after treatment is less than 1 %. Fecal incontinence is thought to be multifactorial. Contributing factors probably include decreased absorptive capacity of irradiated rectal mucosa, chronic inflammatory changes leading to urge incontinence, neurovascular damage to the afferent nerves controlling the anal sphincter, and direct muscle damage to the sphincter itself. Prior abdominal or anorectal surgery or trauma increases the probability of fecal incontinence after treatment (Peeters et al. 2006c; Fiorino et al. 2008).

When the endpoint of fecal incontinence is considered, there is also a strong correlation of clinical endpoint with dose–volume parameters (Peeters et al. 2006c; Fiorino et al. 2008). Unlike late rectal bleeding, where the high dose regions are most predictive, it appears that a large volume of rectum receiving an intermediate dose is most predictive of late fecal incontinence. Fiorino prospectively studied a cohort of over 500 patients and found that there was less than 1.5 % probability of late fecal incontinence requiring pads when V40 $<$ 65 %. Peeters essentially confirmed this finding. Furthermore, the location of radiation exposure also predicts for late fecal incontinence. Several authors have reported that inclusion of large portions of the distal rectum, including the anorectum, predisposes that patient to late rectal bleeding (Vordermark et al. 2003; al-Abany et al. 2004; Heemsbergen et al. 2005). Modern IMRT and 3D-CRT techniques have obviated the need to include large portions of the anorectum in the treatment field and should yield decreases in incontinence rates. See "Radiation Induced Rectal Toxicity" for further discussion of this issue.

5.6 Diagnosis

5.6.1 Atrophy

Irradiation of the prostate gland leads to interstitial fibrosis. Atrophy and calcifications can be seen on CT and MR images (Fig. 6a, b). Radiation changes are also seen in the seminal vesicles, which lose volume and demonstrate low T2-weighted signal intensity on MR images after radiation. The prostatic and membranous urethras are very sensitive to radiation. The irradiated urethral tissue often develops strictures.

5.6.2 Persistence of Cancer

As aforementioned in the pathophysiology section, a vexing issue is persistence of cancer cells, the same is true for follow-up assessment by serial MRIs in follow-up. Comparing pre- to post-RT MRIs might be helpful in this regard, as is MR spectroscopy. Figure 6c illustrates an example of the utility of MR spectroscopy in defining tumor in the prostate.

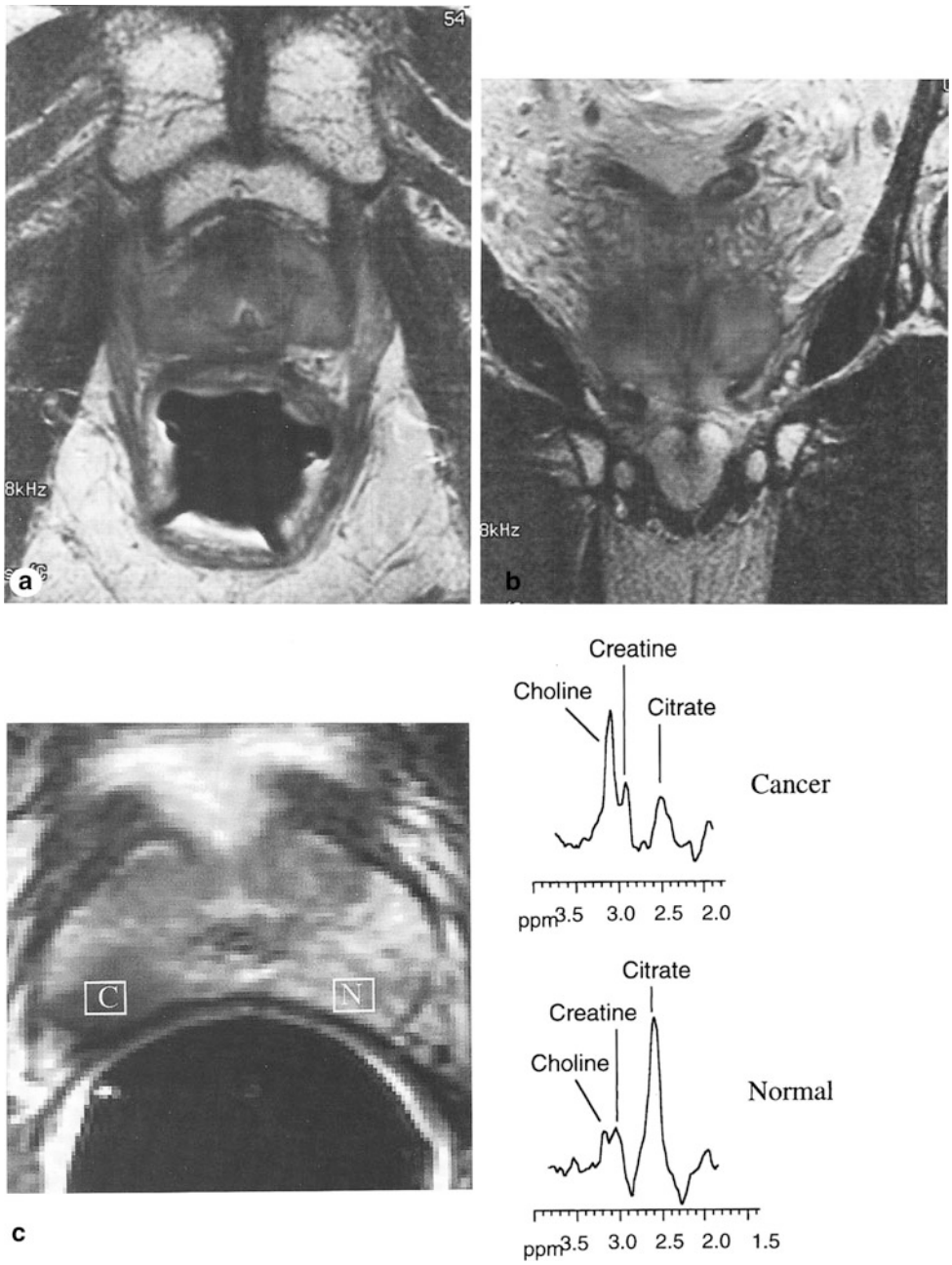


Fig. 6 Imaging changes in the prostate gland. **a**, **b** T2-weighted MR images of the prostate. The zonal anatomy is indistinct (compared to a normal untreated gland), and the peripheral zone shows low signal intensity. **c** Images from a patient with stage T2 adenocarcinoma of the prostate: fast spin-echo T2-weighted axial endorectal magnetic resonance (MR) spectroscopic image through the midgland. Prostate carcinoma appears as an area of abnormal low signal intensity (C) in the normally high signal intensity peripheral zone (N). MR spectra from the area of carcinoma (C) in the right peripheral zone demonstrates abnormal elevation of the choline peak and an abnormally low citrate peak. In comparison, MR spectra from an area of normal peripheral zone (N) demonstrates a normal high citrate peak and a normal low choline peak. Tumor in the right peripheral zone demonstrates contact with a smooth and apparently intact prostatic capsule. Postradiation changes in the prostrate. This patient underwent radiation therapy for prostate cancer. The axial (**a**) and the coronal (**b**) T2-weighted fast spin echo magnetic resonance images show a small, feature gland with a dark peripheral zone indicative of radiation changes in the prostate (with permission from Bragg et al. 2002)

6 Dose, Time, Fractionation: Radiation Tolerance, Predicting RT-Induced Injury and Recommended Dose–Volume Constraints

Since Burman et al. (1991) reported on the modeling of dose–volume effects based on clinical outcomes from the 2D era, the advent of increasingly advanced radiation technologies has led to careful study of the effect of dose–volume relationships on normal tissues during radiation treatment. A great deal of literature is available examining toxicities from and recommended treatment parameters for radiotherapeutic treatment of pelvic malignancies, including those of the distal male GU tract.

6.1 Rectal Constraints

6.1.1 General Rectal Constraints

Although the rectum is covered in a separate chapter, a discussion of this organ is merited here, as the appropriate dose–volume rectal constraints for prostate cancer radiotherapy is the most published area of normal tissue

tolerance in this malignancy. The reason for this interest in rectal tolerance is clear. Unlike bladder toxicity, late rectal toxicity has been found to be directly and consistently correlated with physical treatment parameters such as dose and volume. Rectal complications are the main late toxicities that limit dose escalation in prostate cancer. General trends can be drawn from the available clinical literature regarding these constraints for conventionally fractionated radiation therapy despite institutional differences in prescribed dose, extent of contouring, radiation techniques, and outcomes measurement. Moderate to severe late rectal effects are dose dependent, occurring in around 25 % of men treated with 78 Gy and 13 % in men treated with 70 Gy (Pollack et al. 2002; Peeters et al. 2006a, b; Zietman et al. 2005). Despite this dose dependency, several reports indicate that careful planning techniques and intensity modulation can mitigate this toxicity and allow dose escalation without excess late GI toxicity (Zelefsky et al. 2002; Beckendorf et al. 2004; Peeters et al. 2006a, b).

Numerous studies have been published with late rectal bleeding as an isolated clinical endpoint with consistent contouring of the rectum. Jackson et al. from MSKCC reported on 171 patients treated with 3D conformal radiation therapy to a dose of 70.2 or 75.6 Gy. They found a significant dose–volume correlation with RTOG ≥ 2 late bleeding and recommended, for the techniques and doses used, V40 < 60 % and, for patients treated with 75.6 Gy, a V77 < 14 % (Jackson et al. 2001). An Italian intergroup published two papers using RTOG ≥ 2 late bleeding endpoints in patients treated in the range of 70–78 Gy and ultimately suggested the following dose–volume constraints: V50 < 60 %, V60 < 45 %, and V70 < 25 % (Fiorino et al. 2002, 2003). The recommendation of V70 < 25 %, using the same endpoint, was independently confirmed by the group at William Beaumont Hospital using adaptive image-guided radiation with prescription doses between 70.2 and 79.2 Gy (Vargas et al. 2005). Peeters et al. found that a V65 > 30 % was highly predictive for late bleeding requiring transfusions or interventional laser coagulation in patients treated between 68 and 78 Gy (Peeters et al. 2006c). When SOMA-LENT Grade ≥ 2 late bleeding criteria was used as the clinical endpoint, recommendations are similar: V50 < 55 %, V60 < 40 %, V70 < 25 %, and V75 < 5 % (Fiorino et al. 2008; Fellin et al. 2009). In addition to these straightforward dose–volume constraints, several groups have generated normal tissue complication probability models and nomograms for late rectal bleeding that are generally consistent with the above studies (Rancati et al. 2004; Söhn et al. 2007; Valdagni Rancati et al. 2008).

Dose–volume constraint recommendations are only slightly altered when all forms of late rectal toxicity are included in outcomes analysis. The MD Anderson group reported on rectal complications from their randomized dose escalation trial and found that the rates of rectal complications were similar in both arms (70 and 78 Gy) but found a significant increase in late rectal complications when V70 > 25 % (Storey et al. 2000a, b; Kuban et al. 2008). When a different subset of patients treated in the same general dose range was evaluated from the same institution, the investigators found that the percentage of the rectum exposed to a certain dose, rather than an absolute volume, was predictive of late rectal toxicities. In this paper, the following recommendations were made: V60 < 40 %, V70 < 25 %, V75.6 < 15 %, and V78 < 5 % (Huang et al. 2002). Analysis of the high dose arm (74 Gy) of RTOG 94-06 yielded a recommendation to keep the V65 < 50 % to keep late rectal toxicity Grade I or less (Michalski et al. 2004). A recent report from MSKCC analyzing 478 patients treated to 86.4 Gy found a 4 % rate of CTCAE 3.0 late rectal toxicity with V47 < 53 % and V75.6 < 30 % at a median follow-up of 53 months (Cahlon et al. 2008). Numerous studies have found results similar to the results seen in these trials (Fonteyne et al. 2007; Karlsdóttir et al. 2008).

Taking these individual publications into account, there is general agreement that multiple dose–volume constraints in the intermediate (30–50 Gy) and high range (>70 Gy) regions of a histogram are prudent to shape the dose–volume histogram appropriately and to minimize the probability of late rectal bleeding to rates <10 %. It is also clear that while the volume of the rectum receiving a high dose is more predictive of late rectal toxicity, the amount of rectum receiving lower doses also predicts rectal toxicity, particularly with non-IMRT techniques. The distribution of dose on the rectum is also important, as increasing doses to the posterior rectal wall and upper rectum are associated with increase rates of late rectal toxicity (Skwarchuk et al. 2000; Fiorino et al. 2002; Heemsbergen et al. 2005; Peeters et al. 2006d; Munbodh 2008). A summary of recommended dose/volume constraints for late rectal injury is provided in Table 1. See "Radiation Induced Rectal Toxicity" for additional discussion.

6.1.2 Stool Frequency

Stool frequency has also been correlated with treatment-related dose–volume parameters. Fonteyne et al. reported that the rate of mild diarrhea was correlated with the volume of the rectum receiving 40 Gy, and chronic rectal urgency was correlated with the volume of the rectum receiving 70 Gy (Fonteyne et al. 2007). Similarly, Peeters reported that both the V40 and the mean rectal dose were predictive of stool frequency (Peeters et al. 2006c). See "Biophysiopathology of the Microvasculature and Microcirculation" for additional discussion.

6.1.3 Brachytherapy

The prostate brachytherapy literature has consistently demonstrated that very small volumes of the rectum can tolerate very high doses of radiation, which is an important consideration in this era of highly conformal dose escalation. Snyder et al. found that when the rectum was contoured as a hollow structure from 9 mm below the prostate apex to 9 mm above the top of the seminal vesicles, the rate of grade 2 or greater proctitis was dependent on the volume of rectum receiving the prescription dose of 160 Gy. The rates of proctitis per absolute volume of rectal wall receiving prescription dose were: 0 % if < 0.8 cc, 7–8 % between 0.8 and 1.8 cc, and 25 %, and 24–25 % if $>$ than 1.8 cc (Snyder et al. 2001). D'Amico's group also found that the absolute volume of rectum receiving 100 Gy was predictive of needing argon plasma coagulation for late proctitis after brachytherapy, with no patients needing intervention when the volume of rectum receiving 100 Gy was below 8 cc, whereas 20 % of men needed intervention with argon plasma coagulation when the volume of rectum receiving 100 Gy was greater that 8 cc (Albert et al. 2008). Han et al. found a similar outcome when endoscopically proven radiation proctitis was used as the endpoint and the rectum was contoured as a solid structure, with the volume of the rectum receiving at least 100 % of the prescription dose being 2.5 cc in patients with endoscopically-confirmed proctitis and 0.6 cc in those with no evidence of bleeding (Han and Wallner 2001). The maximum point dose to the rectum after brachytherapy is also predictive of RTOG ≥ 2 bleeding, with a 0.4 % toxicity rate for a maximum point dose of 150 Gy, a 1.2 % rate for a maximum point dose of 200 Gy, and a 4.7 % rate for a maximum point dose of 300 Gy (Waterman and Dicker 2003). Therefore, it is clear that small volumes of the rectum can receive very high doses, leading investigators to embrace more precise brachytherapy strategies, and by extrapolation, external beam treatments in combination with increasingly effective real-time image guidance solutions in an effort to dose escalate the prostate safely while sparing more of the rectum from the very high dose regions. It is evident that the smaller the amount of rectum irradiated, the less likely that late rectal bleeding will occur.

6.1.4 Acute GI Toxicities

Dose volume constraints and their effect on acute GI toxicities from pelvic radiation has been studied less. Nonetheless, these appear also to be highly dependent on dose–volume parameters, typically with mean rectal dose and the volume of rectum receiving greater than 60 Gy. Peeters examined GI effects in the first 6 weeks of treatment and found that the mean rectal dose as well absolute and the relative amount of rectum receiving 5, 15, and 30 Gy were predictive of acute GI toxicity (Peeters et al. 2005a). Vavassori and Cheng also reported DVH correlations with rates of acute toxicity, including the mean dose, and the minimal dose to 10, 20, and 50 % of the rectum (Vavassori et al. 2007; Cheng et al. 2008). Other authors have offered more specific recommendations. Nuyttens' group found that a V75 < 11 cc and a mean dose < 38 Gy minimized acute rectal toxicity (Nuyttens et al. 2002). Another report looking at patients treated with 78 Gy found that a V65 Gy < 20 % was protective against any grade I or higher acute GI toxicity (Karlsdttir et al. 2004). Of note, most of the above studies looking at acute side effects contoured the rectum as a solid structure, including the luminal contents. A summary of recommended dose/volume constraints for acute rectal effects is provided in Table 2.

6.2 Bladder Constraints

The bladder limits the ability to escalate dose in prostate cancer treatment, particularly with adequate rectal constraints, and knowledge of appropriate dose–volume constraints for this organ is important for the treating physician. Compared to the rectum, there are less available data regarding dose–volume relationships, likely due to the difficulty of estimating the volume of the bladder receiving a certain dose unless stringency bladder filling protocols are used. Emami predicted whole bladder tolerance using data from the era of 2D treatment. He recommended a tolerance dose of 65 Gy to keep the probability of serious urinary toxicity less than 5 % and 80 Gy to keep the probability of serious toxicity less than 50 % (Lyman et al. 1991). An excellent review of the literature refined these recommendations and concluded that the whole bladder can be safely irradiated to 30–50 Gy, dysfunction injury is rare with maximum point doses < 65 Gy, and the risk of organ failure is likely at whole bladder doses in the range of 50–60 Gy (Marks et al. 1995). Several studies from the 3D conformal and IMRT era have confirmed that even a small volume of the bladder receiving more than 75 Gy is predictive of severe late toxicity (Cahlon et al. 2008) (Cheung et al. 2007; Zelefsky et al. 2008a, b, c) (Lips et al. 2008; Sanda et al. 2008), suggesting that the bladder behaves like a serial organ.

There also appears to be differential tolerance to radiation exposure in the various regions of the bladder. One study of over 500 patients looked at radiation dose distribution and on surface maps of the bladder found that the dose to the trigone >47 Gy was predictive of an increased probability of late urinary toxicity (Heemsbergen 2008). Most centers have synthesized the available dose–volume and anatomic information by attempting to minimize the hot spots in the bladder while using an intermediate dose constraint such as V47 < 53 % or V40 < 50–60 %. See "Urinary Bladder" for further discussion.

Table 1 Recommended dose–volume constraints from large studies intended to minimize the risks of LATE rectal toxicity for patients with treated with modern radiation techniques and doses for prostate cancer

References	Prescription Doses (Gy)	Suggested constraints	Comments
Jackson et al (2001)	70.2 or 75.6	V40 Gy < 60 % V77 Gy < 14 % (for patients treated at 75.6 Gy)	Bleeding endpoint RTOG Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure
Fiorino et al. (2002)	70–76	V50 Gy < 60 % V60 Gy < 50 %	Bleeding endpoint Modified RTOG Grade ≥2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Included non-conformal patients; excluded pts with rectal volume >100 cc
Fiorino et al. (2003)	70–78	V50 Gy < 60 % V60 Gy < 45 % V70 Gy < 25 %	Bleeding endpoint Modified RTOG Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure V70 more predictive for Grade 3 bleeding
Vargas et al. (2005)	70.2–79.2	V70 Gy < 25 %	Bleeding endpoint CTC 2.0 Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Chronic rectal toxicity, mostly bleeding V50 also correlated (no specific constraints suggested)
Peeters et al. (2006c)	68 or 78	V65 Gy < 30 %	Bleeding endpoint Bleeding requiring lasers/transfusions Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the Sigmoid flexure V55-V65 correlated with V65 most predictive; independent impact of abdominal/pelvic surgery
Fiorino et al. (2008)	70–78	V50 Gy < 55 % V60 Gy < 40 % V70 Gy < 25 % V75 Gy < 5 %	Bleeding endpoint SOMA/LENT Grade ≥ 2 Rectum solid structure contoured With the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Prospectively scored patients; previous abdominal/pelvic surgery independently predictor of bleeding (suggested V70 < 15 %); V75 best predictor of Grade 3 bleeding
Fellin et al. (2009)	70–80	V75 Gy < 5 %	Bleeding endpoint SOMA/LENT Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Prospectively scored patients; previous abdominal/pelvic surgery independently predictor of bleeding (suggested V70 < 15 %) and best predictor of Grade 3 bleeding
Storey et al. (2000a, b)	70 or 78	V70 Gy < 25 %	General toxicity endpoint GI RTOG Grade ≥ 2 Rectum 11 cm long starting 2 cm below ischial tuberosities
Huang et al. (2002)	70 or 78	V60 Gy < 40 % V70 Gy < 25 % V75.6 Gy < 15 % V78 Gy < 5 %	General toxicity endpoint GI RTOG Grade ≥ 2 Rectum 11 cm long starting 2 cm below ischial tuberosities
Michalski et al. (2004)	74	V65 Gy < 50 %	General toxicity endpoint GI RTOG Grade ≥ 2
Fonteyne et al. (2007)	74–80	V40 Gy < 84 % V50 Gy < 68 % V60 Gy < 59 % V65 Gy < 48 %	General toxicity endpoint GI RTOG Grade ≥ 2 All patients were treated with IMRT technique

(continued)

Table 1 (continued)

References	Prescription Doses (Gy)	Suggested constraints	Comments
Karlsdóttir et al. (2008)	70	V40 Gy < 70 %	General toxicity endpoint GI RTOG Grade ≥ 2 A number of cut-offs predictive of toxicity; V40–V43 most predictive
Kuban et al. (2008)	70 or 78	V70 Gy < 25 %	General toxicity endpoint GI RTOG Grade ≥ 2 Rectum 11 cm long starting 2 cm below ischial tuberosities

Modified from Table 1 of Fiorino et al. (2009)

Table 2 Recommended Dose–Volume Constraints From Large Studies Intended to Minimize the Risks of ACUTE Rectal Toxicity for Patients with Treated with modern radiation techniques and doses for prostate cancer

References	Prescription Dose range	Suggested constraints	Comments
Nuyttens et al. (2002)	72–80 Gy 2 Gy/fr	V75 Gy < 11 cc Mean dose < 38 Gy	≥G2 modified RTOG toxicity; acute toxicity during treatment retrospectively assessed; solid rectum including filling
Karlsdóttir et al. (2008)	70 Gy 2 Gy/fr	V40 Gy, V70 Gy	≥G2 modified RTOG toxicity; acute toxicity during treatment; solid rectum including filling
Peeters et al. (2005b)	68–78 Gy 2 Gy/fr	Mean dose V30 Gy, V35 Gy, V60 Gy, V65 Gy absolute V50 Gy, V60 Gy, V65 Gy % rectum length > 5 Gy, > 30 Gy absolute rectum length > 5 Gy, > 15 Gy, > 30 Gy	≥G2 modified RTOG toxicity; acute toxicity during treatment prospectively assessed; rectal wall; DVH of the first 6 weeks of treatment
Michalski et al. (2004)	78 Gy 2 Gy/fr	V65 Gy < 20 %	≥G1 modified RTOG toxicity; acute toxicity within 120 days after onset of RT prospectively assessed; solid rectum including filling
Vavassori et al. (2007)	70–81.6 Gy 1.8–2 Gy/fr	Mean dose	≥G2 modified RTOG toxicity; acute toxicity within one month after RT completion prospectively assessed; solid rectum including filling
Cheng et al. (2008)	63–80 Gy 1.8–2 Gy/fr	Mean dose Minimal dose to 10 %, 20 %, 50 % of rectum	≥G2 RTOG toxicity; including patients who underwent prostatectomy; acute toxicity within 90 days after RT completion prospectively assessed; solid rectum including filling
Arcangeli et al. (2009)	56 Gy 3.5 Gy/fr	V53 Gy < 8 %	≥G2 RTOG toxicity; acute toxicity within two months after RT completion prospectively assessed; solid rectum including filling

Modified from Table 3 of Fiorino et al. (2009)

6.3 Erectile Apparatus Constraints

The appropriate anatomic structures upon which to place dose–volume constraints in an effort to preserve potency after radiation therapy remain undefined. Zelefsky and Eid have recommended limiting to dose to various structures, including the penile bulb, proximal penis, neurovascular bundles, crura, and corpora cavernosa out of concern for sexual morbidity (Zelefsky and Eid 1998). The preponderance of the literature in this realm relates to the dose received by the penile bulb (Fisch et al. 2001; Merrick et al. 2002; Wernicke et al. 2004; Mangar et al. 2006). These publications found that a median dose to the bulb less than 52 Gy (Roach et al. 2004) or a V50 < 20 % and a V40 < 40 % (Mangar et al. 2006) were associated with decreased rates of impotence. However, other studies were not able to demonstrate an effect of penile bulb dose on potency (Kiteley et al. 2002; Selek et al. 2004) (Incrocci et al. 2002). In general, the treating physician should utilize modern highly conformal techniques to minimize dose to the penile bulb and cavernosa whenever possible (Sethi et al. 2003), especially with modern imaging techniques like MRI which permit precise identification of the apex of the prostate (Algan et al. 1995; Perna et al. 2009).

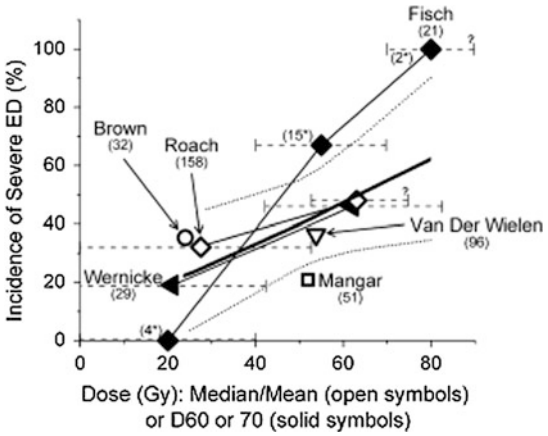


Fig. 7 Dose response for erectile dysfunction (ED) from Quantec (with permission from Roach et al. 2010). Incidence of erectile dysfunction according to the radiation close to the penile bulb. The *x* axis values are estimated according to the range of doses reported. The data for Fisch et al. (2001) at 20, 55, and 80 Gy, represent the reported rates of erectile dysfunction at <40, 40–70, and >70 Gy, respectively. Similarly, for Wernicke et al. (2004), each symbol represent the erectile dysfunction at ≤42 versus >42 and <52.5 versus ≥52.5 Gy respectively. The *dashed horizontal lines* reflect the dose ranges ascribed to each data point. The upper *x*-axis range of the highest data point for Fisch et al. (2001) and Roach et al. (2010) are unknown. The mean dose of van der Wielen et al. (2008) and Mangar et al. (2006) are estimated from the subgroup data. The *x*-axis values for Wernicke et al. (2004) are D60 and for Fisch et al. (2001) or D70 (i.e. minimum dose received by 60 or 70 % of the volume of the penile bulb). A *thick solid line* represents the fitted model with sample size correction. Dotted lines represent 90 % confidence intervals

The current consensus is the penile bulb/crura provides the basis for the tolerance doses for erectile dysfunction. Reviewing the literature, Roach et al. concluded as the mean/median dose increased from 20 to 80 Gy, the incidence of erectile dysfunction increased from 20–30 % to 90–100 % (Fig. 7; Roach et al. 2010 Quantec paper). On the basis of data available, Roach et al. recommend the mean dose to 95 % of the prostatic bulb volume to <50 Gy, and it is prudent to limit the D_{70} and D_{90} to 70 and 50 Gy, respectively. (Roach et al. 2010, Quantec paper ref). Further, they acknowledge, "...that the penile bulb may not be the critical component of the erectile apparatus, but it seems to be a surrogate for yet to be determined structure(s) critical for erectile function for at least some techniques." A summary of clinical and dose/volume parameters that have been correlated with erectile dysfunction is provided in Table 3.

6.4 Penile Dose–Volume Constraints

Some generalities can be made from the published literature regarding the dose–volume guidelines for the penis. In general, skin desquamation is the most common and severe acute toxicity for this organ, the pathophysiology, dose–volume considerations, and management of which is thoroughly addressed in a separate chapter. Desquamation during penile cancer treatment is common by necessity regardless if the patient is treated with external beam radiation or brachytherapy. It is known that treatment of a penile cancer requires significant doses of radiation, as an increased risk of treatment failure is seen in squamous cell carcinomas if the total dose is <60 Gy or the dose per fraction is <2 Gy (Sarin et al. 1997; Zouhair et al. 2001).

The most frequent and challenging late toxicities from radiation treatment of the penis are urethral stenosis and penile soft tissue necrosis. Some technique and dose–volume guidelines are available in the literature to assist the practitioner in minimizing the risk of these complications. For urethral stenosis, hypofractionated external beam treatment regimens beyond 2 Gy per day and implant geometries and/or loading techniques that do not attempt some degree of urethral sparing are associated with higher stenosis rates (Rozan et al. 1995; Crook et al. 2009). In the circumstance of penile radionecrosis, the modality of treatment makes a difference, with brachytherapy causing higher rates of necrosis than external beam radiation (Crook et al. 2009). The size of the penile tumor is also prognostic, with bulky tumors or >T3 tumors having higher rates of necrosis after radiation therapy (Mazeron et al. 1984; Rozan et al. 1995). Dose also clearly plays a role, as Rozan et al. also found that doses in excess of 60 Gy were associated with higher rates of necrosis (Rozan et al. 1995) while Chaudhary et al. found 0 % necrosis at doses of 50 Gy (Chaudhary et al. 1999). However, as previously mentioned, 50 Gy is considered a subtherapeutic dose for most squamous cell carcinomas of the penis because it is associated with an increased rate of local failure.

6.5 Seminal Vesicle Constraints

There is scant literature available regarding dose–volume limits of the seminal vesicles themselves as an isolated organ. Most of the available literature regarding seminal vesicle tolerance is from prostate cancer literature, specifically looking at the question of toxicity and outcomes varying with amount of the seminal vesicles included in the target volume. PSA level, clinical stage, volume of disease, and Gleason score are predictive of seminal vesicle invasion, with 99 % of men with biopsy proven Gleason score 6 or less disease unlikely to have invasion of the seminal vesicles in the PSA era (Han et al. 2004). In general, inclusion of increasing amounts of the seminal vesicles in addition to the prostate for localized disease causes increased doses to the bladder and rectum (Bayman and Wylie 2007). However, it is unclear if these increased doses lead to a detriment in quality of life. Pinkawa et al.

Table 3 Parameters associated with erectile dysfunction, from Quantec Roach et al. 2010

Reference	*N*	Assessment method[a]	Prescribed dose, treatment	OAR definition	Severe ED rate (%)	Correlated parameters	
						Dose–volume	Clinical
Fisch et al. 2001	21	Questionnaire[b]	65–72 Gy, 3D	Penile bulb	33[c]	D70 ≥ 70 Gy[d]	No other endpoints analyzed
Roach et al. 2004	158	Patient report (RTOG)[e]	68.4 Gy, 73.8 Gy, 3D	Penile bulb[f]	41	Median penile bulb dose ≥ 52.5 Gy[f]	No other endpoints analyzed
Wernicke et al. 2004	29	Questionnaire[b]	66–79.2 Gy, 3D	Penile bulb[g]	NS	D30 ≥ 67 Gy[f] D45 ≥ 63 Gy[f] D60 ≥ 42 Gy[f] D75 >20 Gy[f]	Alcohol and smoking not significant, dose and volume significant
Selek et al. 2004	28	Questionnaire[b]	78 Gy. 3D	Penile bulb[g]	35.7% at 2 y	Mean dose to penile structure 38.2 Gy, no dose–volume effect was found	Up to 68 % may have had ED post-treatment? ED correlated with hypertension
Mangar et al. 2006	51	Questionnaire[b]	64 Gy, 74 Gy. 3D	Penile bulb, crura and cavemosum[h]	24	Dl 5, D30, D50, D90 of penile bulb[f]	Adjusted for age, bulb volume, hypertension, and previous pelvic surgery
Zelefsky et al. 2006	561	Patient report (NCI)[i]	81 Gy. IMRT	j	49	Not evaluated	Hormone therapy
Brown et al. 2007	32	Questionnaire[b]	NS. EMRT	Penile bulb	34	No relationship noted	Hypertension, pre-RT erectile function
Cahlon et al. 2008	478	Patient report (NCI)[i]	86.4 Gy, IMRT	j	30	Not evaluated	Age >70 y, diabetes hormone therapy
van der Wielen et al. 2008	10	Questionnaire[b]	68 versus 78 Gy	Penile bulb	36	No correlations between ED and dose–volume of crura, or the penile bulb[j]	Adjusted for diabetes and history of cardiovascular disease
Pinkawa et al. 2009a, b	123	Questionnaire[b]	70.2–72 Gy, 3D	NS	73[k]	Not evaluated	Age, diabetes

OAR organs at risk; *ED* erectile dysfunction; *RTOG* radiation therapy oncology group; *NCI* National Cancer Institute;
[a] All assessments are patient-reported, based on questionnaires of morbidity scoring scales (e.g., RTOG, NCI), as noted
[b] All questionnaires are self-administered
[c] Potency scale declined ≥2
[d] DX is dose delivered to the x % penile bulb volume
[e] RTOG radiation morbidity scoring scale
[f] Penile bulb was defined as proximal portion of the penis
[g] The penile bulb is here specifically defined as proximal enlargement of the corpus spongiosum that is secured to the urogential diaphragm and covered by the bulbospongiosus muscle
[h] The penile bulb was here defined as a structure whereas the crura and cavernosum as a separate one
[i] NCI common toxicity criteria for adverse events
[j] Penile bulb not defined as a specific structure
[k] No erections firm enough for sexual intercourse

examined a cohort of 283 patients who were either treated to the prostate alone or to the prostate and seminal vesicles to a dose of 72 Gy. Although the prostate and seminal vesicle group had higher volumes included for any dose point on the bladder and rectal dose volume histogram, there was no appreciable difference in quality of life between the two groups (Pinkawa et al. 2009a, b).

Minimal conclusions can be made based on the radiographic and histologic observation of seminal vesicle tissue treated with radiation therapy. Based on MRI radiographic analysis, over one-third of patients with radiation to the seminal vesicles had decreased intraluminal fluid contents or disseminated low signal tubular intensity (Chan and Kressel 1991). These radiographic analyses are consistent with previous pathologic studies of irradiated patients and have shown that replacement of normal perivesical fibro-adipose tissue and luminal narrowing secondary to fibrotic change (Bostwick 1982).

Due to the lack of published literature on the subject, further dose–volume recommendations cannot be made for the seminal vesicles.

7 Chemotherapy Tolerance

7.1 Androgen Deprivation and Radiation Therapy

ADT in conjunction with radiotherapy is routinely recommended for patients with locally advanced prostate cancer. Randomized trials have demonstrated improved outcomes, including an overall survival benefit compared with radiotherapy alone. In addition, studies have demonstrated that ADT can improve local eradication of the locally advanced tumors by reducing the size of the mass or the concurrent elimination of tumor clonogens inherently resistant to radiotherapy, or both. ADT can effectively reduce the size of larger prostate volumes by 30–40 %, thereby improving the ability to deliver maximal radiation dose levels without exceeding the tolerance of the surrounding normal tissues. This section will outline the putative mechanisms of benefit for ADT with radiotherapy, summarize the results of published randomized trials, and highlight the indications for its use in clinical practice.

Randomized trials have demonstrated improved outcomes when ADT is combined with EBRT delivered at dose levels of 70 Gy.

8 Special Topics

8.1 Host Factors

Diabetes mellitus has been found to have a higher risk of late rectal bleeding (Herold et al. 1999; Skwarchuk et al. 2000). Investigators from Fox Chase Cancer Center reported that 13 % of patients treated with external radiation for prostate cancer from 1989 to 1996 treated with 3D-CRT had diabetes mellitus. When these patients were analyzed, patients with either type I or type II diabetes experienced significantly more late grade 3 toxicity (28 vs. 17 %) (Herold et al. 1999). The mechanism by which diabetes affects late toxicity is thought to be secondary to microvascular damage contributing to late radiation effects. Aggressive rectal blocking was promoted for diabetic patients in the 3D era, and prescription doses were often lowered for these patients before the advent of IMRT (Fiorino et al. 2008).

8.2 Acute Gastrointestinal Toxicities of Radiation Therapy

Patients treated with pelvic radiation therapy are at risk for acute GI toxicity secondary to acute inflammatory changes involving the rectal and small bowel mucosa. Clinical manifestations of acute GI toxicity are wide ranging and include abdominal cramping, abdominal pain, tenderness with defecation, mucous discharge, tenesmus, rectal urgency, and increased frequency of bowel movements. It can be difficult to differentiate between acute rectal and small bowel toxicity during treatment, especially when the pelvic lymph nodes are included in the treatment field. In general, symptoms of abdominal pain, increased flatus and abdominal cramping are usually from acute small bowel toxicity (acute enteritis) while tenderness with defecation, rectal urgency, and tenesmus are typically associated with rectal toxicity (acute proctitis). Similar to acute genitourinary effects, gastrointestinal signs and symptoms typically begin in the first two weeks of irradiation and resolve within 4 months after completion of therapy.

A range of acute GI toxicity rates have been published in the literature, with 8–45 % of prostate cancer patients treated with radiation having moderate to severe acute GI side effects, with rates depending on such heterogeneous variables as radiation technique, inclusion of pelvic lymph nodes in the irradiation portal, use of androgen deprivation therapy and toxicity instrument used (Cahlon et al. 2008; Fiorino et al. 2009). With contemporary external beam doses of the order of 78 Gy, 40 % of men have moderate to severe acute GI toxicity, with higher rates of toxicity seen in patients whose pelvic lymph nodes are included in the irradiation field (Peeters et al. 2006a, b; Zietman et al. 2005; Dearnaley et al. 2007).

Several coexisting medical conditions can alter the probability of acute GI toxicity during radiation therapy. Androgen deprivation therapy before treatment has been found to decrease acute toxicity by decreasing the volume of the prostate and therefore the amount of rectal wall receiving high dose radiation (Peeters et al. 2005b; Vavassori et al. 2007). Furthermore, patients with diabetes mellitus are more likely to experience acute severe diarrhea and patients with hemorrhoids have significantly higher rates of acute rectal bleeding, tenesmus, and overall GI toxicity during treatment (Peeters et al. 2005b). The administration of antihypertensives and anticoagulant medications during treatment may also lessen the likelihood and severity of acute GI symptoms (Peeters et al. 2005b). Based on these factors, Valdagni et al. have published

nomograms that are predictive of acute rectal toxicity, with use of anticoagulants being protective and history of diabetes mellitus, hemorrhoids, mean rectal dose, and pelvic nodal irradiation predisposing to increased toxicity (Valdagni et al. 2008).

Several publications have confirmed an association between the risk of developing acute and late GI reactions after pelvic radiotherapy (Peeters et al. 2005a; Vargas et al. 2005; Zelefsky et al. 2006), and some authors have proposed a causal relationship, so-called consequential late damage from acute toxicity. However, this mechanism for late toxicity has never been definitely proven. In general, when rectal dose volume parameters are considered, the impact of acute toxicity rates on late toxicity disappears. Likely explanations for the correlation between acute and late GI effects include the possibility that patients who experience severe acute effects are more likely to report late effects. However, some authors continue to explore the potential for at least a partial consequential role for acute reactions to contributing to late GI toxicity (Wang et al. 1998) (Heemsbergen et al. 2006).

8.3 Acute Genitourinary Toxicities of Radiation Therapy

The most common acute urinary morbidities during external beam radiation therapy for pelvic malignancies are classified as irritative and are caused by acute inflammation and epithelial denudation of the urethra and possibly the bladder neck. Symptoms from urethritis and cystitis tend to occur within 2–4 weeks of initiation of radiotherapy and can continue for several weeks after the completion of radiation, when re-epithelization is complete. During external radiation over 50 % of patients experience some degree frequency, urgency, and dysuria (Ryu Winter et al. 2002; Zietman et al. 2005; Peeters et al. 2006a, b; Dearnaley et al. 2007). In general, these irritative symptoms resolve within 4 weeks after the completion of external radiation therapy (Pinkawa et al. 2008). Although less common, acute obstructive symptoms including hesitancy, intermittency, dribbling, and incomplete emptying, are also noted in approximately one-third of patients undergoing radiation. The probability of obstructive symptoms is proportional to the size of the prostate gland, particularly in glands larger than 43 cm^3. (Pinkawa et al. 2008). Acute obstructive symptoms tend to linger longer than irritative symptoms, resolving 8 weeks or more after treatment.

The acute and late urinary toxicity profiles for external beam radiation therapy and brachytherapy are slightly different. Men treated with brachytherapy tend to have more severe irritative symptoms, longer lasting GU symptoms, higher rates of obstructive symptoms, and lower rates of GI toxicity as compared to men treated with external beam radiation therapy (Lawton et al. 1991; Gelblum et al. 1999; Pickles et al. 2010). In a contemporary matched pair analysis for men having EBRT or LDR brachytherapy, men receiving brachytherapy had a higher overall rate of acute Grade 3 GU toxicity (2.9 vs. 0.7 %) and catheterization rates for obstructive symptoms of (15 vs 0 %). Brachytherapy patients also had more late GU toxicity, but less late GI toxicity, than the external beam arm (Pickles et al. 2010). These results are consistent with other similar analyses. In men receiving brachytherapy, prostate size and pre-treatment urinary function are important considerations. One study from MSKCC found that pre-implant IPS scores >7 and prostate volumes >35 cc were predictive of increased rates of acute urinary morbidity (Gelblum et al. 1999).

8.4 Late Genitourinary Toxicities of Radiation Therapy

Late genitourinary toxicities of radiation therapy to the pelvis include chronic cystitis, chronic urethritis, bladder neck contracture, urethral strictures, hematuria, and urinary incontinence. The mechanism of late toxicity is thought to be from changes in the microvasculature of the affected tissue, including increased endothelial proliferation and an obliterative endarteritis, leading to hypoxia, fibrosis, epithelial atrophy, and other vascular changes including telangiectasia formation. The overall rate of late GU toxicity with modern radiation techniques is relatively rare. Analysis of RTOG randomized trials found an overall rate of approximately 10 % Grade 3 or higher toxicity (Lawton et al. 1991, 2008.

Approximately one-half of moderate to severe late GU toxicity is from urethral strictures (Lawton et al. 1991). In men treated with between 60 and 70 Gy for prostate cancer, the incidence of urethral strictures is 0–5 % for those without a prior TURP and 5–15 % for those with a prior TURP (Coia et al. 1995). The time to stricture is usually in the range of 2 years, but symptoms before diagnosis are retrospectively reported as slowly progressive. Cystoscopy is the diagnostic test of choice for a suspected stricture. Strictures have a pale "washed leather" appearance on cystoscopy and are accompanied by other stigmata of radiation, including induration and telangiectasia.

8.5 Late Gastrointestinal Toxicities of Radiation Therapy

Late gastrointestinal effects of radiation therapy include hematochezia, anorectal ulcerations and strictures, mucous discharge, pain, rectal urgency, incontinence, mucosal

changes including telangiectasia and congestion, and chronic loose stools. Fistulas are a very rare late complication usually associated with unnecessary biopsies or procedures involving the portion of the rectum that received radiation, especially in the setting of prior prostate brachytherapy. In general, late genitourinary side effects can take up to 2 years after radiation treatment to develop and are likely clinical manifestations of the chronic pathologic inflammatory processes seen in the rectal microvasculature including submucosal alterations with atypical fibroblasts, abundance of collagen, thickened arterioles, and telangiectatic veins (Coia et al. 1995). Crook et al. found that in a cohort of approximately 200 patients treated for prostate cancer with external beam radiation, 67 % of patient only had minor GI side effects, 9 % reported rectal bleeding, 20 % reported rectal urgency, and 4 % had a grade 3 GI toxicity (Crook et al. 1996). The most common late GI toxicity is late rectal bleeding. However, the evaluating oncologist must remember that a myriad of non-radiation etiologies for bleeding must be included in the differential diagnosis, including metachronous malignancy and less serious conditions such as hemorrhoids and benign anal lesions. Furthermore, the lifetime prevalence of rectal bleeding in the overall population is estimated to be around 18–25 %, with most of these patients having an episode in the previous 1 year (Crosland 1995; Talley and Jones 1998). Bleeding is more common in younger patients (Talley and Jones 1998) and those who regularly examine their stool or toilet paper after bowel movements (Kang 2003).

IMRT techniques are especially useful in minimizing GI toxicity when the pelvic lymph nodes are irradiated because GI toxicity is greater with this larger field (Sanguineti et al. 2006; Guerrero Urbano and Nutting 2004; Luxton et al. 2004; Mangar et al. 2005). The most significant published experience is from Memorial Sloan-Kettering Cancer Center (MSKCC), where patients treated with IMRT had significantly less GI toxicity a decade after treatment when compared to a similar cohort of men treated with conventional techniques to lower total doses (5 % for high dose IMRT arm vs. 13 % for low dose conventional arm) (Zelefsky et al. 2008a, b, c).

Other clinical parameters, most notably prior surgery, diabetes mellitus, and a history of androgen deprivation therapy, are associated an increased risk of rectal bleeding after radiation therapy to the pelvis. Prior surgery to the abdomen or pelvis is consistently associated with a significantly higher risk of rectal bleeding after surgery. Peeters examined a cohort of 641 patients and found that prior abdominal surgery significantly increased the risk of needing blood transfusion or laser coagulation after radiation with an HR of 2.7 (Peeters et al. 2006c). Fiorino found that prior abdominopelvic surgery increased the risk of post-radiation bleeding with an even higher HR of 4.4 (Fiorino et al. 2008). Other publications have confirmed this finding (Fonteyne et al. 2007; Smit 1990). The mechanism by which prior surgery promotes post-radiation bleeding is undefined; possible explanations include spatial fixation of bowel in these patients preventing normal anatomic motion which "smears" hot spots in patients without history of surgery or decreased blood supply to the irradiated area causing poor healing of tissues after treatment (Fiorino et al. 2009).

Androgen deprivation therapy has been variably associated with the development of late rectal bleeding. In the neoadjuvant setting, it is generally accepted that it may decrease rates of late rectal toxicity by creating a more favorable anatomy and by reducing the amount of rectum in the irradiated field (Zelefsky and Harrison 1997; Forman et al. 1995; Sanguineti et al. 2003). However, it is critical to note that this advantage is only seen when the treatment planning process accounts for the downsizing of the prostate gland. If not accounted for, an increased rate of late rectal toxicity can be seen (Schultheiss et al. 1995).

Unlike the neoadjuvant setting, adjuvant androgen deprivation has been found to be associated with increased rates of late rectal bleeding after radiation therapy in numerous studies. Patients who receive adjuvant androgen deprivation therapy have approximately a 2–3 times greater risk of grade 2 or higher late rectal bleeding as compared to patients who did not. The mechanism by which androgen deprivation may increase rectal bleeding is not clearly defined. Considering neoadjuvant androgen deprivation is not consistently associated with late rectal bleeding, the most plausible mechanism is inhibition of the normal tissue repair processes that normal occur after the insult of radiation therapy.

8.6 Biopsy of the Distal Rectum After Prostate Brachytherapy

Physicians should be aware of the high risk of morbidity in biopsying the distal rectum after a prostate brachytherapy procedure. Numerous publications have shown a causative effect between biopsy procedures of the anterior rectal wall and progressive ulcerations/fistulas, especially when the procedure was performed for rectal bleeding after radiation therapy (Gelblum and Potters 2000; Theodorescu et al. 2000; Tran et al. 2005). These studies are also consistent in demonstrating that biopsies performed to evaluate rectal bleeding after prostate brachytherapy typically show only histologic stigmata of chronic radiation changes. It is strongly recommended that biopsies of the anterior rectal wall be avoided as a part of the workup for rectal bleeding after prostate brachytherapy unless a rectal malignancy is

suspected. When they do occur, these lesions are clinically difficult to manage. Repairs of vesicorectal or urethrorectal fistulas are complex surgical procedures involving excision of the fistula site and multilayer interposition of well-vascularized, non-irradiated tissue. Rarely, partial pelvic exenteration with urinary and/or fecal diversion is necessary when less morbid open repair is impossible.

9 Prevention and Management of Radiation Toxicity

Even with the more stringent attention to minimizing dose to normal tissues of the distal pelvis in the planning process, acute and late morbidities will occur. Proper management of these toxicities will contribute to improved quality of life of the patient during and after treatment and will increase the likelihood of successfully completing the prescribed course of radiotherapy. A variety of medications and conservative management techniques can bring relief of symptoms, the recommendations below are certainly not meant to be exhaustive (see Table 4). It is up to the managing physician and the patient to determine the most effective appropriate management strategy for each clinical situation. For the medications listed, review the latest manufacturer-provided instructions to ensure proper indications for use, dosing, route of administration, frequency of use, and side effect profile.

9.1 Erectile Dysfunction

For erectile dysfunction in the post-treatment setting, first-line phosphodiesterase inhibitors such as sildenafil 25–100 mg po prn, tadalafil 10 mg po prn, vardenafil 5–20 mg po can be considered. Treatment with these phosphodiesterase inhibitors can significantly improve function in approximately 2/3 of patients with radiation-induced impotence (Weber et al. 1999; Zelefsky et al. 1999; Incrocci et al. 2001, 2006). It also appears that early versus later use of these agents is associated with improved erectile function and a more favorable health-related QOL (Miller et al. 2006; Schiff et al. 2006). There are also ongoing multi-institutional studies examining these agents before and during radiation therapy to see if they have a protective effect against the development of erectile dysfunction after radiation therapy. Counseling and social support have also been found to improve post-radiation erective dysfunction, with one study showing that attending four counseling sessions improved levels of overall distress and global male sexual function at 3 months (Canada et al. 2005). If ED is refractory to counseling and oral agents, referral to a urologist and consideration of trimix injections, bimix injections, and penile prostheses can be offered to the patient with varying degrees of success. For cases of drying of the ejaculate, which is quite distressing to some patients, there is no proven intervention. It is therefore important for the pre-treatment informed consent process to include this subject so that the patient is aware of the potential for this toxicity.

9.2 Skin Reactions

Skin reactions may be seen during definitive treatment of pelvic malignancies, particularly for penile cancers or during irradiation of the pelvic lymph nodes. For skin dryness or irritation, Aquaphor (OTC) original or healing ointment or Eucerin (OTC) lotion of cream applied to the affected area two or three times a day will bring relief. For moist desquamation, Domeboro soaks (OTC) for 20 min or Silvadene cream 1 % applied for three or four times a day is recommended. Strict attention to skin hygiene in the genital and perineal area is essential during periods of wet desquamation, with sitz baths for perineal desquamation and baking soda and water soaks for testicular or penile desquamation. Telfa (OTC) non-adhesive pads helps with symptoms from the affected area rubbing against clothing or other parts of the body. Hyrdogel wound dressings also bring symptomatic relief. Diphenhydramine 25–50 mg po every 6 h or the use of 0.5–1 % hydrocortisone cream will address pruritic symptoms. For patients recovering from penile desquamation, sexual activity should be held for several weeks, after which time a lubricant without desiccants, irritants, or alcohol should be used. For vigorous desquamations out of proportion to clinical situation or radiation dose, testing for connective tissue diseases or HIV must be considered.

During the management of the penile cancer patient, acute skin reactions remain the most common management challenge. However, these patients can also experience acute adhesions, late strictures, and areas of soft tissue necrosis, the management recommendations of which Crook et al. have published elegantly (Crook et al. 2009, 2010). Acute adhesions can often be managed by dilation with a thoroughly lubricated 18 French Foley catheter. For areas of penile radionecrosis or ulceration, expectant management with best supportive care is recommended with biopsy reserved for only scenarios where there is a high likelihood of tumor recurrence. Biopsy of areas of benign necrosis carries a great risk of leading to deeper and more extensive necrotic involvement. Best supportive care of radionecrotic penile lesions includes fastidious skin care and hygiene, oral analgesics, culture of any areas of suspected infection with appropriate topical or oral antibiotics if positive, and corticosteroids/Vitamin E topically as appropriate. Anecdotal reports exist of particularly deep or

Table 4 Commonly prescribed medications in the management of radiation toxicity of the distal male genitourinary tract

Medication	Indication	Dose	Notes
Skin			
Aquaphor (OTC)	Dry desquamation	Apply to affected area BID-TID	Emollient
Eucerin (OTC)	Dry desquamation	Apply to affected area BID-TID	Emollient
Domeboro soaks (OTC)	Moist desquamation	Moist soak 20 min BID-TID	Astringent
Silvadene cream 1 %	Moist desquamation	Apply to affected area TID	Antibacterial
Telfa (OTC)	Moist desquamation	Apply to affects area as needed	Tissue protectant
Hydrogel wound dressings	Moist desquamation	Apply to affects area as needed	Tissue protectant
Hydrocortisone cream 0.5–1 %	Pruritis	Apply to affected area TID	Topical corticosteroid
Urinary			
Naproxen 220 mg	Dysuria	220 mg PO BID	NSAID
Pyridium	Dysuria	200 mg PO TID-QID	Mucosal topical analgesic
Tamsulosin	Bladder outlet obstruction	0.4-0.8 mg po qd	Selective Alpha 1a blocker
Alfuzosin	Bladder outlet obstruction	10 mg po qd	Selective Alpha 1a blocker
Doxazocin	Bladder outlet obstruction	1–8 mg po qd (start at lowest dose)	Alpha 1 blocker
Terazosin	Bladder outlet obstruction	1–10 mg po qhs (start at lowest dose)	Alpha 1 blocker
Tolterodine	Bladder spasm	2 mg po bid	Anticholinergic
Flavoxate	Bladder spasm	100–200 mg po tid-qid	Anticholinergic
Oxybutynin	Bladder spasm	5 mg po bid-tid	Anticholinergic
Gastrointestinal			
Loperamide	Diarrhea	4 mg po once, then 2 mg po after each unformed stool, maximum 16 mg/day	Anti-diarrheal
Atropine/ diphenoxylate	Diarrhea	1–2 tabs po tid-qid, maximum 8 tabs/day	Anti-diarrheal
Simethicone	Flatus	80–150 mg po bid	Anti-flatulent
Metamucil	Constipation	1–3 tablespoons qd with meals, mix with juice	Bulking agent
Colace	Constipation	100 mg po bid	Stool softener
Bisacodyl	Constipation	10 mg po or pr	Laxative
Senna	Constipation	2–4 tabs po qd-bid	Stool softener and laxative
Fleet enema	Constipation	1 pr as needed	Cathartic
Anusol HC	External anal dermatitis/proctitis	1–2.5 % ointment QID for external use/ 25 mg supp pr bid-tid	Topical steroid
ProctoFoam HC	Proctitis	2.5 % apply pr tid-qid	Topical steroid
Erectile dysfunction			
Sildenafil	Erectile dysfunction	25–100 mg po qd or prn	Do not use with nitrates, use great caution in patients with coronary artery disease or hypertension
Tadalafil	Erectile dysfunction	10–20 mg po qd or prn	Do not use with nitrates, use great caution in patients with coronary artery disease or hypertension
Vardenafil	Erectile dysfunction	5–20 mg po qd or prn	Do not use with nitrates, use great caution in patients with coronary artery disease or hypertension

Modified from Eric K Hansen and Mack Roach III (editors), Handbook of Evidence-based Radiation Oncology, 2007, Springer Science + Business Media, LLC, New York, New York

painful lesions responding to courses of hyperbaric oxygen (Crook et al. 2009). The management of late radiation-induced urethral strictures is discussed in detail below.

9.3 Acute Dysuria

For radiation-related acute dysuria related to prostate cancer treatment, NSAIDS such as naproxen 220 mg po bid are excellent front-line agents. Pyridium 200 mg po tid-qid is also effective but will turn the urine orange and is bothersome for some patients. If infection is suspected, a urine analysis and culture is recommended. Patients receiving radiation are susceptible to urinary tract infections from simulation procedures (catheterization, urethrograms, interstitial fiducial marker placement), urinary retention from obstructive symptoms, and from loss of epithelial integrity from inflammation. Front-line antibiotics for simple urinary tract obstructions include trimethoprim/sulfamethoxazole DS 1 tab po bid for 5–7 days and ciprofloxacin 250 mg po bid for 3–7 days. Consider the possibility of prostatitis, with a tender and boggy prostate on exam. If present, antibiotics may be necessary for several months.

For patients with symptoms of bladder spasm (classically frequency, urgency, and dysuria without hesitancy or intermittency), anti-cholinergic agents can be considered. For example tolterodine 2 mg po bid, flavoxate 100–200 mg po tid-qid, or oxybutynin 5 mg po bid-tid. In patients with chronic radiation cystitis or hematuria, pentoxifylline 400 mg po tid or vitamin E 1000 IU po qd have been reported to improve healing and fibrotic reactions by promoting submucosal blood flow. Pentoxifylline should be used with extreme caution in patients with a history of CNS or retinal hemorrhage.

9.4 Obstructive Symptoms

Obstructive symptoms should be screened for before and during treatment of the patient with prostate cancer. Formal urodynamic studies have been found to be of great use in predicting urinary obstruction or retention after radiation therapy. One study from University of California, San Francisco discovered that peak flow rate before prostate implant was highly predictive of acute urinary obstruction after the procedure (Ikeda and Shinohara 2009). Based on this study, the role of pre- and post-radiation urodynamic studies will likely expand in the future for both brachytherapy and external beam patients. While undergoing radiation treatment, patients reporting urgency or dysuria in combination with hesitancy and intermittency are likely experiencing obstructive symptoms, and the degree of urinary retention can be confirmed with a post-void residual bladder scan. Review the patient's medication list for agents that can increase obstructive symptoms, including anti-cholinergics, antihistamines, decongestants, and antispasmodics. Alpha-blockers are the agents of choice for obstructive symptoms, especially selective alpha-1a blockers such as tamsulosin 0.4–0.8 mg po qd or alfuzosin 10 mg po qd. These agents act by blockade of the α_{1a}-adrenoreceptor, which is the predominant subtype in the human prostate stroma. Blockade reduces prostate smooth muscle tone and inhibits the dynamic component urinary obstruction (Forray et al. 1994), inhibits growth of prostate cells, and leads to increased apoptosis in benign and prostate cancer cells (Tahmatzopoulos et al. 2004). Less specific alpha blockers are also effective but are more likely to cause hypotensive changes and take longer to decrease symptoms. These medications should be started at the lowest dose level and the patient should be carefully screened for symptoms. These agents include doxazocin 1–8 mg po qd and terazosin 1-10 mg po qhs. If complete, or near complete obstruction, Foley catherization may be indicated. If this is the case, some physicians discontinue radiation until the catheter is removed.

9.5 Urethral Strictures

Urethral strictures are typically managed with simple endoscopic urethrotomy or balloon dilation. Open repair is typically reserved for patients with multiply recurrent of complex strictures. The possibility of other causes than late radiation fibrosis causing the worsening symptoms must be considered, including recurrence of tumor. Furthermore, any intervention has the potential to worsen the fibrotic process, so the short-term benefits of any potential procedure should be carefully weighed against potential to worsen the long-term clinical situation. Merrick et al. reported that approximately one-third of recurrent strictures requiring repeat urethrotomy become refractory obliterative strictures requiring suprapubic urinary diversion (Merrick et al. 2006). Therefore, in some cases, conservative management may offer a superior therapeutic ratio. In a subset of patients, chronic self-catheterization can be used with success for strictures that are refractory to or not appropriate for surgical management (Marks et al. 1995). More complex interventional management options, especially for complex of refractory strictures include: excision and primary urethral anastomosis urethroplasty; prostatectomy with vesicourethral reanastomosis; onlay flap urethroplasty; suprapubic urinary diversion; or combined abdominal-perineal urethroplasty.

9.6 Urinary Incontinence

For the very rare occasion of radiation-related urinary incontinence or decreased urethral resistance, surgical interventions are again the mainstay of treatment. Treatment options include injection of substances such as collagen or implantation of artificial sphincters. For chronic urinary bleeding, endoscopic evaluation followed by coagulation or application of dilute formalin, alum, or silver nitrate has been shown to be effective. For refractory or brisk bleeding causing anemia, a bladder diversion procedure or substitution can be considered (Marks et al. 1995).

9.7 Altered Bowel Movements

9.7.1 Symptoms of Diarrhea

Symptoms of diarrhea during or after radiation therapy should be carefully evaluated. The practitioner should evaluate duration and severity of symptoms, including urgency, association with urination, consistency of stool, presence of abdominal cramping and gas, and weight changes. An infectious process should be ruled out, if clinically indicated. For radiation-induced diarrhea not responsive to a low residual, high pectin diet, try loperamide 4 mg × 1 and then 2 mg po after each unformed stool. If still refractory, atropine/diphenoxylate 1–2 tabs po three to four times a day may improve symptoms. Tincture of opium should be reserved for extremely refractory cases. For bothersome flatulence, simethicone 80–150 mg po at morning and night or over the counter Beano 1–3 servings before meals is effective.

9.7.2 Symptoms of Constipation

Patients occasionally develop constipation during or after treatment. If constipation does not respond to conservative measures like an increase in fiber and hydration, several agents can be considered: Metamucil 1–3 tablespoons in juice with meals will act as a bulking agent, Colace 100 mg po bid will soften stool, Bisacodyl 10 mg po or pr acts a laxative, and Senna 2–4 tabs po qd-bid acs a both a laxative and stool softener.

9.7.3 Acute Radiation Proctitis

For acute radiation proctitis or tenesmus, anti-inflammatory medications may be useful in the acute setting if symptoms are not accompanied by bleeding. Several topical steroidal agents also bring relief, including Anusol HC 25 mg suppositories two to three times a day or proctofoam HC 2.5 % applied pr 2–3 times per day. For perianal pain or irritation, rule out fungal infection or rectal fissure, then use hydrocortisone cream 1–2.5 % applied four times a day or a 1:1:1 ratio of Desitin cream, 2 % lidocaine jelly, and nystatin cream applied to the perianal area. Also consider sitz baths and temporarily switching from dry toilet paper to a moistened product without alcohol-based agents like baby wipes. For symptomatic inflamed hemorrhoids, OTC Preparation H suppositories are usually effective. If not, offer steroid suppositories for internal hemorrhoids or hydrocortisone 1–2.5 % for external hemorrhoids.

If chronic diarrhea persists or starts after pelvic radiation therapy, malabsorptive conditions should be considered and ruled out by a gastroenterologist, if necessary. Helpful dietary changes include increasing fiber intake and decreasing intake of dairy containing products or fatty foods. If no change, loperamide, diphenoxylate/atropine, or difenoxin/atropine can be considered. For symptoms of radiation proctitis, rectal bleeding or radiation-induced rectal ulceration, encourage a high fiber diet with plenty of hydration. Steroid suppositories as listed above should be first-line agents. If not effective, a hydrocortisone retention enema pr qhs (retaining for 1 hour) or mesalamine rectal suspension enema pr qhs can be attempted. Sulfasalazine or sucralfate po may also bring relief. If still no improvement, referral to a gastroenterologist is appropriate, where argon plasma coagulation or application of dilute formalin may be attempted. Other potentially effective treatment options include pentoxifylline, vitamin E, and hyperbaric oxygen.

9.8 Rectal Bleeding

The evaluation of a patient with rectal bleeding and a history of radiation therapy varies between physicians. Endoscopy is typically the diagnostic intervention of choice, but the extent of necessary evaluation (rectoscopy, sigmoidoscopy, or full colonoscopy) is unclear. When to perform a diagnostic intervention as opposed to observation and conservation management of rectal bleeding is also controversial. In general, if the bleeding is accompanied by other gastrointestinal symptoms, including change in bowel habits, painful defecation, abdominal pain, or new constitutional symptoms, diagnostic intervention is warranted. Furthermore, the timing of onset of rectal bleeding can offer diagnostic clues as to the etiology. Most radiotherapy-related late GI toxicities begin to manifest within 3 years of treatment (Fiorino et al. 2009). Although rectal dose–volume and spatial considerations have been found to be predictive of late rectal toxicity, endoscopic findings of apparent radiation change after treatment do not always correlate administered dose distributions (van Lin et al. 2007; Goldner et al. 2007). Regardless, endoscopic evaluation of a patient with rectal bleeding and other symptoms should occur until a source of bleeding is diagnosed (Moore

et al. 2000). Further management of symptomatic radiation proctitis is discussed below.

10 Future Direction and Research

Standard methods to define the penile bulb and associated critical structures should become more widely used. A standard method to score ED should be more widely adopted. Systematic prospective clinical trials that attempt to relate the three-dimensional dose–volume parameters from all of the potentially critical structures to clinical outcomes should be considered. Such studies may help to identify which pelvic structures are critical for ED. Dosimetric/imaging studies estimating uncertainties in the overall accumulated "true dose distribution" should be considered. This may be a key cause of inconsistencies between reported results. Anatomic studies to better define the critical anatomic sites for RT-associated ED may be helpful. Well-characterized data (including full dose distribution and imaging information) should be pooled from multiple studies where possible.

11 History and Literature Landmarks

Approximately 20 years after Roentgen reported the discovery of X-rays in 1895, Pasteau and Degrais first reported the use of radiation therapy to treat prostate cancer (Chassagne et al. 1985). By the 1950s, contemporary external beam radiation therapy was generally acknowledged as curative for localized prostate cancer (Bagshaw 1967; Del Regato 1967). Further technical refinements over the next several decades led to the development of three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT) which allowed escalation of dose while sparing adjacent critical normal structures, leading to less short- and long-term toxicity rates and improved clinical outcomes (Leibel 2000; Leibel et al. 2002; Cahlon et al. 2008; Zelefsky et al. 2008a, b, c; Morris et al. 2005). Multiple randomized trials have confirmed that the dose escalation permitted with these modern techniques has led to improved clinical outcomes in patients with prostate cancer treated with external beam radiation therapy (Zietman et al. 2005; Peeters et al. 2006a, b; Dearnaley et al. 2007; Kubanzker et al. 2008; Zietman et al 2010). Furthermore, given the unique radiobiology of prostate cancer with a low α/β ratio of the order of 1.85 (Daşu 2007), an emerging body of data suggests that hypofractionated radiation schedules, where a higher dose per fraction is delivered in a smaller number of fractions, may be superior to conventional fractionation schemes in terms of both tumor control and toxicity profile for adenocarcinoma of the prostate. Many such treatment schedules have been reported with promising early results (Lloyd-Davies et al. 1990; Lukka et al. 2005; Tsuji et al. 2005; Soete et al. 2006; Yeoh et al. 2006; Junius et al. 2007; Martin et al. 2007; King et al. (in press); Livsey et al. 2003; Kupelian et al. 2007; Madsen et al. 2007; Fuller et al. 2008).

Refinements in permanent low-dose-rate interstitial and temporary high-dose-rate interstitial brachytherapy techniques have led to these modalities being curative as monotherapy in the low risk setting (Zelefsky et al. 2007; 2007) and beneficial as a boost added to external radiation in higher risk disease (Zelefsky et al. 2008a, b, c). Additionally, HDR brachytherapy is now being used to deliver hypofractionated re-irradiation as salvage treatment to those patients who have recurrence after external beam radiation therapy (Lee et al. 2007; Tharp et al. 2008). These definitive and salvage brachytherapy procedures have added to the fund of knowledge regarding the tolerance of normal tissues to radiation while introducing new considerations into dose–volume guidelines. Furthermore, ongoing national studies are examining the possible role for adding chemotherapy to definitive radiation and neoadjuvant, concurrent, and adjuvant androgen deprivation therapy for high risk group prostate cancer patients. The outcomes of these combined chemoradiation studies will likely further change and further refine our understanding of accepted normal tissue tolerances of radiotherapy.

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The Testes

Jill P. Ginsberg and Alan W. Katz

Contents

Abstract

- Germ cells develop into sperm, and the sertoli cells support and nurture developing germ cells.
- Testosterone is transported from Leydig cells to the seminiferous tubules, where it acts to enhance spermatogenesis.
- Alkylating agents are gonadotoxic, and risk depends on cumulative dose.
- Fractionated radiation is more efficient than single doses in destroying germ cells.
- Hodgkin's disease patients treated with six or more courses of mechlorethamine, vincristine, procarbazine, and prednisone are likely to have permanent azoospermia.
- Leydig cell dysfunction may be observed following treatment with alkylator-based regimens.
- Oligospermia occurs at doses as low as 10 cGy, and azoospermia at 35 cGy, which is generally temporary.
- Data regarding Leydig cell function following radiation comes primarily from studies in boys who received direct testicular irradiation for acute lymphoblastic leukemia.
- Permanent (or at least very long-term) azoospermia has been seen after 140–260 cGy of fractionated scatter radiation.
- Cryopreservation of sperm has become standard practice, and should be offered to all newly diagnosed postpubertal males at risk for potential infertility.

Abbreviation

ALL	Acute lymphoblastic leukemia
DHT	Dihydroxytestosterone
FSH	Follicle-stimulating hormone
HD	Hodgkin's disease
IMRT	Intensity modulated radiation therapy
ICSI	Intracytoplasmic sperm injection
LH	Luteinizing hormone

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MOPP	Mechlorethamine, vincristine, procarbazine, and prednisone
NHL	Non-Hodgkin's lymphoma
TBI	Total body irradiation
TESE	Testis sperm extraction

1 Introduction

The testes are extremely sensitive to chemotherapy, radiation, and surgical interventions. Cancer therapy can interfere with reproductive ability and libido in men. The differential sensitivity of spermatozoa—producing Sertoli cells compared to the testosterone—producing Leydig cells allows for greater effects on the reproductive capacity of men than effects on their sexual function. Furthermore, since the testes are more sensitive than the ovary to cytotoxic therapies, the ensuing injury is more damaging to male fertility than to females. Comparison of fertility in treated men to women revealed a 0.76 adjusted relative fertility (Byrne et al. 1987). In this chapter, we review the pathophysiology of the testes and clinical manifestations of the testicular injury in response to gonadotoxic therapies. Furthermore, we will outline methods for screening males for gonadotoxicity and suggest potential preventative measures that can be used in certain instances. Biocontinuum of adverse early and late effects is shown in Fig. 1.

2 Anatomy and Histology

2.1 Overview of Normal Gonadal Development

Although the chromosomal and genetic sex of an embryo is determined at fertilization, male and female morphological sexual characteristics do not differ until the seventh week of gestation (Moore 1988). This initial period of early genital development is referred to as the indifferent stage of sexual development. During the fifth week, proliferation of the mesothelial cells and of the underlying mesenchyme produces a bulge on the medial side of the mesonephros, known as the gonadal ridge. Next, finger-like epithelial cords grow into the underlying mesenchyme. The indifferent gonad now consists of an outer cortex and inner medulla (Moore 1988). During the sixth week, the primordial germ cells enter the underlying mesenchyme and incorporate into the primary sex cords. In embryos with an XY sex chromosome complex, testis organizing factor (H-Y antigen) regulated by the Y chromosome determines testicular differentiation (Moore 1988); the medulla differentiates into a testis and the cortex regresses. The gonads can be recognized as testes 7–9 weeks post-fertilization (Figs. 2 and 3a, b).

The first stage of testis differentiation is the formation of testicular cords consisting of Sertoli precursor cells packed tightly around germ cells. The diploid germ cells, the prespermatogoonia, undergo meiosis in the fetal testis and remain in meiotic arrest until puberty. Sertoli cells, which provide a location for support and proliferation of spermatogonia are derived from the mesonephros and proliferate only during fetal life and in the neonatal period (Styne 1982). After the 8th week of fetal life, the Leydig cell of the fetal testis secretes testosterone resulting in masculinization of the external genitalia and urogenital sinus. By the third month, the penis and prostate form (Conte and Grumbach 1990). Normal testes descend by the 7th month of gestation with little likelihood of continuing spontaneous descent after 9 months (Czeizel et al. 1981).

2.2 Anatomy of Normal Testis

The adult testis is an oblong organ, approximately 4.5 cm in length, weighing 34–45 g (Steinberger 1989) (Fig. 2). The testis is composed of three principal cell types: germ cells that develop into sperm, Sertoli cells that support and nurture developing germ cells and are also the site of production of the glycoprotein hormone inhibin, and Leydig cells that are responsible for testosterone synthesis (Sklar 1999). Seminiferous tubules, the sites of spermatogenesis, are formed by germ cells and Sertoli cells (Fig. 3a). The Leydig cells that are responsible for the production of testosterone lie near the basal compartment of the seminiferous tubules, enabling them to deliver high concentrations of testosterone necessary for normal spermatogenesis and male secondary sexual characteristics (Morris 1996; Sklar 1999) (Fig. 2).

The seminiferous tubules are embedded in a connective tissue matrix containing interspersed Leydig cells, blood vessels, and lymphatics and are surrounded by a basement membrane (tunica propria) upon which the seminiferous epithelium rests. Spermatogenesis takes place in the seminiferous epithelium. The least differentiated germ cells, the spermatogonia, divide to form spermatocytes that immediately undergo meiosis (Fig. 3b). The haploid cells (the spermatids) that are formed develop into flagellate motile spermatozoa. This process requires up to 74 days (Smith and Rodgriguez-Rigau 1989). Since spermatozoa are continuously produced in adult men, a constant supply of germ cell precursors is necessary. The newly formed spermatozoa are transported through the lumen of the seminiferous tubules into the epididymis where they are stored.

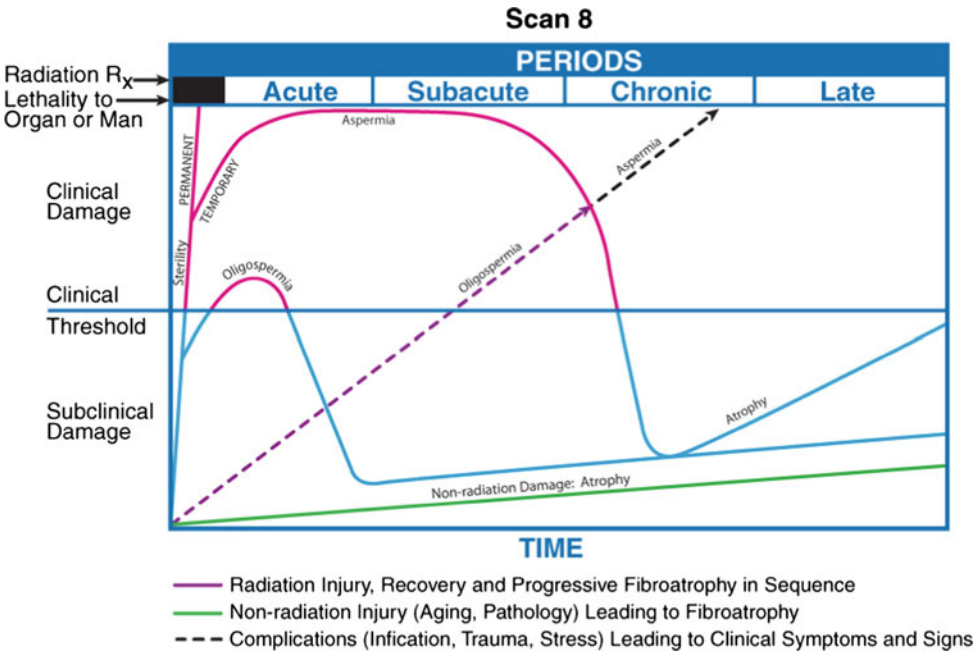

Fig. 1 Biocontinuum of adverse early and late effects for the testis (with permission From Rubin and Casarett 1968)

3 Biology, Physiology, and Pathophysiology

3.1 Hypothalamic-Pituitary-Testicular Axis

The primary regulators of testicular function are the anterior pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are released in response to the hypothalamic releasing factor, GnRH (Fig. 4). GnRH is secreted from the median eminence into the hypophyseal portal system in a pulsatile manner and acts on the gonadotropes of the pituitary gland to stimulate secretion of LH and FSH (Morris 1996). LH regulates Leydig cell function by binding to specific LH receptors on the plasma membrane of Leydig cells. This leads to the formation of the cAMP that drives testosterone biosynthesis via a complex cascade starting with cholesterol (Morris 1996; Sklar 1999). Testosterone is transported from Leydig cells to the seminiferous tubules, where it acts to enhance spermatogenesis (Sklar 1999). Testosterone is also a pro-hormone for two different and metabolically active hormones, dihydroxytestosterone (DHT) and estradiol. DHT mediates male sexual differentiation and virilization, whereas estradiol mediates bone maturation, mineralization, and epiphyseal fusion (Smith et al. 1994). Testosterone controls pituitary LH secretion by a negative feedback mechanism; LH levels will rise when the Leydig cells are unable to produce testosterone (Figs. 4, 5a, b, Tables 1, 2, 3).

Sertoli cells are the only cell type of the testis that possess FSH receptors (Sklar 1999). FSH is delivered to the interstitial area of the testis by way of the arterial system. It then passes through the basement membrane of the seminiferous tubule to reach the Sertoli cells that line this membrane. FSH binds to the FSH receptors of the Sertoli cell and then mediates the synthesis of a variety of proteins and enzymes including the inhibins (Morris 1996). Inhibin is a major feedback regulator of FSH and may thus be useful as a marker of spermatogenesis (Hayes et al. 1998; Schmiegelow et al. 2001). The production of androgen transport protein by Sertoli cells can be induced and maintained by FSH.

FSH triggers an event in the immature testis that is essential for the completion of spermatogenesis. Thereafter, spermatogenesis will proceed continuously as long as an adequate and uninterrupted supply of testosterone is available. The lack of negative feedback from germinal epithelium results in an elevated FSH level.

3.2 Normal Developmental Stages

A neonatal surge in testosterone secretion is caused by high LH and FSH concentrations that occur during the first few months of life. From the age of about 3 months until the onset of puberty, plasma concentrations of LH and FSH are quite low and the testes are relatively quiescent (Sklar 1999). At the onset of puberty, pulsatile secretion of LH (and to a lesser extent, FSH) occurs during sleep that is associated with increased nighttime plasma concentrations of testosterone (Sklar 1999). As puberty progresses, the increased pulsatile release of gonadotropins and the high concentrations of testosterone are maintained throughout the day and night (Sklar 1999) (Tables 1, 2).

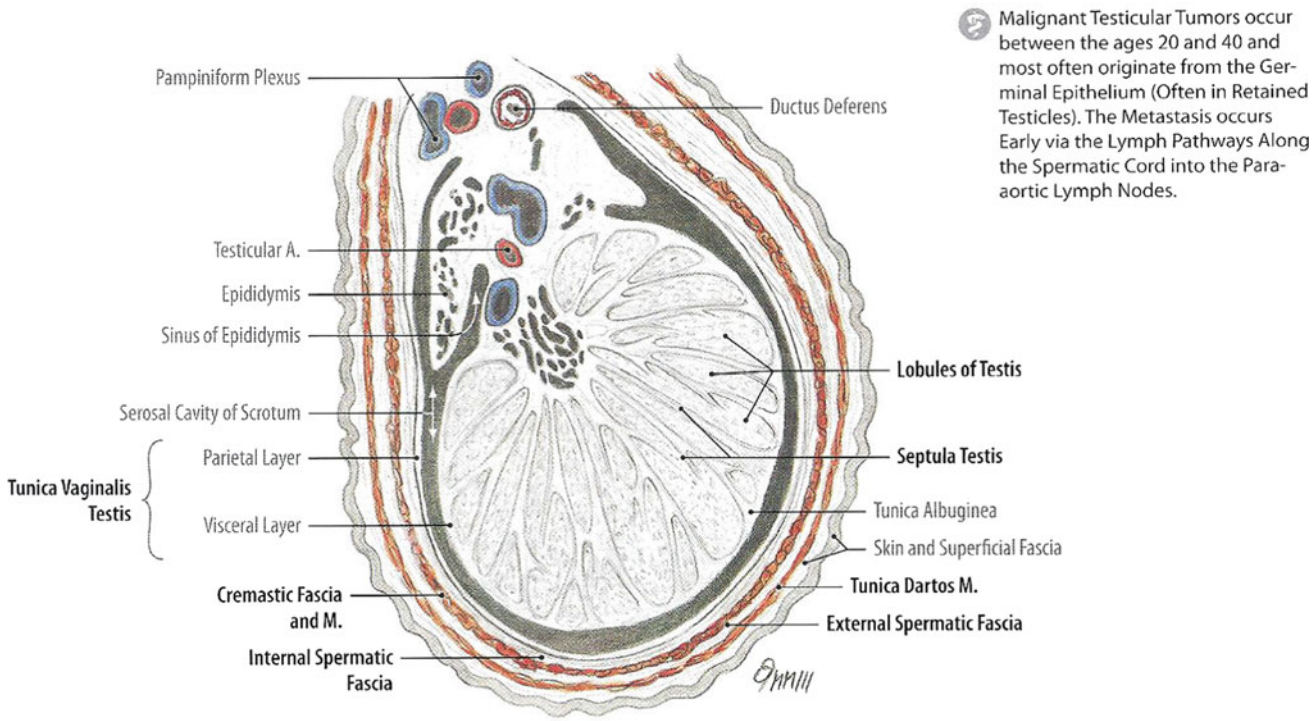

Fig. 2 Anatomy (with permission from Tillman 2007): schematic of a cross section through the testis

In a normal male the first sign of puberty is enlargement of the testis to greater than 2.5 cm (Styne 1982). This is due to seminiferous tubule growth, although Leydig cell enlargement contributes as well. Androgens synthesized in the testes are the driving force behind secondary sexual development, although adrenal androgens also play a role in normal puberty. The range of onset of normal male puberty extends from 9 to 14 years of age. Boys complete pubertal development in 2–4.5 years (mean 3.2 years) (Styne 1982). The development of the external genitalia and pubic hair has been described in stages by Marshall and Tanner (1970) (Tables 1 and 2). The first appearance of spermatozoa in early morning urinary specimens (spermarche) occurs at a mean age of 13.4 years, at gonadal stages 3 and 4 (pubic hair stages 2 through 4) simultaneous with the pubertal growth spurt.

3.3 Pathophysiology: Cytotoxic Effects of Therapy

3.3.1 Testicular Irradiation

Soon after the discovery of X-rays by Roentgen, investigators noted that spermatogenesis is exquisitely sensitive to radiation (Albers-Schonberg 1903; Regaud and Blanc 1906). The testes are directly irradiated in rare situations such as testicular relapse of acute lymphoblastic leukemia (ALL). Although the testes are usually not directly in the radiation field, they can still receive irradiation via body scatter. Scatter occurs when X-rays interact with tissues near the target of interest, resulting in secondary X-rays that then hit the target (Khan 2003). The amount of scattered radiation is a function of the proximity of the radiation field to the target, the field size and shape, the X-ray energy, and the depth of the target. Of these, distance from the field edge is the most important factor. Scatter dose to the testes becomes a real issue when treating a field that extends into the pelvis as in some cases of Hodgkin's disease, seminoma or soft tissue sarcoma of the thigh. Small children, because of their shorter trunk length, can be at greater risk from scattered radiation than larger individuals (Table 3, Fig. 5a, b).

The germinal epithelium is most sensitive to radiation and some effect on spermatogenesis will be seen at doses of 10 cGy (Table 3 shows radiation dose response, and Fig. 5a, b shows early and late histopatholgic correlates) (Ash 1980). Permanent sterilization may be seen with doses as low as 100 cGy (Ash 1980). Speiser et al. reviewed experimental data in mammals that indicated that the total radiation dose required to induce permanent azoospermia was lower if a fractionated regimen was used than if a single dose was given (Speiser et al. 1973). The details of these experiments cannot be extrapolated to humans because there are significant differences in germ cell radiosensitivity between different species. However, the general conclusion that fractionated radiation is more efficient than single doses in destroying germ cells appears to be true in humans as well.

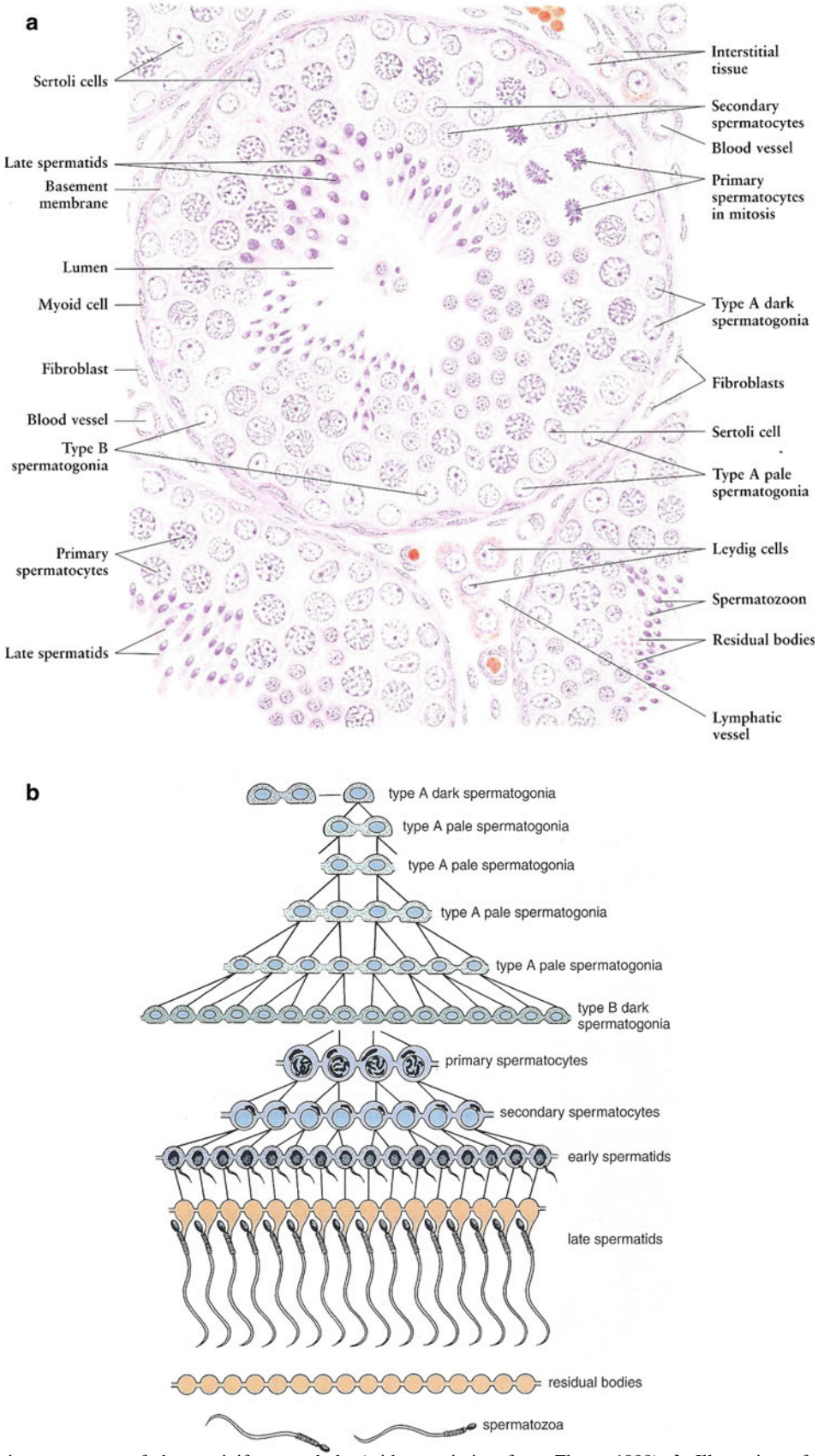

Fig. 3 **a** Microscopic appearance of the seminiferous tubule (with permission from Zhang 1999). **b** Illustration of spermatogenic cell generations. This diagram shows the clonal nature of the successive generations of spermatogenic cells. Cytoplasmic division is complete only in the primitive type A dark spermatogonia that serve as stem cells. All other spermatogenic cells remain connected by intercellular bridges as they undergo mitotic and meiotic division and differentiation of the spermatids. The cells separate into individual spermatozoa as they are released from the seminiferous epithelium. The residual bodies remain connected and are phagocytosed by the Sertoli cells. (with permission from Ross and Pawlina 2011)

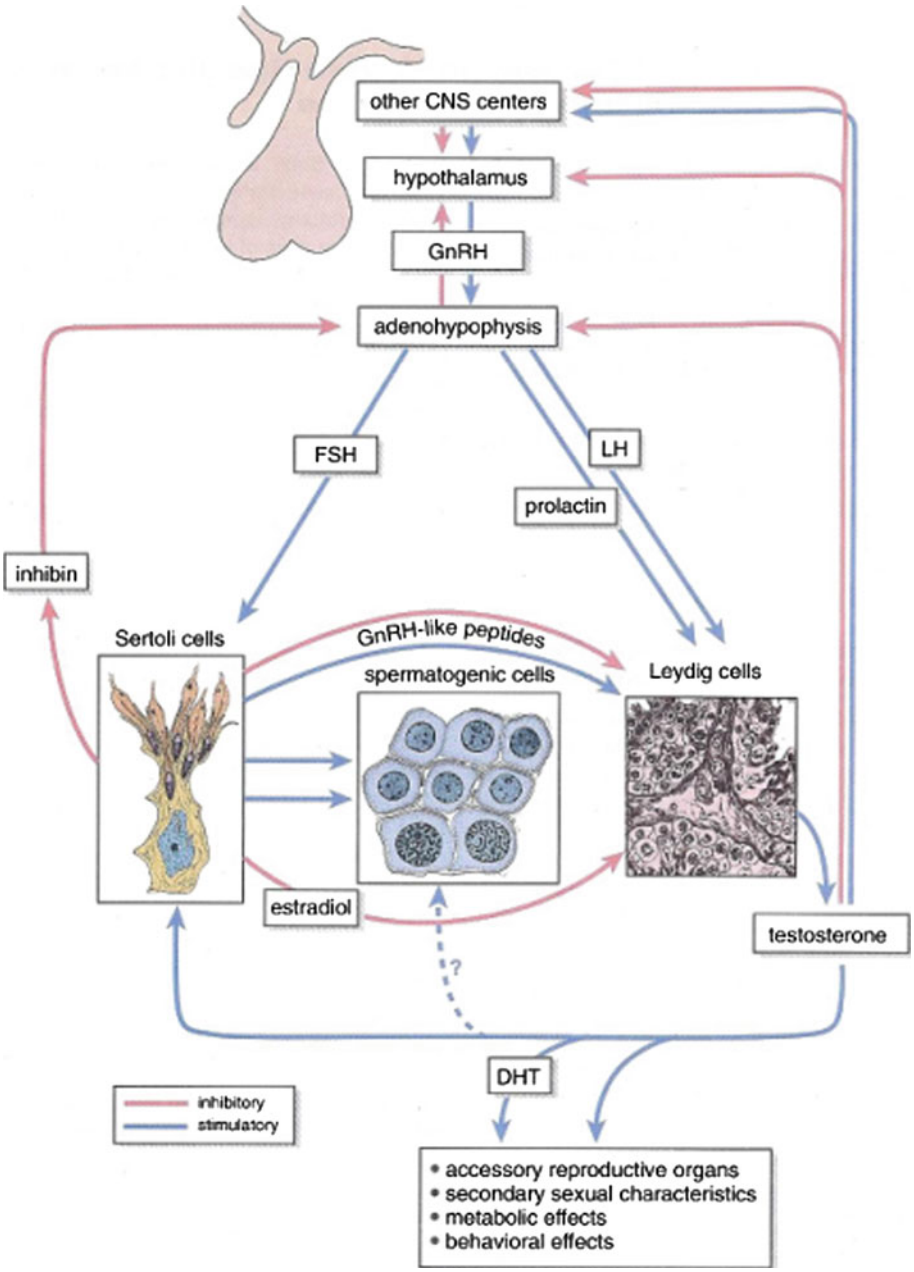

Fig. 4 Hormonal regulation of the testis (*Blue arrows*) indicate stimulatory action on the system; (*red arrows*) indicate inhibitory feedback (with permission from Ross and Pawlina 2011)

To fully understand, the paradox of fractionated doses of radiation being more efficient than a single dose of radiation, one needs to appreciate the cell cycle kinetics of the testis germinal tissue. The spermatogenic germinal epithelium undergoes 4 cycles within 64 days and is more radiosensitive when the intermitotic interval is short (Spermatogonia type A). As the intermitotic interval lengthens (Spermatogonia B) the cells become less radiosensitive. Once mitosis is completed meiosis begins and the spermatids reduce their chromosomes to a haploid number and form spermatozoa which are very radioresistant.

Classically, a single large dose of radiation is more effective and efficient ablating the cancer rather than fractionating the dose. Fractionation allows for the 4 R's: repair, reoxygenation, reassortment, and repopulation of the tissue. Thus the total fractionated dose is greater than a single large dose to achieve the same degree of cell kill i.e. the Strandquist lines apply to normal tissues and tumors.

As noted in the "Law of Bergonie and Tribondeau" experiments, small fractionated doses to the testes are more effective and efficient than a large equivalent single dose for testicular sterility to occur without scrotal skin injury. These experiments can be considered the search for radiation oncology's equivalent to the "Holy Grail". That is, there is an optimal fractionation dose schedule which can ablate tumors without causing significant damage to normal tissues.

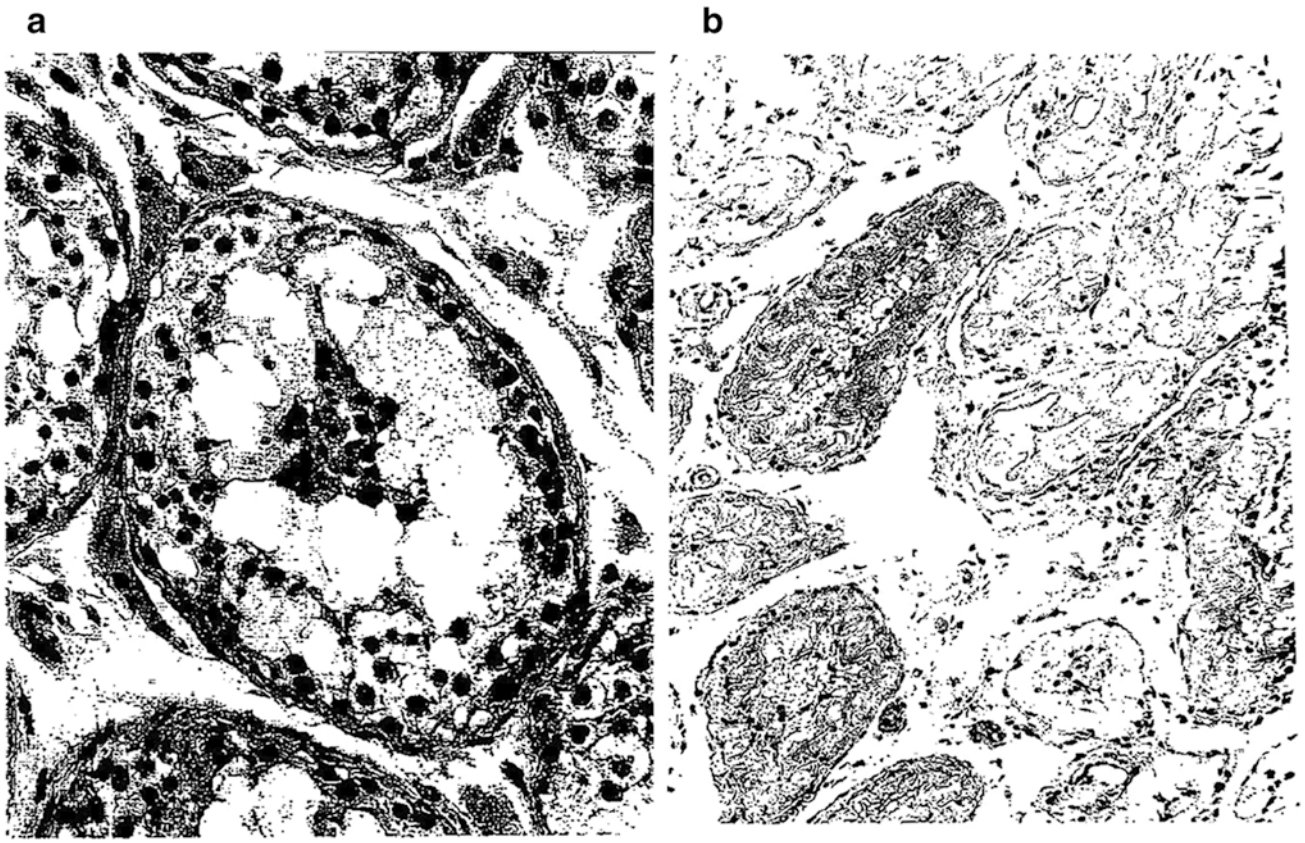

Fig. 5 **a** Early necrosis of germ cells of the type observed hours to a few days after administration of large single doses of radiation. In comparison with the normal germ cells, there is a marked decrease in the layers of germ cells, absence of spermatozoa, and groups of necrotic cells in the center of the lumen. The stroma is not altered. **b** Late testicular atrophy: this 60 year old man received an estimated dose of cGy of fractionated radiation to both testes during irradiation pelvis and perineum in the course of therapy for carcinoma of the prostate. Notice, one year later, the convoluted basement membrane in the midst of thick tubular walls. In this very advanced degree of testicular atrophy, Sertoli cells are no longer present in most tubules…tubular lumina are either empty of contain "foam cells" (with permission from Fajardo 2001)

Table 1 Genital development stages (Marshall and Tanner 1970; O'Dell 1989)

Stage	Description	Mean age at onset (year)
		(Range 95 %)
1	Preadolescent. Testes, scrotum, and penis are about same size and proportion as in early childhood	
2	Scrotum and testes have enlarged; change in texture and some reddening of the scrotal skin. Testicular length > 2 cm < 3.2 cm	11.6
		(9.5–13.8)
3	Growth of penis has occurred, at first mainly in length but some increase in breadth; further growth of testes and scrotum. Testicular length > 3.3 cm < 4.0 cm	12.9
		(10.8–14.9)
4	Penis further enlarged in length and breadth with development of glans. Testes and scrotum are further enlarged. Scrotal skin has darkened. Testicular length > 4.1 cm < 4.9 cm	13.8
		(11.7–15.8)
5	Genitalia are adult in size and shape. No further enlargement takes place after stage 5 is reached. Testicular length > 5 cm	(14.9)
		(12.7–17.1)

Extreme fractionation of dose enhances cell kill of the testis stem cell population in which "dose-time relationships are such that there is a *maximum* degree of mitosis linked deaths with a *minimum* of wasted radiation". Casarett reproduced these results in experiments in Beagle dogs (Casarett 1964). That is, small doses 3 cGy per week given in small daily doses of 0.6 cGy for 5 days a week, to total cumulated doses of 475 cGy, was able to cause complete and

Table 2 Pubic hair developmental stages (Marshall and Tanner 1970; O'Dell 1989)

Stage	Description	Mean age at onset (year)
		(Range 95 %)
1	Preadolescent. No pubic hair	
2	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled appearing chiefly at base of penis	13.4
		(11.2–15.6)
3	Hair is considerably darker, coarser, and curlier and spreads sparsely	13.9
		(11.9–16.0)
4	Hair is now adult in type but area it covers is still smaller than most adults. There is no spread to medial surface of the thighs	14.4
		(12.2–16.5)
5	Hair is adult in quantity and type, distributed as an inverse triangle. The spread is to the medial surface of the thighs	15.2
		(13.0–17.3)

Table 3 Impairment of spermatogenesis and Leydig cell function after fractionated radiotherapy (Ash 1980)

Testicular dose (cGy)	Effect on spermatogenesis	Effect on Leydig cell function
<10	No effect	No effect
10–30	Temporary oligospermia	No effect
30–50	Temporary azoospermia at 4–12 months after radiation. 100 % recovery by 48 months	No effect
50–100	100 % temporary azoospermia for 3–17 months after radiation	No effect
	Recovery begins at 8–26 months	
100–200	100 % azoospermia from 2 months to at least 9 months. Recovery begins at 11–20 months	Transient rise in LH
		No change in testosterone
200–300	100 % azoospermia beginning at 1–2 months. May lead to permanent azoospermia. If recovery takes place, it may take years	Transient rise in LH
		No change in testosterone
1200	Permanent azoospermia	Elevated LH. Some patients may have decreased basal testosterone or in response to HCG stimulation. Replacement therapy not needed to ensure pubertal changes in most boys
2400	Permanent azoospermia	Elevated LH. Many patients, but not all, will have decreased testosterone. Replacement therapy needed to ensure pubertal changes in most boys

permanent aspermia where as a single large dose of 2000 cGy failed to achieve this endpoint. As state, the population of spermatogonia comprises two subpopulations, spermatogonia A and B, which differ in duration of the intermitotic interval. The most effective fractionation schedule to achieve complete and permanent sterilization of seminiferous epithelium efficiently kills the Type A spermatogonia subpopulation with the shorter intermitotic period and initiates each spermatogenic cycle with more frequent mitoses. Thus, spermatogonia A is more likely to be irradiated during mitosis resulting in depletion of stem cell population.

More attention has been focused on the effects of radiation on spermatogenesis than on its effects on Leydig cell function. The data available, indicates that chemical changes in Leydig cell function are observable following direct testicular irradiation with the effect more pronounced with 2400 cGy than with 1200 cGy (Sklar et al. 1990). The severity of the effect is more marked the younger the patient at the time of radiotherapy (Castillo et al. 1990). Sertoli cell function may also be affected at doses of 3000 cGy (Tsatsoulis et al. 1990). In general, progression through puberty and testosterone production proceeds normally in males subjected to radiation therapy.

3.3.2 Chemotherapy

Testicular dysfunction is among the most common long-term side effects of chemotherapy in men. The germinal epithelium is particularly susceptible to injury by cytotoxic drugs

secondary to a high mitotic rate. Leydig cells in contrast, appear relatively resistant to the effects of chemotherapy (Tsatsoulis et al. 1990). In 1948, azoospermia after an alkylating agent (nitrogen mustard) was described in 27 of 30 men treated for lymphoma (Spitz 1948) Subsequently, it has become apparent that all alkylating agents are gonadotoxic (Heikens et al. 1996; Mackie et al. 1996; Papadakis et al. 1999). Antimetabolite therapy in general (e.g., methotrexate, mercaptopurine) does not have an adverse impact on male fertility. Cisplatin-based regimens result in temporary impairment of spermatogenesis in all patients but with recovery in a significant percentage (Hansen and Hansen 1993).

Initial reports suggested that the immature testis was relatively resistant to chemotherapy. More recently, however, it has become apparent that both the prepubertal and pubertal testes are vulnerable to cytotoxic drugs (Ben Arush et al. 2000; Hobbie et al. 2005; Howell and Shalet 1998). Impairment of spermatogenesis may be irreversible in the months to years following chemotherapy. However, late recovery of spermatogenesis up to 14 years following chemotherapy has been reported (Buchanan et al. 1975; Watson et al. 1985). In summary, testicular damage is agent-specific and dose-related. The chance of recovery of spermatogenesis following cytotoxic chemotherapy and the extent and speed of recovery are related to the agent used and the dose received (da Cunha et al. 1984; Howell and Shalet 2001; Pryzant et al. 1993; Watson et al. 1985). In contrast to the germinal epithelium, Leydig cells appear relatively resistant to the effects of chemotherapy (Shalet et al. 1989). However, a few studies have demonstrated a reduction in testosterone concentrations following treatment with gonadotoxic agents, and there is evidence to suggest that the Leydig cell impairment following chemotherapy may be clinically relevant.

4 Clinical Syndromes

The data for gonadal function following fractionated radiotherapy in humans comes from patients with cancers who have been treated with either fields near the testes in which there is scatter dose or diseases such testicular cancers or ALL in which the testes are thought to be at risk of harboring disease and irradiated directly (Fig. 6 and Table 4).

Ash summarized data from several older studies (Hahn et al. 1976; Sandeman 1966; Speiser et al. 1973) that examined testicular function following radiation for patients who were treated for a range of cancers including Hodgkin's disease, prostate cancer, and testicular cancer (Ash 1980). They found that oligospermia occurred at doses as low as 10 cGy and azoospermia at 35 cGy, which was generally reversible. However, 200–300 cGy could result in azoospermia that did not reverse even years after irradiation.

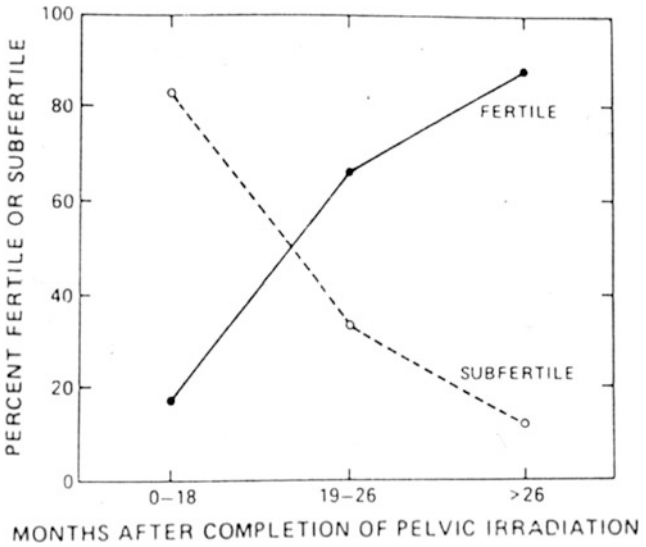

Fig. 6 Recovery of spermatogenesis following pelvic irradiation for Hodgkin's disease (with permission from Pedrick and Hoppe 1986)

A decrease in sperm counts can be seen 3 to 6 weeks after irradiation, and, depending on the dosage, recovery may take 1–3 years (Fig. 6). The germinal epithelium is damaged by much lower dosages (<1 Gy) of radiation than are Leydig cells (20–30 Gy). Complete sterilization may occur with fractionated irradiation above doses of 2–4 Gy.

These results have been supported by other reports. In a study of 17 males treated for Hodgkin's disease who received 6–70 cGy of scatter dose to the testes, in those patients who received <20 cGy, FSH levels stayed within the normal range (Kinsella et al. 1989). Those receiving ≥20 cGy had a dose-dependent increase in serum FSH levels with a maximum difference seen at 6 months following radiation. In all patients the FSH normalized within 12–24 months. Eight patients had normal pretreatment sperm counts. Most of these patients continued to have high sperm counts following irradiation although two developed transient oligospermia with complete recovery of sperm count by 18 months. Four patients, all of whom had received 23 cGy or less, went on to father children. Ortin et al. reported on children treated for Hodgkin's disease (Ortin et al. 1990). Seven boys received pelvic radiation as part of their treatment without any chemotherapy. Three of them fathered children. Three had azoospermia 10–15 years after irradiation, and one had testicular atrophy diagnosed by biopsy a year after irradiation. However, these results are difficult to interpret because there was no measurement or estimate of dose received to the testes in these children.

Similar data exist for patients treated for soft tissue sarcomas (median age at diagnosis 49 years; range 14–67) (Shapiro et al. 1985). These patients were estimated to have received between 1 and 2500 cGy (median dose 80 cGy) of scatter dose to the testes. Patients who received 50 cGy or

Table 4 LENT SOMA toxicity scoring for testicular injury from radiation

	Grade 1	Grade 2	Grade 3	Grade 4
Testes				
Subjective				
Libido	Occasionally suppressed	Intermittently suppressed	Persistently suppressed	
Objective				
Fertility			Oligospermia	Azoospermia
Appearance				Atrophy
Management				
Fertility			In vitro fertilization	Sperm retrieval if previously banked
Libido		Testosterone		
Analytic				
FSH/LH	Increased FSH/nl LH	Increased FSH/increased LH		
Testosterone				Decreased
Spermatoanalysis	Assessment of sperm number, motility and morphology			
Flow cytometric analysis	Assessment of sperm chromatin integrity			
DNA chromatin analysis	Assessment of sperm chromatin integrity			

more to the testes had a greater elevation in FSH than did those who received less than 50 cGy. Only the latter group showed normalization of FSH levels by 12 months whereas in the former, FSH levels remained above baseline as long as 30 months out.

There are also data on germ cell function after treatment for testicular cancer. Hahn et al. examined gonadal function in 14 patients who were irradiated to the paraaortic and ipsilateral pelvic/inguinal lymphatics with a "hockey stick" field following orchiectomy for seminoma (Hahn et al. 1982). The scatter dose to the remaining testicle in these 14 patients ranged from 32 to 114 cGy (median 82 cGy). Ten patients, all of whom received $\geq$70 cGy to the testes, developed azoospermia between 10 and 30 weeks following radiation. All patients except for two had recovery of spermatogenesis, and the recovery time from azoospermia was dose dependent. Centola et al. studying males with seminoma also showed that the recovery time from oligospermia/azoospermia was dose-dependent (Centola et al. 1994).

The previous data includes only patients who received incidental irradiation to the testes; however, there are situations in which children receive direct irradiation to the testes. Sklar et al. examined testicular function in 60 long-term survivors of childhood ALL (Sklar et al. 1990). All the patients had received identical chemotherapy; however, the RT fields varied significantly: (1) craniospinal radiation and 1200 cGy to the abdomen and testes ($n = 11$), (2) craniospinal RT with 1800 or 2400 cGy (estimated gonadal dose 36–360 cGy; $n = 23$) or (3) cranial RT with 1800 or 2400 cGy (negligible testicular dose; $n = 26$). Based on measurements of serum FSH and testicular volume, which commenced at either 12 years of age or 7 years after diagnosis of ALL, gonadal function abnormalities occurred in 55, 17, and 0 % of patients in groups 1, 2, and 3, respectively. Because many of the patients were adolescents at the time of testing, when evaluation of germ cell function can be difficult, this study probably underestimated the incidence of this problem. Castillo et al. (1992) examined 15 boys with ALL given 1200–2400 cGy to the testes prior to puberty (median age 6.8 years; range 5–12 years), either as prophylaxis or for testicular relapse (Castillo et al. 1990). Semen analyses, performed at least 9 years following testicular irradiation, showed azoospermia in seven out of seven cases. Six of these patients had received 1200 cGy and one had received 1500 cGy.

4.1 Detection and Diagnosis (Assessment of Testicular Function)

The male reproductive tract is very susceptible to the toxic effects of chemotherapy and radiation, which may disrupt the endocrine axis or damage the testes directly. Assessment of testicular maturation and function involves pubertal staging, plasma hormone analysis, and semen analysis. Pubertal staging provides clinical information about both of the testicular functions. The development of normal secondary

sexual characteristics would suggest intact Leydig cell function with normal steroidogenesis, while testicular volumes are an important indicator of spermatogenesis. Testicular volume of <12 ml, determined using the Prader orchidometer is strongly suggestive of impaired spermatogenesis.

Hormone analysis involves measurement of plasma FSH, LH and sex steroids. However, in prepubertal children this is an unreliable predictor of gonadal damage since the prepubertal hypothalamic pituitary-testicular axis is quiescent. In post-pubertal boys elevated LH and diminished testosterone levels would indicate Leydig cell dysfunction, while elevated FSH and diminished inhibin B would support germ cell failure. Table 4 shows the LENT-SOMA clinical toxicity scoring system that can be used to categorize and grade testicular late effects.

There has been an interest in estimating the gonadal function of male cancer survivors directly by measuring the serum levels of the bioactive gonadal peptide hormone inhibin B using a newly developed enzyme-linked immunosorbent assay (Andersson et al. 1998). It is postulated that inhibin B is produced by the Sertoli cells and the germ cells of the testes and reflects the degree of seminiferous tubular damage (Jensen et al. 1997; Petersen et al. 1999; Schmiegelow et al. 2001). Furthermore, inhibin B exerts negative feedback regulation of pituitary production and FSH release (de Kretser and McFarlane 1996). In a study examining gonadal status of childhood brain tumor survivors, researchers found a significant inverse correlation between basal FSH and inhibin B, and a significant correlation between inhibin B and total testicular volume (Schmiegelow et al. 2001).

Following pubertal staging and hormone analysis, semen analysis is necessary to confirm spermatogenesis. The sample should be fresh and properly collected. This usually involves abstaining from sexual intercourse for 3–5 days and collecting the specimen by masturbation. Sperm count and quality can provide useful information about the likelihood of natural fertility or whether assisted reproduction may be required. The sperm count should be at least 20×10^6 per ml. Since recovery from damage to germinal epithelium may occur 5–10 years (or even later) after therapy, these counts should be repeated from time to time if such evaluation is indicated.

4.2 Leydig Cell Function Following RT

Leydig cells in the testes are more resistant to radiation than germ cells. In the study cited previously of patients with Hodgkin's disease who received 6–70 cGy of scatter dose to the testes, no patient showed any elevation in LH levels or decrease in testosterone levels (Kinsella et al. 1989). In the study of men treated for sarcomas by Shapiro et al. discussed above (Shapiro et al. 1985), maximal increases in LH levels relative to baseline were seen at 6 months following radiation, but these elevations were statistically significant only in the group that received >200 cGy of scatter irradiation to the testes, not for the groups that received 50–200 or <50 cGy. For those receiving >200 cGy, the elevation in LH levels persisted until the last follow-up, 30 months out. No statistically significant changes in testosterone levels were seen for any of these three dose levels.

Higher doses to the testes result in more marked Leydig cell damage. In one study 18 men who had undergone orchiectomy for a unilateral testicular cancer were subsequently found to have carcinoma in situ for which they received 2000 cGy in ten fractions to the remaining testis (Giwercman et al. 1991). Eight of the men already had evidence of Leydig cell dysfunction even before they received radiation, a finding previously described in patients with testicular cancers (Howell and Shalet 2002; Schilsky 1989; Willemse et al. 1983). There was a statistically significant increase in LH levels and decrease in HCG stimulated testosterone levels over the course of the study.

Petersen et al. followed 48 patients who received 1400–2000 cGy of radiation for carcinoma in situ in a remaining testis following orchiectomy for testicular carcinoma (Petersen et al. 2002). Out of 42 men for whom data was available 18 received hormonal supplementation therapy because of symptoms of androgen insufficiency. All patients had serial hormone analyses and at least one testicular biopsy more than a year after irradiation. 2000 cGy led to a complete eradication of germ cells; however, Sertoli and Leydig cells were still present in the seminiferous tubules and in the intertubular space, respectively.

Data regarding Leydig cell function following radiation comes primarily from studies in boys who received direct testicular irradiation for ALL. In the analysis by Sklar et al. only 1 out of 53 boys tested for gonadotropins had an increased LH levels, and only 2 out of 50 patients tested had a reduced testosterone level (Sklar et al. 1990). None of the boys in this study had received greater than 1200 cGy to the testes. In the study by Castillo et al., out of 15 boys who received testicular radiation, only two showed evidence of Leydig cell failure, both of whom had received 2400 cGy. The remaining 13 boys who had received 1200–1500 cGy to the testes all had normal pubertal development, and normal testosterone levels basally and in response to HCG stimulation. Another study examined 12 boys with ALL who received 2400 cGy of testicular irradiation for either overt disease or prophylaxis (Brauner et al. 1983). Ten of the twelve patients had evidence of impaired Leydig cell function by either low serum testosterone in response to HCG stimulation or elevated LH levels basally and/or after LHRH stimulation. Similarly, Blatt et al. followed seven boys who received 2400 cGy testicular irradiation for

relapsed ALL (Blatt et al. 1985). All seven had elevated FSH levels. Four of these boys had documented bilateral testicular disease, and three of these showed delayed sexual maturation with low testosterone levels.

There are data to suggest that the prepubertal testis is more susceptible to Leydig cell injury that the adult testis. Shalet et al. examined Leydig cell function in three groups of patients: (1) 16 adults who underwent unilateral orchiectomy for testicular teratoma and did not receive postoperative RT, (2) 49 adults who underwent orchiectomy for testicular seminoma and then received radiation during adulthood to the remaining testis (3000 cGy in 20 fractions), and (3) five adults who had received scrotal irradiation (2750–3000 cGy) between the ages of 1 and 4 years for various pediatric malignancies (Shalet et al. 1989). The median LH level was lower in group 1 than in group 2 (6 vs. 16 IU; $p < 0.0001$), an expected result since the former group had not received radiation. However, group 3 patients had far higher LH levels than either group 2 or group 1 20 IU/l in one patient and greater than 32 IU/l in four patients. Similarly, the median testosterone level was lower in group 2 than in group 1 (12.5 vs. 16 nmol/l; $p < 0.02$). However, the median testosterone level in group 3 was 0.7 nmol/l. Four subjects had prepubertal levels (<2.5 nmol/l) and the fifth had a level of 4.5 nmol/l. Other studies have confirmed that a significant proportion of boys with ALL who are prepubertal at the time when they receive 2400 cGy to the testes will develop overt Leydig cells failure and require androgen replacement therapy (Leiper et al. 1986; Shalet et al. 1985).

Based on statistical analysis of the raw data in the studies mentioned above as well as several others, Izard estimated that approximately 20 % of males who receive 100 cGy in fractionated doses to the testes will have an abnormally high LH level while approximately 1200 cGy is required to see an abnormal testosterone level in the same percentage of men (Izard 1995). The estimated doses needed to see these effects in 50 % of men were correspondingly higher 1400 cGy for LH and 3300 cGy for testosterone. Consistent with the high tolerance of the Leydig cells to radiation injury, Sklar reported that two men who received more than 4000 cGy to the testes in late adolescence still maintained normal testosterone levels as adults (Sklar 1999).

5 Radiation Tolerance and Predicting RT-Induced Injury

5.1 Radiation Tolerance

The spermatogenic capacity of the testes can be suppressed by particularly low doses of radiation. As little as 10–20 cGy of scattered radiation in a fractionated regimen

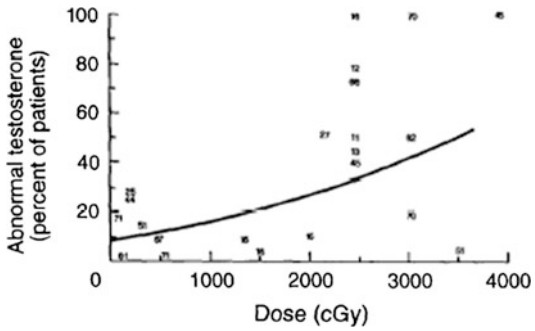

Fig. 7 Dose response for abnormal testosterone levels: This graph shows the percentage of patients with an abnormal testosterone value compared against the stated dose of radiation to the testes based on a review of the literature. A *curve* showing best fit was extrapolated from the values by log-rank regression (with permission from Izard 1995)

can lead to transient oligospermia and elevated FSH levels. Complete loss of sperm production appears to require somewhat higher doses and has been observed following 35 cGy. However, this effect may be transient. Permanent (or at least very long-term) azoospermia has been seen after 140–260 cGy of fractionated scatter radiation. Doses used for testicular ALL which are an order of magnitude larger than these doses (1200–2400 cGy), are expected to lead to permanent azoospermia in virtually all patients (Table 3).

In marked contrast to spermatogenic cells, doses of 70 cGy or less do not result in any increases in LH levels that might be suggestive of subclinical Leydig cell damage. LH elevation can be seen following fractionated regimens delivering 200 cGy to the testes. However, clinically relevant damage (failure of normal pubertal maturation; decreases in testosterone requiring replacement therapy) requires much higher doses, perhaps an order of magnitude greater (Fig. 7). 1200 cGy does not appear to cause loss of pubertal development in most boys who were prepubertal at the time of irradiation. However, this problem will occur in most prepubertal boys given 2400 cGy. The data between 1200 and 2000 cGy are less clear-cut with some studies showing normal sexual maturation in prepubertal boys who received these doses (Castillo et al. 1990; Sarafoglou et al. 1997) but others showing decreases in testosterone levels and subsequent requirement for androgen supplementation in a significant percentage of boys and men treated to these doses (Petersen et al. 2002; Sanders et al. 1986). The reason for the conflicting data regarding Leydig cell function at these intermediate doses probably has to do with the heterogeneity of patients in the various studies with differences in the underlying diseases, which might themselves affect Leydig cell function (i.e., testicular carcinoma, testicular ALL), the age of the patients at the time of irradiation, the use of alkylating agents, especially in transplantation studies, and the frequency and timing of the subsequent laboratory investigations to identify Leydig cell dysfunction

6 Chemotherapy

The extent and reversibility of cytotoxic damage generally depends on the agent and cumulative dose received, although significant individual variation has been observed consistently (Table 5). The effects of alkylating agents on testicular function have been studied extensively (Tables 5 and 6).

Cyclophosphamide, either alone or in combination with other agents, is known to damage the germinal epithelium. Meta-analysis of 30 studies that examined gonadal function following various chemotherapy regimens, noted that gonadal dysfunction correlated with total cumulative dose of cyclophosphamide; more than 300 mg/kg was associated with >80 % risk of gonadal dysfunction (Rivkees and Crawford 1988). Studies of men treated for pediatric solid tumors have reported permanent azoospermia in 90 % of men treated with cyclophosphamide doses >7.5 g/m^2 (Aubier et al. 1989; Kenney et al. 2001; Thomson et al. 2002).

Although tumor cytotoxicity data indicates that 1.1 g/m^2 cyclophosphamide is approximately equivalent to 3.8 g/m^2 ifosfamide (Colvin 1982), the relative gonadotoxic effect is not well known. In a series of male childhood survivors of osteosarcoma who were a median of 9 years from completion of therapy, the incidence of azoospermia related to ifosfamide therapy (median 42 g/m^2) versus no ifosfamide was statistically significant ($P = 0.005$). Fifteen of the 19 azoospermic patients received ifosfamide. Infertility in the others may have been related to cisplatin (560–630 mg/m^2). One patient had oligospermia (Longhi et al. 2003).

Hodgkin's disease (HD) patients treated with six or more courses of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) have also demonstrated permanent azoospermia attributable to both of the alkylating agents; mechlorethamine and procarbazine. Procarbazine appears to play a major role in this process. Hassel et al. studied testicular function after OPA/COMP (vincristine, prednisone, adriamycin/cyclophosphamide, vincristine, methotrexate, prednisone) chemotherapy without procarbazine in boys with HD. These patients showed no major testicular damage compared to boys who had received OPPA/COPP (includes procarbazine). Again pointing out that procarbazine is a potent gonadotoxic agent (Hassel et al. 1991). Treatment of Hodgkin's disease with combination chemotherapy regimens such as ChlVPP (chlorambucil, vinblastine, procarbazine and prednisolone) or COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) have also been reported in a number of studies to result in permanent azoospermia in 99–100 % of patients treated with 6–8 courses of these regimens (Charak et al. 1990; Mackie et al. 1996), after ChlVPP, FSH and LH were elevated in 89 and 24 %, respectively, with azoospermia in all seven patients tested. Charak et al. found azoospermia in all 92 patients following treatment with six or more cycles of COPP; 17 % of patients had been treated more than 10 years previously, suggesting that germinal epithelial failure is likely to be permanent (Charak et al. 1990). CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP-like regimens such as are used for non-Hodgkin's lymphoma (NHL) are generally less gonadotoxic than those used for HD, presumably due to the absence of procarbazine in the treatment for NHL (e.g. VAPEC-B, VACOP-B, MACOP) (Muller and Stahel 1993; Radford et al. 1994). Azoospermia occurring on therapy for NHL is likely to recover within the following year (Pryzant et al. 1993). Efforts to reduce the risk of sterility after Hodgkin disease include the use of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine – an effective combination that does not contain the alkylating agents chlorambucil or procarbazine) (Kulkarni et al. 1997; Viviani et al. 1985) and other related regimens. Viviani et al. showed that while recovery of spermatogenesis after MOPP was rare, all who experienced oligospermia after ABVD recovered completely by 18 months. (Viviani et al. 1985). Hybrid regimens (i.e., alternating cycles of ABVD with ChlVPP or MOPP) are also less gonadotoxic than MOPP, ChlVPP, or COPP given alone (Table 6).

Nitrosureas, used in the treatment of brain tumors in childhood, may also cause gonadal damage in boys (Ahmed et al. 1983; Livesey and Brook 1988; Schmiegelow et al. 2001). In nine children treated for medulloblastoma with craniospinal radiation and a nitrosurea (carmustine or lomustine plus vincristine in four and procarbazine in three) there was clinical and biochemical evidence of gonadal damage. Specifically, these children presented with elevated serum FSH and small testes for the stage of pubertal development (compared with eight children similarly treated but without

Table 5 Gonadotoxic chemotherapeutic agents

Alkylating agents
Cyclophosphamide
Ifosfamide
Nitrosoureas, e.g. BCNU and CCNU
Chlorambucil
Melphalan
Busulfan
Procarbazine
Vinca-Alkaloids
Vinblastine
Antimetabolites
Cytarabine
Other
Cisplatin

Table 6 Fertility in adult men following various chemotherapy regimens

Fertility in adult men following chemotherapy for treatment of maligancies	
Diagnosis and treatment	Fertility posttreatment
Hodgkin disease	
MOPP	Azoospermia in >90 %
COPP	Azoospermia in >90 %
ABVD	Temporary azoospermia with normal sperm count in all at 18 months
Non-Hodgkin lymphoma	
CHOP	Permanent azoospermia in ~30 %
VACOP-B	Normospermia in >95 %
VEEP	Normospermia in >95 %
Bone marrow transplant for a variety of malignancies	
Cyclophosphamide alone	FSH raised in 40 %
High-dose melphalan	FSH raised in 95 %
BEAM	FSH raised in 95 %
Testicular cancer	
Cisplatin/ carboplatin	Normospermia in 50 % at 2 year based therapy and 80 % at 5 year

ABVD doxorubicin hydrochloride, bleomycin, vinblastine, and dacarbazine; *BEAM* carmustine, etoposide, Ara-C, and melphalan; *CHOP* cyclophosphamide, vincristine, procarbazine, and prednisolone; *FSH* follicle-stimulating hormone; *MOPP* mustine, vincristine, doxorubicin, procarbazine, and prednisolone; *VACOP-B* vinblastine, doxorubicin, prednisolone, vincristine, cyclophosphamide, and bleomycin; *VEEP* vincristine, etoposide, epirubicin, and prednisolone. Adapted from Meistrich et al. (2005)

chemotherapy). The authors concluded that nitrosureas were responsible for the gonadal damage, with procarbazine also contributing in the three children who received this drug.

PVB (cisplatin, vinblastine, and bleomycin) is standard chemotherapy with minimal effects on long-term testicular function that is used in patients with germ cell tumors. Such patients however, can be affected by ejaculatory failure caused by damage to the thoracolumbar sympathetic plexus during retroperitoneal lymph node dissection and by preexisting germ cell defects. Hansen et al. found that for patients treated with either orchiectomy or orchiectomy plus PVB, sperm production was similar 1.5 years after treatment. Approximately half in each group had sperm counts below the normal control reference level (Hansen et al. 1989). Lampe et al. analyzed data on 170 patients with testicular germ cell cancers who underwent treatment with either cisplatin or carboplatin based chemotherapy (Lampe et al. 1997). A median of 30 months after completion of chemotherapy, 54 (32 %) were azoospermic and 43 (25 %) were oligospermic. The probability of recovery to a normal sperm count was higher in men: (a) with a normal pretreatment sperm count, (b) men who received carboplatin rather than cisplatin-based therapy, and (c) men treated with less than 5 cycles of chemotherapy. Recovery continued for more than 2 years, with the calculated chance of spermatogenesis at 2 years being 48 %, and a calculated chance of spermatogenesis at 5 years being 80 % (Lampe et al. 1997; Howell and Shalet 2001).

Heyn et al. described the late effects of therapy on testicular function in patients 10 months to 19 years of age with paratesticular rhabdomyosarcoma as a result of cyclophosphamide, radiation, and retroperitoneal lymph node dissection. Eight had loss of normal ejaculatory function. Elevated FSH values and/or azoospermia occurred in greater than half the patients where data was available. Testicular size was decreased in those who received cyclophosphamide or testicular irradiation (Heyn et al. 1992).

The importance of alkylating agents in the induction of gonadal toxicity is noted by contrasting the above outcomes to those of children with ALL. In general, testicular function is normal in boys after chemotherapy for ALL. All 37 survivors of childhood ALL evaluated at two time points after the completion of treatment (median age 9.7 years and again 18.6 years later) completed pubertal development normally and had a testosterone concentration within the normal adult range (Wallace et al. 1991). Six men showed evidence of severe damage to the germ epithelium with azoospermia or elevated FSH; all of these patients had received cyclophosphamide as part of their chemotherapy regimen (Wallace et al. 1991). In contrast to alkylating agents, the classic antimetabolites used in the treatment of childhood ALL are not associated with long term gonadal toxicity. Both vincristine and corticosteroids can cause immediate inhibition of spermatogenesis, however following the cessation of these agents, spermatogenesis recovery occurs (Kreuser et al. 1988).

6.1 Treatment-Induced Leydig Cell Failure from Chemotherapy

Leydig cells are much less vulnerable to damage from cancer therapy than germ cells, likely due to their slow rate of turnover (Shalet et al. 1989). For example, chemotherapy induced Leydig cell failure resulting in androgen insufficiency and requiring testosterone-replacement therapy is rare. However, studies suggest that Leydig cell dysfunction may be observed following treatment with alkylator-based regiments. Specifically, raised plasma concentrations of LH combined with low levels of testosterone are the hallmarks of Leydig cell dysfunction. When Leydig cell dysfunction occurs prior to or during puberty, affected individuals will experience delayed and/or arrested pubertal maturation and lack of secondary sexual characteristics (Sklar 1999). If the insult follows completion of normal pubertal development,

observed symptoms include loss of libido, erectile dysfunction, decreased bone density, and decreased muscle mass (Sklar 1999). Measurements of testosterone and gonadotropin concentrations are therefore warranted following chemotherapy treatment. Males with a raised LH concentration in the presence of a low testosterone levels should be considered for androgen replacement therapy.

7 Special Topics

7.1 Testicular Function Following Total Body Irradiation

There are data on germ cell function following TBI as part of transplant conditioning. Sarafoglou et al. followed 17 boys who had received cyclophosphamide and TBI (either 1375 or 1500 cGy in 125 cGy tid fractionation) prior to puberty as part of a transplantation regimen for leukemia (Sarafoglou et al. 1997). Fourteen of seventeen patients (82 %) entered puberty spontaneously, with 13 having normal testosterone levels. Of the three that did not enter puberty spontaneously, one had received a 1200 cGy testicular boost in addition to the TBI, and in the remaining two, the levels of FH and LH were very low, consistent with a prepubertal state.

Couto-Silva et al. (2001) followed 29 boys who received TBI for different malignancies in association with a variety of chemotherapy regimens (Couto-Silva et al. 2001). The TBI was given as a single 1000 cGy fraction in twelve patients and in 200 cGy × 6 fractions (1200 cGy) in 17 patients. At the last follow-up 19/29 (66 %) had tubular failure associated with elevated FSH. Eight (28 %) also had Leydig cell failure. There was no relationship between the age at BMT and serum FSH, LH, or testosterone levels.

Bakker et al. followed 25 boys who were prepubertal at the time of bone marrow transplantation for hematological malignancy (Bakker et al. 2000). Transplantation included cyclophosphamide and TBI (single doses of 500, 750, or 800 or 1200 cGy in six fractions). Nineteen boys who had not received additional testicular boost as part of their treatment all underwent puberty normally and achieved normal adult testosterone levels at some point following the onset of puberty. However, episodic elevations of LH were seen in ten of the patients, and in five patients these elevations were accompanied by decreased testosterone. Elevation of FSH was seen in all patients.

These reports and others (Leiper et al. 1987; Ogilvy-Stuart et al. 1992) indicate that most boys who receive TBI, either single-dose or fractionated as part of a transplantation regimen, will proceed through puberty and have normal testosterone levels.

8 Prevention and Management

8.1 Prevention of Testicular Damage

The cytotoxic effect of chemotherapy on germinal epithelia function launched a search for possible fertility preservation strategies in men undergoing therapy. Cryopreservation of sperm has become standard practice, and should be offered to all newly diagnosed postpubertal males at risk for potential infertility (Ginsberg et al. 2008). Many improvements have been made in the techniques used to store sperm and advances in assisted reproductive technology using intracytoplasmic sperm injection (ICSI) has increased the chance of successful pregnancies using banked sperm (Muller et al. 2000; Palermo et al. 1995; Pfeifer and Coutifaris 1999).

Ejaculatory azoospermia is not the same as testicular azoospermia (Chan et al. 2001). Therefore, studies on the gonadotoxicity of chemotherapy have to be interpreted in the era of assisted reproductive technology in which it is possible to use testis sperm to conceive. The level of sperm necessary for sperm to exist in the testis is far less than that required for sperm in the ejaculate (Chan et al. 2001). Therefore with testis sperm extraction (TESE), followed by ICSI it is now possible for patients who did not sperm bank, and have azoospermia on semen analysis, to be evaluated for TESE/ICSI. A retrospective study by Damani et al. evaluated 23 men with ejaculatory azoospermia and a history of chemotherapy. They underwent TESE in search of usable sperm. Spermatozoa were found on TESE in 15 (65 %) of 23 men. The subsequent fertility rate was 65 % and pregnancy occurred in 31 % of cycles (Damani et al. 2002). Men with post-chemotherapy azoospermia must be fully evaluated before they are considered sterile.

Unfortunately, at this time there are only experimental options for prepubertal male patients. The presence of spermatogonial stem cells in the testis offers a possibility for preservation and restoration of fertility. Scientists have developed the ability to reinject germ cells into rodents and restore spermatogenesis (Brinster 2002, 2007; Brinster and Zimmermann 1994; Orwig and Schlatt 2005). At this time, the science of expanding the spermatogonial stem cells needs to be achieved in humans before this becomes a viable opportunity. There has been no demonstrated protective effect of using GnRH analogues with and without testosterone to suppress testicular function during chemotherapy (Johnson et al. 1985; Ortin et al. 1990; Waxman et al. 1987). As pediatric oncologists, we must continue to attempt to reduce the gonadotoxicity of our treatment regimens while maintaining superior cure rates.

8.2 Method to Minimize Testicular Radiation Dose

As discussed above, in most cases, the testicular dose from a radiation treatment is mostly due to scatter, not direct irradiation. Scatter is difficult to prevent, but methods have been developed to decrease this dose. Frass et al. reported on a gonadal shield that formed a cup around the testes to reduce the testicular dose (Fraass et al. 1985; Shapiro et al. 1985). They found that this led to a 3- to 10-fold reduction in the dose to the testes, depending on the distance from the proximal edge of the field. In almost all cases, the measured dose to the testes was less than 1 % of the prescription dose.

Modern treatment planning and delivery techniques, particularly intensity modulated radiation therapy (IMRT), can significantly reduce dose to normal tissues outside the irradiated treatment fields (Group 2001). Several studies have shown that using IMRT for anal cancer substantially reduces dose to organs at risk, especially the external genitalia (Lin and Ben-Josef 2007; Milano et al. 2005). In children, Koshy et al. (2004) have shown that for patients whose treatment site was in the abdomen or pelvis, IMRT reduced the median dose to the testis to 159 mSv compared to 434 mSv for patients receiving conventional radiation therapy. However, there were too few patients for statistical analysis of this difference.

9 Future Direction and Research

As more and more pediatric cancer survivors are entering their reproductive years, fertility issues have become an increasingly important quality of life concern. Oncologists and reproductive endocrinologists need to be aware of the effects both chemotherapy and radiotherapy have on the testes. Furthermore, patients should be counseled as to their risks and fertility preservation options should be presented.

10 Review of Literature and Landmarks

1906 Bergonie and Tribondeau: Made fundamental observation on differential effect of radiation on the skin of the scrotum versus spermatogonia, leading to so-called “law of radiosensitivity”.

1906 Regaud and Blanc: Showed that X-ray sterilization of the testes is not associated with castration changes in the accessory reproductive organs or secondary sexual characteristics.

1947 Glucksmann: Discussed the effects of radiation on reproductive organs, stating that 500–600 R will give permanent sterility.

1952 Oakes and Lushbaugh: Documented a case of temporary radiation sterility in a man followed with serial studies for three years.

1957 Casarett and Casarett: Presented their histologic investigations of the mechanisms of X-ray effects on spermatogenesis in the rat.

1965 Zuckerman: Presented a critical review of experimental and clinical data on the sensitivity of the gonads to radiation.

1968 Rubin and Casarett: Comprehensive review of the experimental and clinical data and presentation of physiopathology.

1995 Rubin and Constine: Presented a grading system for testes as LENT SOMA.

2003 Truth and Rubin: Common Toxicity Criteria for Male Testes, Sex Organs V 3.0 includes both radiation and chemotherapy effects.

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Ovary, Uterus (Fallopian Tube, Cervix), Vagina, and Vulva

Ann H. Klopp and Patricia J. Eifel

Contents

Abstract

- *Introduction* The female genital organs-the ovaries, uterus, vagina, and vulva-differ from one another in their sensitivity to radiation and the time course over which radiation-related adverse effects develop. It is critical for physicians prescribing radiation to the female pelvis to understand the somewhat complex interactions between these organs and the age-dependent nature of their responses.
- *Ovary* The risk of ovarian failure causing infertility and premature menopause increase with dose and age. Relatively-low doses of RT (<10 Gy in young women and <4 Gy in women in their 30's) can result in ovarian failure. At doses >20 Gy, ovarian failure occurs in >75 % of patients.
- *Uterus* Uterine irradiation can reduce the ability to achieve or sustain pregnancy increasing the rate of spontaneous abortion.
- *Vagina* The vaginal mucosa is frequently treated to high doses of radiation. This often leads to vaginal atrophy, dryness and shortening, that can all negatively affect sexual function. More severe complications, such as necrosis, ulceration, and fistula are fortunately rare.
- *Vulva* Long-term adverse effects frequently include atrophy, edema, telangiectases, loss of skin pigmentation, and loss of sweat and sebaceous gland function.

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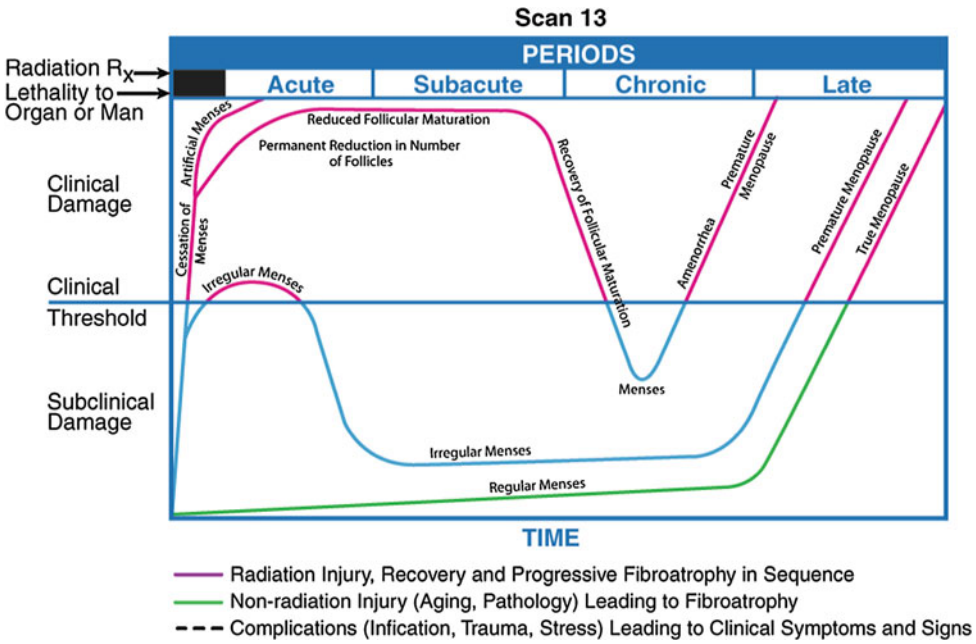


Fig. 1 Biocontinuum of adverse and late effects for the female reproductive system (with permission from Rubin and Casarett 1968)

1 Introduction

The long history of treatment of cervical cancer with high doses of radiation has led to an appreciation of the adverse effects of radiation on the gynecologic tract. The female genital organs—the ovaries, uterus, vagina, and vulva—differ from one another in their sensitivity to radiation and the time course over which radiation-related adverse effects develop. For example, the ovaries are the most sensitive gynecologic organs to radiation, but radiation-induced ovarian failure may take years to develop. By contrast, desquamation of the vulva due to radiation develops in the first few weeks of radiation treatment Fig. 1.

The uterus and vagina are not required for daily living but are needed intermittently for reproduction and sexual activity. As a result, there is a conception that the gynecologic organs are tolerant of radiation. In fact, it is more accurate to state that loss of uterine or vaginal function is an accepted consequence of radiation therapy. In fact, the limiting adverse effect for the treatment of gynecologic cancer is generally not an effect on the target organ, as for many cancers, but instead it has effects due to effects on the adjacent critical organs, the bowel and the bladder. Most women accept the loss of childbearing potential resulting from pelvic irradiation—either because they have completed childbearing, or because effective treatment of malignancy requires it. The impact of irradiation of gynecologic organs on sexual functioning can be difficult to quantitate and is often multifactorial. Recent development of validated questionnaires has led to a better assessment of these adverse effects.

The most common adverse effects of pelvic irradiation for gynecologic cancer are gastrointestinal and genitourinary. Most women (approximately 70–80 %) experience diarrhea and dysuria during radiation treatment; these adverse effects are generally grade 1 or 2 and can be managed readily with medications (Vaz et al. 2008). Acute gynecologic adverse effects of pelvic irradiation are less common than gastrointestinal and genitourinary effects (except in the case of vulvar irradiation, which as previously mentioned produces desquamation of the vulva in the first few weeks of radiation treatment). However, pelvic irradiation can produce long-term gynecologic adverse effects that can significantly reduce patients' quality of life. Recent studies have shed light on the long-term impact of radiation therapy on the function of the gynecologic tract. These studies have more clearly defined the impact of radiation-related adverse effects on the quality of women's lives with regard to changes in body image and sexual functioning (Vaz et al. 2008; Bruner et al. 1993; Jensen et al. 2003; Frumovitz et al. 2005; Park et al. 2007).

The side effects of radiation therapy for gynecologic malignancies can be difficult to separate from complications of the cancer itself or complications of other modalities of cancer treatment, such as surgery and chemotherapy. For example, vaginal dryness can be caused by both ovarian failure and vaginal irradiation. A superimposed yeast infection can be mistaken for skin reaction following vulvar irradiation. And sexual dysfunction in patients treated with a radical hysterectomy and radiation therapy is likely to be multifactorial.

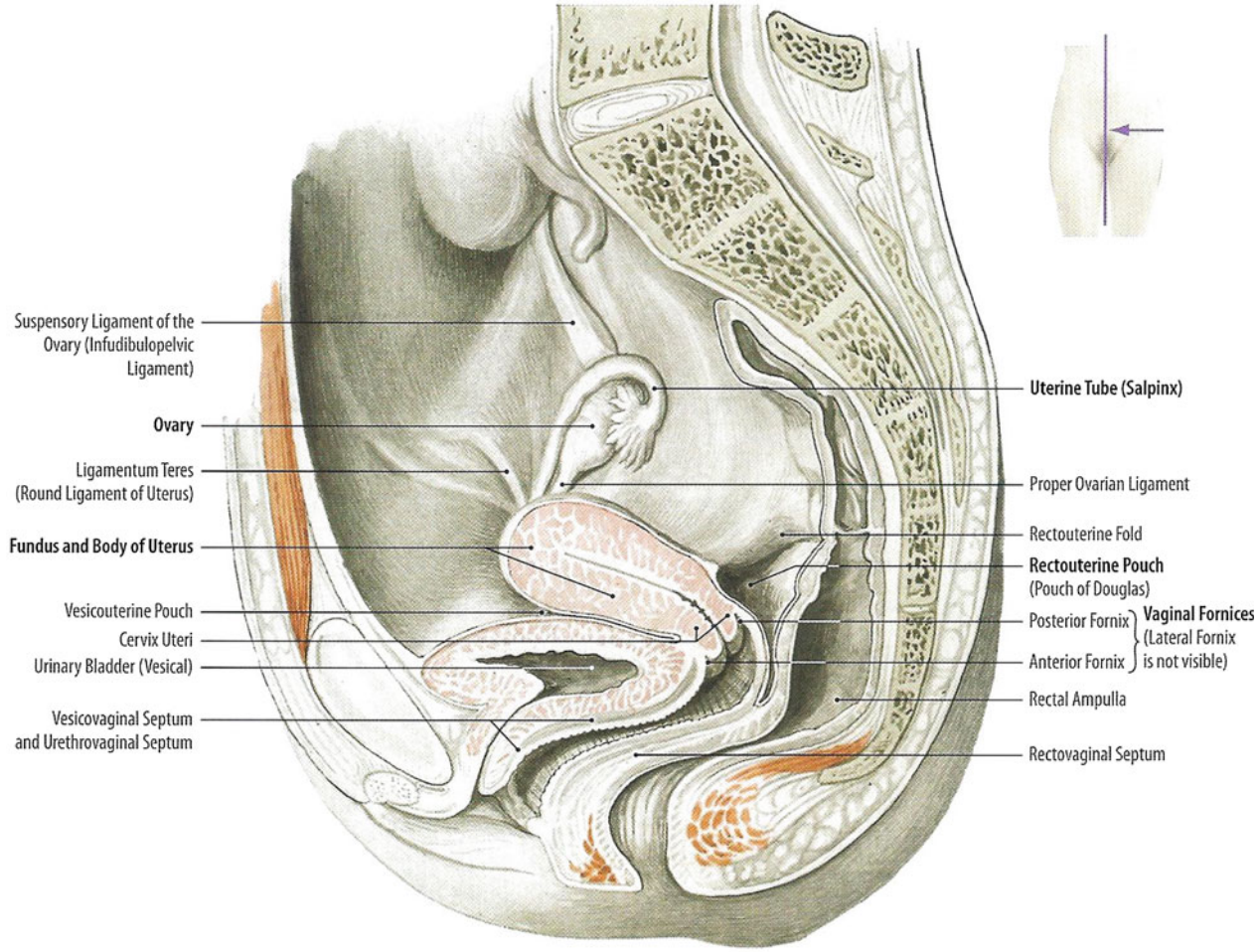


Fig. 2 Anatomy: Pelvic organs of the woman: Median sagittal section, medial view of the right cut surface (with permission from Tillman 2007)

Much of the information available on toxicity to the gynecologic organs comes from the treatment of women with cervical cancer, because of the need to treat to high doses for definitive treatment. Furthermore, because of the high rate of success of radiation therapy for cervical cancer and the fact that many patients with cervical cancer are young, women who develop toxicity to the gynecologic tract may suffer for years from radiation-related adverse effects. As a result, understanding and minimizing radiation damage to the gynecologic tract is of particular importance.

Figure 1 illustrates the Biocontinuum of adverse and late effects of the ovary.

2 Anatomy

2.1 Ovary

The ovaries are approximately 3 cm long, 1.5 cm wide, and 1 cm thick and lie lateral to the uterus near the pelvic wall in the ovarian fossa. They lie anterior to the ureter and internal iliac artery. Each ovary is attached to the uterus via the ovarian ligament and is surrounded by the infundibulum of the fallopian tube superiorly and laterally (Fig. 2).

2.2 Uterus

The uterus is a flexible organ that has evolved to expand to accommodate a growing fetus. The uterus lies in the midline of the pelvis, posterior to the bladder, and anterior to the rectum. It is attached to the pelvis by two ligaments; the broad ligaments, which stretch with expansion of the pregnant uterus, and the uterosacral ligaments that attach the posterior cervix to the pelvic sacrum. The cardinal ligaments attach the lateral aspects of the cervix to the ischial spines.

2.3 Cervix

The cervix is cylindrical or conical and projects into the vagina. The areas around the cervix within the vagina are referred to as the vaginal fornices. There are two lateral

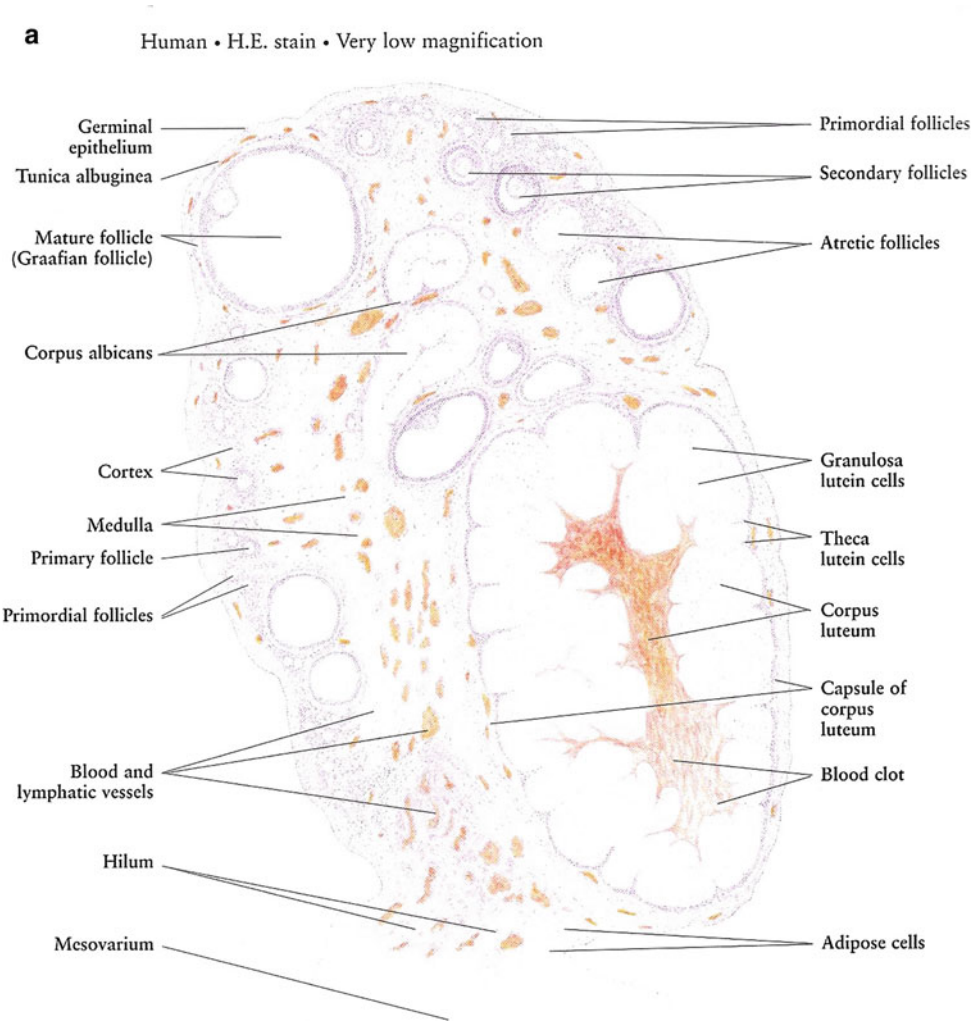


Fig. 3 Histology: **a** Ovary **b** Growth of Ovarian follicles **c** Uterus **d** Uterine cervix **e** Vagina **f** Vagina mucosa (with permission from Zhang 1999)

fornices anterior and posterior fornices. The posterior fornix is deeper than the anterior fornix as the vaginal wall is longer posteriorly than anteriorly.

2.4 Vagina and Vulva

The vagina is a flexible muscular tube extending from the cervix to the vestibule that has evolved to permit passage of the fetus through the vaginal canal and coitus. The vestibule is enclosed by the inner labia, the labia minora. The labia minora meet anteriorly at the clitoris and posteriorly form the fourchette. The most external portion of the vulva, forming the mons pubis, is the labia majora.

3 Histology and the Functional Subunit

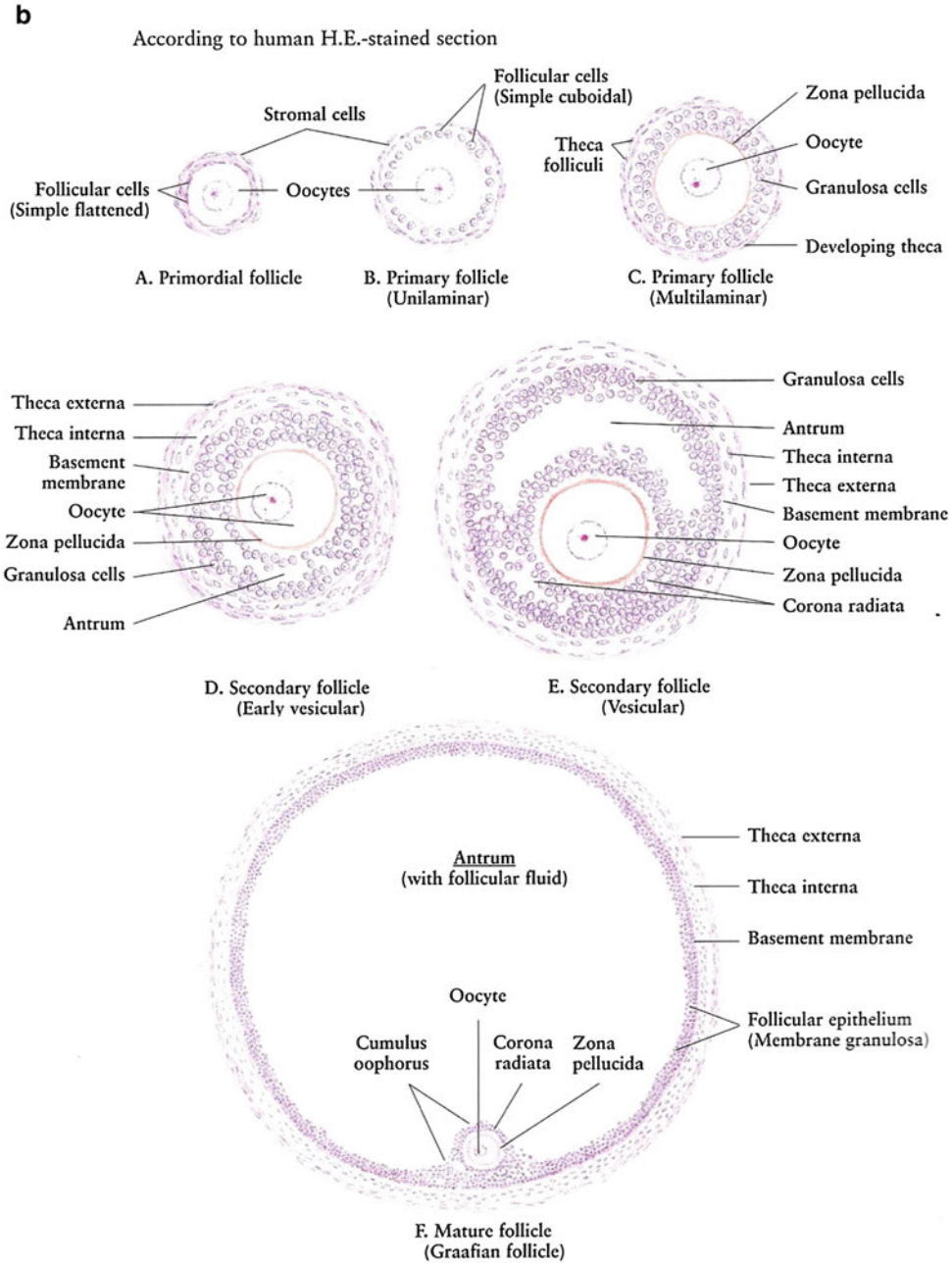
3.1 Ovary

Prior to menarche, the ovaries comprised of the primordial follicles, containing the oocytes, surrounded by a single layer of granulosa cells within the ovarian stroma. The oocytes are dependent on estrogen and other growth factors secreted by the granulosa cells for maturation through the process of folliculogenesis. During folliculogenesis, the granulosa cells proliferate, forming Graafian follicles. The granulosa cells secrete estrogen, which is aromatized from androgens secreted by the theca interna, a luteinizing hormone-responsive stromal cell that surrounds the granulosa cells in the developing follicles. The process of folliculogenesis, or oocyte maturation, begins at menarche and then occurs continually over 13 menstrual cycles, so that the ovary of a fertile woman will contain follicles in all phases of development. These follicles decrease from approximately 500,000 at menarche to 25,000 at the age of 37 (Fig. 3a, b).

3.2 Uterus

The innermost layer of the uterus, the endometrium, is comprised of columnar gland-forming cells. The muscular myometrium is comprised of randomly interlocking smooth muscle fibers. The peritoneum covers the fundus of the

Fig. 3 (continued)



uterus, forming an outer serosal coat that extends laterally in the broad ligaments (Fig. 3c).

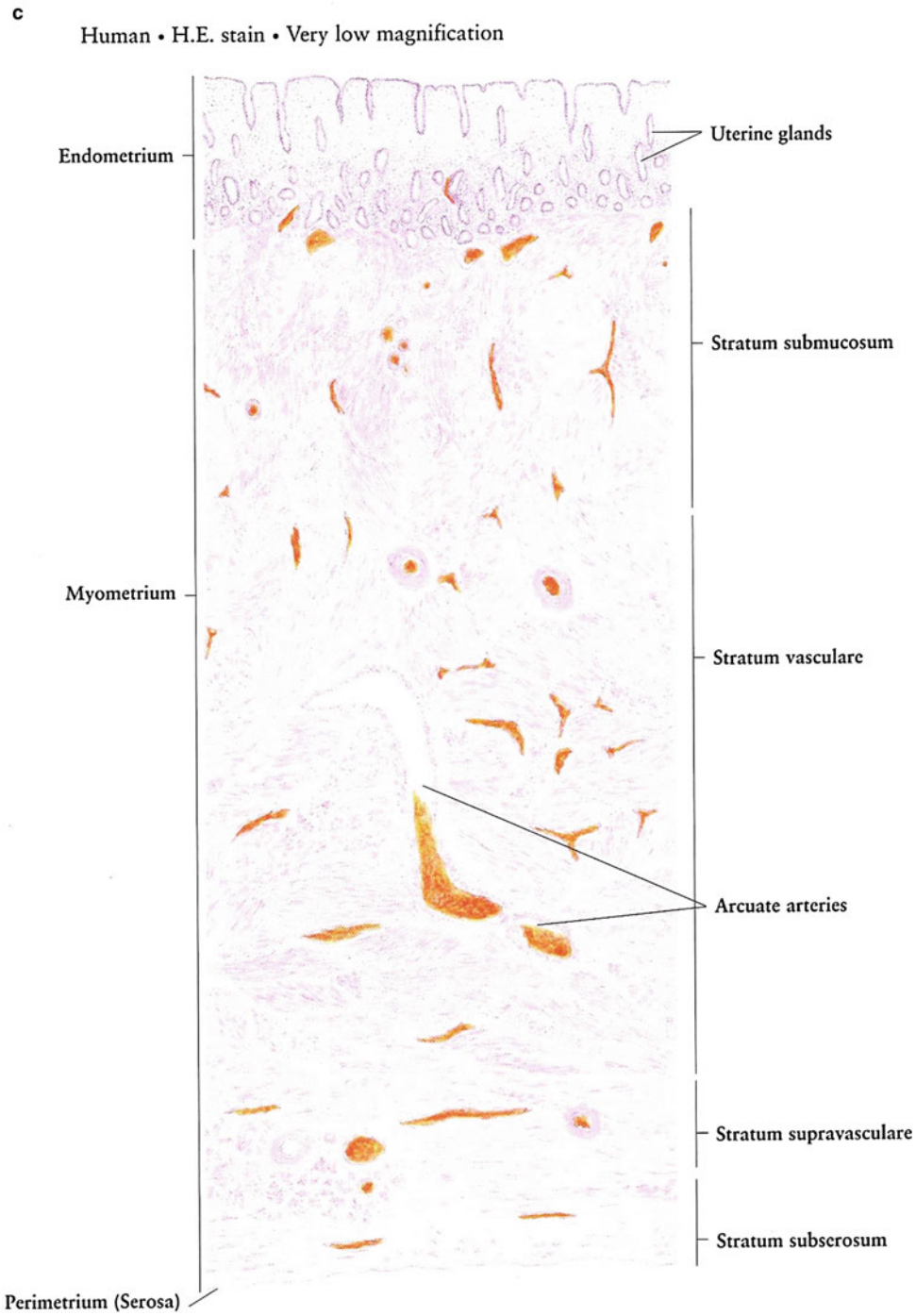
3.3 Cervix

The inner surface of the cervix is lined with columnar epithelium, whereas the outer surface is lined with squamous epithelium (Fig. 3d, e).

3.4 The Vagina and Vulva

The vagina and vulva are lined with stratified squamous epithelium, keratinized in the vulva, which overlies connective tissue containing elastic fibers, mucus-forming glands, sweat glands, and sebaceous glands. The glands are required for vaginal lubrication, which is necessary for coitus (Fig. 3f).

Fig. 3 (continued)



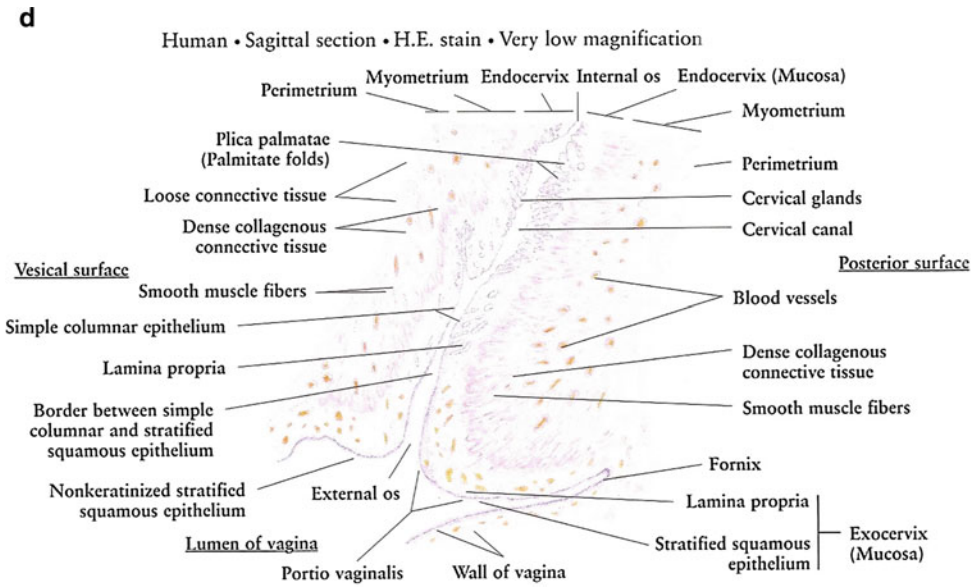
4 Physiology

The principle functions of the system include: (1) production of female gametes, the ova, by a process of oogenesis; (2) reception of male gametes, the spermatozoa; (3) provision of a suitable environment for fertilization of ova by spermatozoa and for development of the fetus; (4) a mechanism for the expulsion of the developed fetus to the external environment (Zhang 1999).

4.1 Ovary

Ovaries are responsible for the production of oocytes and the synthesis of the hormones estrogen and progesterone. These hormones promote development of the ovarian follicles and the development of the uterine endometrium, respectively (Zhang 1999).

Fig. 3 (continued)



4.2 Uterus

In humans, the endometrium undergoes hormonally modulated alterations, known as the menstrual cycle, which is usually of 28 days duration. The uterus provides a suitable environment for implantation of the fertilized ovum and development of the embryo and fetus during pregnancy (Zhang 1999).

4.3 Vagina

Vagina is an expansible fibromuscular tube. It is specialized for the reception of the penis during copulation and the passage of the fetus to the external environment (Zhang 1999).

5 Pathophysiology

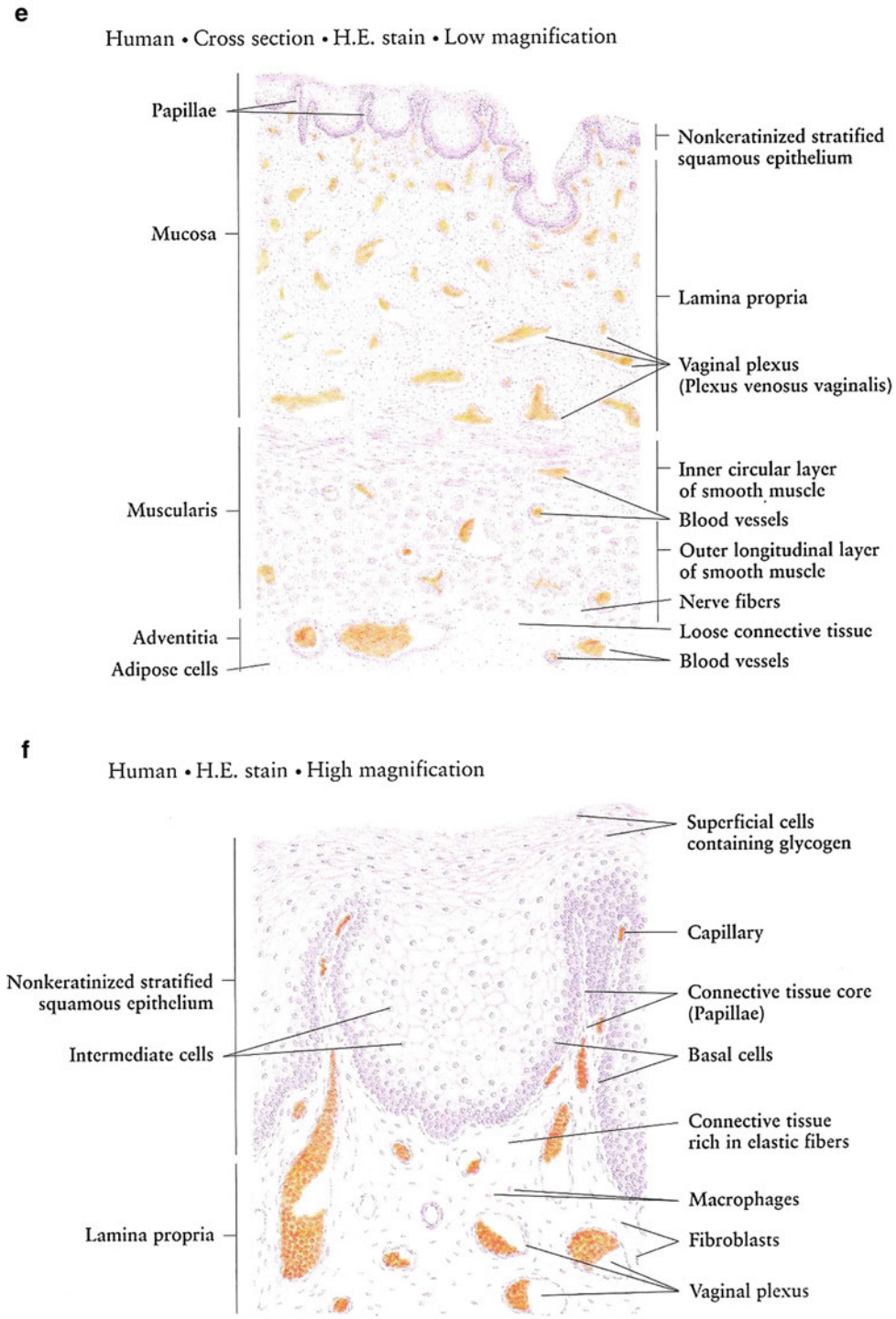
5.1 Ovary

The rapidly proliferating granulosa cells in ovaries are radiosensitive (more so than the oocytes), and within hours of irradiation, the granulosa cells show morphologic changes such as pyknosis, degenerative changes, and early necrosis. The granulosa cells secrete paracrine factors—including estrogen, which is required by the oocytes for maturation. As a result, the risk of infertility is closely tied to the risk of premature menopause in women and children exposed to ovarian irradiation. The granulosa cells are dividing most rapidly during the mid-portion folliculogenesis and are most sensitive to radiation at this time (Grigsby et al. 1995). As a result, the toxicity of ovarian radiation, which includes both menopause due to loss of estrogen secretion and infertility, due to loss of functional oocytes, is due to damage to the radiation sensitive estrogen secreting granulosa cells.(Grigsby et al. 1995). The primordial follicles are arrested in meiosis and are relatively radiation resistant. Of note, it is possible for fertility to be temporarily preserved following radiation therapy owing to the survival of *developed* oocytes, which are not dependent on granulosa cell proliferation for their survival (Fig. 4a).

Generalized acute changes from irradiation of the ovary include endothelial cell swelling and microvascular thrombi. Years after radiation therapy, the ovaries appear grossly contracted and fibrotic, similar to postmenopausal atrophic ovaries; microscopically, the ovaries lack follicles and have thick-walled hyalinized arterioles and venules with a fibrotic collagenous cortex (Fajardo and Berthrong 1978; Cole 1964; Fajardo 2001) (Fig. 4a).

Some may consider the radiation response of the ovary to be paradoxical in that the radiation dose needed to produce sterility is higher for children (>2000 cGy) than for adults (≤600 cGy) (for many other endpoints children are *more* sensitive to the effects of radiation than are adults). The adult approaching menopause requires a smaller dose with age because the total number of oogonia is progressively reduced. The ovum germ cells epithelium the oogonia cease after birth and ovaries contain a limited number (0.5×10) which progressively reduce with time after the onset of puberty. The number of oogonia decreases monthly with the onset of ovulation and sex activity. In ovogenesis, the proliferating oogonia found in fetal life are very radiosensitive as vegetative and differentiating intermitotic cells. Once oogonia undergo meiosis, these secondary oocytes are relatively radioresistant. With the onset of menopause, involution occurs (Halperin et al. 2010).

Fig. 3 (continued)



5.2 Uterus/Cervix

Radiation therapy delivered to the uterus can result in loss of the ability to achieve or sustain pregnancy, but the uterus is not generally a dose-limiting structure for the treatment of gynecologic cancer. Microscopically, after irradiation of the uterus, mild cell and stroma atrophy, occasional atypia, and rare nuclear fragmentation may be observed. Regions of the endometrium that are in direct contact with intracavitary sources may develop late changes such as ulceration and fibrinopurulent necrosis. In endometrial gland cells that have received high doses of radiation, histologic changes include pseudopapillary hyperplasia, microcystic degeneration, nuclear atypia, and vacuolar degeneration. Muscle cells

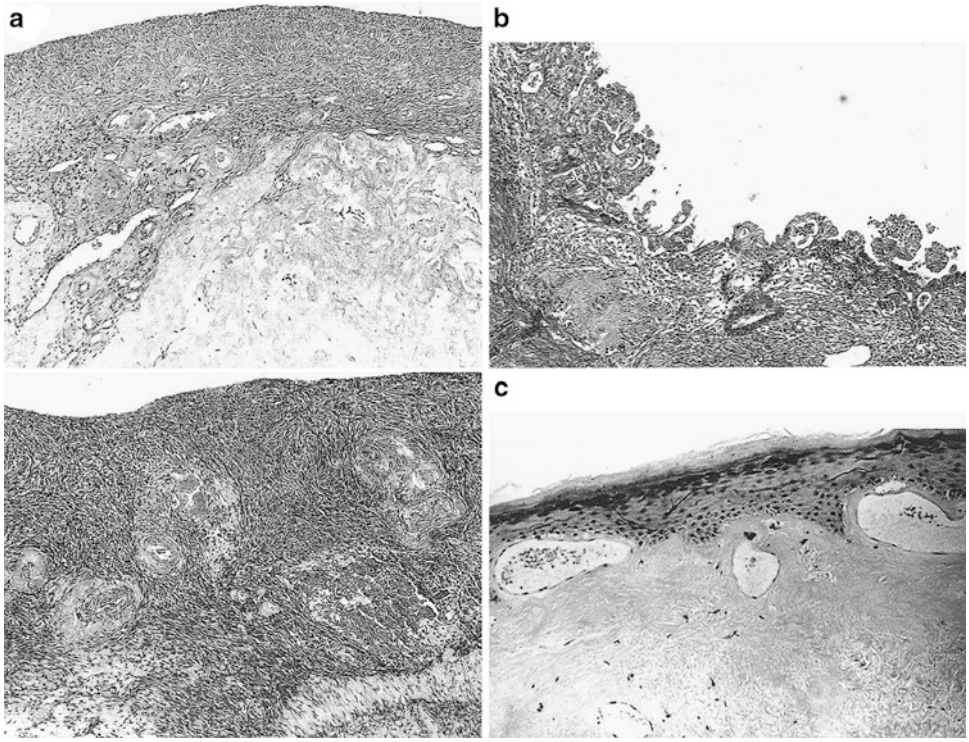


Fig. 4 **a** Atrophic ovary: cortical atrophy and hyaline fibrosis of the hilum are severe in the irradiated ovary are shown above. Normal Ovary shown below. **b** Photomicrograph of endometrium 6 weeks postradiation shows pseudopapillary and atypical hyperplasia. The nuclei are occasionally hyperchromatic and enlarged, and microcystic abnormalities are present. The endometrial stroma shows hyaline sclerosis. **c** This photomicrograph shows a characteristic postradiation injury of the cervix with hyperkeratosis, mild atypical squamous epithelial changes, subepithelial telandiectasias, and amorphous hyaline fibrosis of the submucosa. (Reproduced from Fajardo Pathology of Radiation Injury, Masson Publishing, USA, NY, 1982, with permission.)

within the myometrium may be swollen, granular, and pale; dense collagen scar with atypical fibroblasts and rare glands with atypical nuclei will be found in these areas after healing (Fajardo 2001). In young women who have received uterine irradiation, the uterus will appear similar to a postmenopausal uterus: grossly shrunken, with an atrophic endometrium and cervix. In the long term, the uterus will become shrunken and firm, and the cervix becomes atrophic, especially in older women or women treated to a higher dose. Histologically, the endometrium may exhibit atypical hyperplasia with hyaline sclerosis in endometrial stroma (Figure 4b). The cervix develops atypia in squamous epithelia with hyaline fibrosis of the submucosa after radiation (Figure 4c).

5.3 Vagina

In radiation therapy for primary cervical or vaginal cancers, the vaginal mucosa is frequently treated to high doses. Early changes after irradiation include endothelial cell injury in the lamina propria and adventitia with edema and smooth muscle necrosis. Longer term changes include extensive fibrosis with loss of muscle and elastic tissue in high-dose areas. Stenosis and vaginal shortening may occur. Fistulas to the urethra, rectum, and bladder develop rarely (Abitbol and Davenport 1974; Perez et al. 1988).

5.4 Vulva

When the vulva is irradiated, erythema, and edema occur during radiation therapy and in the weeks that follow. Dry desquamation may develop owing to loss of the cells in the germinal basal layer of the epidermis. Moist desquamation then develops as a result of progressive edema and an inflammatory cell response. Death of basal epithelial cells and damage to endothelial cells with microvascular occlusions may lead to ischemia and necrosis. Long-term changes after irradiation include loss of vulvar hair; loss of pigmentation; indurated fibrosis and edema; and atrophy of glands, resulting in dryness.

6 Clinical Syndromes

For each of the organs, the corresponding SOMA-LENT tables are provided in Tables 1, 2, 3, 4 and representative clinical endpoints (segregated as subclinical versus clinical,

Table 1 SOMA-LENT: Ovary/reproductive

Ovary/Reproductive				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Hot flashes	Occasional	Intermittent	Persistent	
Dysmenorrhea	Occasional	Intermittent	Persistent	
Menstruation		Oligomenorrhea	Amenorrhea	
Objective				
Ovulation			Anovulation in premenopausal women	
Involuntary infertility			Infertility	
Osteoporosis			Radiographic evidences	Fracture
Management				
Dysmenorrhea,		Hormone replacement		
Hot flashes				
Menstruation		Hormone replacement		
Osteoporosis		Hormone replacement		
		Calcium supplements		
Analytic				
FSH/LH/Estradiol	Assessment of hormonal production			
Bone densitometry	Quantify bone density			

and focal versus global) in Tables 5, 6, 7, 8. (Tables 1, 2, 3, 4 and 5, 6, 7, 8).

6.1 Ovary

The adverse effect of ovarian irradiation is ovarian failure resulting in loss of fertility and menopausal symptoms. Ovarian failure can occur either as an acute event, during or immediately after therapy, or can manifest as premature menopause which is defined as menopause before the age of 40. Infertility most often occurs in conjunction with menopause, since both effects can be attributed to loss of the ovarian granulosa cells. The granulosa cells secrete estrogen which oocytes depend for maturation. Acute ovarian failure can be caused by 10–30 Gy ovarian irradiation in patients treated during childhood and adolescence (Green et al. 2009). In the childhood cancer survivors study, doses to the ovary $\geq$20 Gy were associated with acute ovarian failure in 70 % of patients (Green et al. 2009) (Tables 1 and 6).

In addition to dose, older age is a risk factor for developing acute ovarian failure or premature menopause. This effect is attributed to the fact that young women have a higher number of remaining oocytes, and can tolerate loss of more follicles prior to manifesting loss of estrogen secretion or mature follicles as ovarian failure and premature menopause.

Because the developing oocytes are more radiation resistant than the granulosa cells that they depend on, it is possible for mature oocytes but not developing oocytes to survive ovarian irradiation. As a consequence, fertility could be temporarily preserved following radiation therapy owing to the survival of developed oocytes which are no longer dependent on granulosa cell proliferation. This subsequent period of infertility could then be followed by eventual restoration of fertility due to survival of the less radiation-sensitive primordial follicles (Grigsby et al. 1995).

6.2 Uterus/Cervix

In the treatment of cervical cancer, the uterus is treated to high doses with intracavitary radiation therapy. Short-term adverse effects of irradiation of the uterus include pelvic pain, dysmenorrhea, and vaginal bleeding, but these are uncommon. Amenorrhea after radiation is nearly universal after definitive treated of cervical cancer. This may occur either as a primary effect of irradiation of the uterus or due to premature menopause caused by ovarian irradiation. The uterine cervix can become stenosed following radiation therapy, which can lead to the development of a hematometra if the endometrium remains functional (Tables 2 and 6).

Patients treated to radiation doses that damage the endometrium generally become infertile. Even if ovarian function is preserved, radiation damage affects the ability of the uterus to sustain a pregnancy, increasing the risk of

Table 2 SOMA-LENT: Uterus/Cervix

Uterus/Cervix				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Amenorrhea	Asymptomatic	Symptomatic		Infertility
Dysmenorrhea	Asymptomatic	Symptomatic		
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Bleeding	Occasional, normal hemoglobin	Intermittent < 10 % decrease in hemoglobin	Persistent, 10–20 % decrease in hemoglobin	Refractory > 20 % decrease in hemoglobin
Objective				
Pyometra	Asymptomatic	Symptomatic		
Hematometra	Asymptomatic	Symptomatic		
Necrosis	Asymptomatic	Symptomatic		
Ulceration	Superficial, ≥ 1 cm^2	Superficial, >1 cm^2	Deep ulcer	Fistulae
Incompetent				Infertility
Cervical Os Stenosis	Asymptomatic	Symptomatic		
Management				
Pain	Occasional nonnarcotic	Regular nonnarcotic	Regular narcotic	Surgical intervention
Amenorrhea, Dysmenorrhea, Hematometra	Occasional hormone replacement	Intermittent hormone replacement		
Pyometra		D&C, antibiotics		
Necrosis		Debridement	D&C	Hysterectomy
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Cervical Os Stenosis			D&C	Hysterectomy
Ulceration	Conservative	Antibiotics	Debridement, surgical management	Hysterectomy
Incompetent				Obstetrical management
Analytic				
MRI	Assessment of wall thickness, parametrial infiltrates, sinus and fistula formation			
Ultrasound	Assessment of wall thickness, parametrial infiltrates, sinus and fistula formation			
EUA cytology/biopsy	Assessment of mucosal surfaces and ulcers			

spontaneous abortion. A study of childhood cancer survivors in Denmark found that they had a higher rate of spontaneous abortion than control women without a history of cancer (Winther et al. 2008). The authors reported a relative risk for spontaneous abortion of 1.2 for all cancer survivors and 2.8 for women treated 1–40 Gy to the uterus and ovaries. In another study, the authors examined the effects of isolated uterine irradiation in 311 young women treated with intracavitary radium for menorrhagia. Approximately, 24 Gy was delivered to the uterus and 1 Gy to the ovaries. Of 33 conceptions in this group, there were 13 miscarriages, 7 stillbirths, and 6 live births (Dickson 1969). After a similar dose of whole abdomen radiation (20–26.5 Gy), four pregnancies all ended in second trimester abortions, demonstrating that the radiation to this dose limits the ability of the uterus to sustain pregnancy.

Critchley et al demonstrated that uterine irradiation impacts the uterine musculature and vascularity (Critchley et al. 1992). Radiation reduced the length of the uterus in adulthood (4.3 versus 7.3 cm). In addition, delivery of exogenous estrogen did not result in thickening of the endometrial stripe in response and uterine blood flow was reduced in women who had received abdominal irradiation (Critchley et al. 1992).

6.3 Vagina

Short-term adverse effects of vaginal irradiation resemble those of irradiation of other mucous membranes and include the progressive development of erythema, pain, and desquamation. Reepithelialization begins during or shortly

Table 3 SOMA-LENT: Vagina

Vagina				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dyspareunia	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciation
Dryness	Occasional	Intermittent	Persistent	Refractory
Bleeding	Occasional	Intermittent	Persistent	Refractory
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective				
Stenosis/length	>2/3 normal length	1/3–2/3 normal length	<1/3 normal length	Obliteration
Dryness	Asymptomatic	Symptomatic	Secondary dysfunction	
Ulceration/necrosis	Superficial, ≥ 1 cm^2	Deep ulcer	Fistulae	
Atrophy	Patchy	Confluent	Nonconfluent	Diffuse
Appearance	Telangiectasia without bleeding	Telangiectasia with gross bleeding		
Synechiae		Partial	Complete	
Bleeding		On contact	Intermittent	Persistent
Management				
Dyspareunia/pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Atrophy	Occasional hormone cream	Intermittent hormone cream	Regular hormone cream	
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Stenosis	Occasional dilation	Intermittent dilation	Persistent dilation	Surgical reconstruction
Dryness	Hormone replacement	Artificial lubrication		
Ulceration	Conservative	Debridement	HBO2	Graft, Surgical repair
Analytic				
MRI	Assessment of wall thickness, sinus and fistula formation			
Ultrasound	Assessment of wall thickness, sinus and fistula formation			
EUA Cytology/ biopsy	Assessment of wall diameter and length and mucosal surface			

after radiation and may take 3 or more months to be completed. Irradiation of the vagina with high doses, such as those delivered for the treatment of cervical cancer, can also result in atrophy and thinning of the vaginal mucosa which increases vaginal dryness and dyspareunia. The mucosa may appear pale, and telangiectases can develop. Stenosis and shortening of the vagina are common. The most severe complication of vaginal irradiation is development of necrosis with ulceration, which can progress to formation of a rectovaginal, vesicovaginal, or urethrovaginal fistula. Reported estimates of the incidence of adverse effects of vaginal irradiation vary widely, from 1.5 to 88 % (Abitbol and Davenport 1974; Brand et al. 2006; Denton and Maher 1999; Eifel et al. 2004; Hartman and Diddle 1972; Khor et al. 2007). This wide variation is most likely due to the variability in the methods of reporting and the lack of a consensus grading system for adverse effects of irradiation on the vagina (Tables 3 and 7).

A study from The University of Texas M. D. Anderson Cancer Center compared sexual functioning and quality of life in women with cervical cancer treated with radical hysterectomy, women with cervical cancer treated with radiation therapy, and a group of age- and race-matched control women (Frumovitz et al. 2005). Patients treated with radiation had lower health-related quality of life (physical and mental health), higher levels of psychosocial distress, and lower levels of sexual functioning. The disparity in sexual function remained significant in a multivariate analysis. Patients in this study treated with radiation had primarily stage 1B2 tumors, whereas patients treated with radical hysterectomy had primarily stage 1B1 tumors. The results might have been affected by other factors that

Table 4 SOMA-LENT: Vulva

Vulva				
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dryness	Occasional	Intermittent	Persistent	
Pruritus	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective				
Pigmentation change	Patchy	Confluent		
Alopecia	Partial	Complete		
Atrophy	Patchy	Confluent		
Appearance	Telangiectasia without bleeding	Telangiectasia with gross bleeding		
Ulceration/ necrosis	Superficial ≥ 1 cm^2	Superficial >1 cm^2	Deep	Fistulae
Fibrosis			Partial	Complete
Edema			Partial	Complete
Introital stenosis			Partial	Complete
Serous transudate	Occasional	Intermittent	Persistent	Refractory
Management				
Pruritus/Atrophy	Occasional hormone cream	Intermittent hormone	Regular hormone cream	
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Ulceration	Conservative	Wound care	Debridement	Graft
Introital stenosis	Occasional dilation	Intermittent dilation	Persistent Dilation	Surgical repair
Analytic				
Color photograph	Assessment of changes in skin, mucous and telangiectasia			

Table 5 Representative clinical endpoints, categorized as shown: ovary

	Focal	Global
Ovary		
Subclinical	n/a	1. Loss of primordial follicles 2. Stromal atrophy 3. Future premature menopause
Clinical	n/a	1. Infertility 2. Amenorrhea, menopausal symptoms 3. Decreased libido

Table 6 Representative clinical endpoints, categorized as shown: uterus

	Focal	Global
Uterus		
Subclinical	1. Ulceration, necrosis (after brachytherapy)	1. Glandular and stromal atrophy
Clinical	1. Stenosis of cervical os, hematometra 2. Ulceration, necrosis	1. Spontaneous abortion (inability to carry a pregnancy) 2. Amenorrhea

Table 7 Representative clinical endpoints, categorized as shown: vagina

	Focal	Global
Vagina		
Subclinical	1. Vaginal telangiectasias 2. Localized mucosal atrophy	1. Mucosal atrophy
Clinical	1. Bleeding/ulceration/pain 2. Decreased length 3. Ulceration, fistula	1. Narrowing, obliteration 2. Dryness 3. Dyspareunia 4. Sexual dysfunction

Table 8 Representative clinical endpoints, categorized as shown: vulva

	Focal	Global
Vulva		
Subclinical	1. Telangiectasia	1. Atrophy
Clinical	1. Ulceration, necrosis	1. Dryness, pruritus 2. Pain 3. Edema 4. Sexual dysfunction

could influence treatment decisions, and prospective assessment of sexual functioning is likely to yield a more accurate estimate of the effects of radiation.

Jensen et al. conducted a prospective study to determine the extent of sexual dysfunction in women treated with radiation for cervical cancer (Jensen et al. 2003). Compared with age-matched control women, women treated with radiation were more likely to complain of a lack of lubrication (40 versus 5 %), dyspareunia (17 versus 4 %), and reduced vaginal size (29 versus 9 %). Despite these symptoms, 63 % of women who were sexually active before cancer diagnosis were sexually active after radiation treatment, albeit at a diminished frequency. Another study by the same group found that women treated with radical hysterectomy for earlier-stage cervical cancer also experienced a decrease in sexual interest and diminished vaginal lubrication. Among these patients treated with hysterectomy, in those who were sexually active before treatment, the rate of return to sexual activity after treatment was 91 %—higher than the corresponding rate in women treated with radiation (Jensen et al. 2004).

A study of quality of life and sexual functioning in Korean women with cervical cancer treated with various modalities found that women treated with the combination of surgery and radiation had higher rates of sexual dysfunction than patients treated with radiation or surgery alone. Patients treated with radiation alone had rates of sexual dysfunction similar to those of women treated with surgery alone except that dyspareunia was more common in women treated with radiation (46 % of women treated with radiation experienced dyspareunia, compared to 28 % of control women) (Park et al. 2007). The impact of concurrent chemotherapy on sexual functioning is not well understood and is an important area of future investigation.

6.4 Vulva

Irradiation of the vulva causes significant acute adverse effects. The overlying skin folds in the vulva increase the absorbed dose to the vulvar skin and the discomfort caused by resultant friction. During a typical course of fractionated radiation therapy for vulvar cancer, erythema and edema of the vulva develop over the first 2–3 weeks. Moist desquamation generally follows within the next 2–3 weeks. Long-term adverse effects frequently include atrophy, edema, telangiectases, hair loss, which may be permanent, loss of skin pigmentation, and loss of sweat and sebaceous gland function. Late effects such as fibrosis have been estimated to occur in 37 % of patients treated to 45–79 Gy (Thomas et al. 1991; Perez et al. 1993). More serious complications occur in a smaller percentage of patients, who may develop ulceration and necrosis (Tables 4 and 8).

6.5 Detection and Diagnosis

Sexual dysfunction is a common clinical endpoint for many of the abnormalities described above. The SOMA-LENT system provides a reasonable manner to grade global sexual dysfunction (Table 9) that usually arises from a cluster of symptoms (Table 10). Thus, radiation toxicity can usually be well assessed via patient's subjective symptoms. Objective findings may also be appreciated on physical exam. Radiation changes can also be seen on CT and MRI. In general, the soft tissues can appear edematous, as would be seen acutely following vulvar irradiation. The uterus can appear shrunken and fibrotic on CT or MRI after pelvic radiation. Similarly, the ovaries of premenopausal women after pelvic radiation will appear similar to the ovaries of

Table 9 SOMA-LENT: Sexual dysfunction-female

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dyspareunia	Occasional	Intermittent	Persistent	Refractory
Dryness	Occasional	Intermittent	Persistent	Refractory
Desire	Occasional	Intermittent	Seldom	Never
Satisfaction	Occasional	Intermittent	Seldom	Never
Objective				
Vaginal stenosis/length	>2/3 normal length	1/3–2/3 normal length	<1/3 normal length	Obliteration
Synechiae			Partial	Complete
Frequency		Decreased from normal	Rare	Never
Orgasm	Occasional	Intermittent	Seldom	Never
Management				
Dryness	Hormone replacement	Artificial lubrication		
Stenosis/Synechiae	Occasional dilation	Intermittent dilation	Persistent dilation	Surgical reconstruction
Dyspareunia	Occasional hormone cream	Intermittent hormone cream	Persistent hormone cream	
Analytic				
Psychosocial	Evaluate quality of life/sexual satisfaction			
Vaginal measurement	Evaluate degree of vaginal stenosis			

postmenopausal women; smaller in size and lacking developing follicles. A barium enema can be useful to identify a rectovaginal fistula (Tables 9 and 10).

7 Radiation Tolerance

7.1 Tissue Tolerance and Rates of Radiation-Induced Injury

7.1.1 Ovary

The median dose (LD50) resulting in infertility after ovarian irradiation has been estimated to be 4 Gy but is highly dependent on age. The risk of premature menopause and sterility depend on the ovarian reserve—the number of remaining primordial follicles. The dose required to induce ovarian failure thus decreases with increasing age. A dose of 5–10 Gy is required to induce amenorrhea in women younger than 40 years, while 3.75 Gy will induce amenorrhea in nearly any women older than 40 years. This effect was demonstrated in a study that found that women with breast cancer treated to the pelvis with the goal of ablating ovarian function with 4.5 Gy developed amenorrhea in an age-dependent manner (Cole 1964) (Tables 11, 12, 13).

Protecting a single ovary appears to preserve fertility in young women. Stillman et al. studied 182 girls 14 years of age or older who were treated with abdominal irradiation with a dose of 12–50 Gy (Stillman et al. 1981; 1982). 68 % (17 of 25) of girls with both ovaries in the radiation field had ovarian failure, while 14 % (5/35) of girls developed ovarian failure when the ovaries were at the edge of the field. There were no cases of ovarian failure when the ovaries were out of the field.

The childhood cancer survivors' study identified risk factors associated with acute ovarian failure (defined in the study as never developing menses or cessation of menses within 5 years after treatment) and premature menopause (defined as menopause prior to age 40) (Chemaitilly et al. 2006; Sklar 1991; Sklar et al. 2006). Acute ovarian failure developed in children in a dose-dependent fashion, with children who were older at diagnosis (those 13–20 years of age) having higher rates of menopause (Fig. 5). Approximately 30 % of children who were 0–12 years of age at diagnosis and were treated with pelvic irradiation to doses of 10–20 Gy experienced acute ovarian failure, compared to 65 % of children who were 13–20 years of age at diagnosis and were treated with the same dose. In children treated with pelvic irradiation with doses greater than 20 Gy, rates of acute ovarian failure were high: 75–90 %. Premature menopause also developed in a dose-dependent fashion. Children treated with greater than 10 Gy had a relative risk of premature menopause 110 times that of their untreated siblings. The relative risk was lower—4.3 times that in untreated siblings—after treatment with low doses (1–99 cGy) (Sklar et al. 2006).

The risk of genetic abnormalities in the offspring of women who have undergone pelvic irradiation appears to be very low (Lushbaugh and Casarett 1976; Kaplan 1958).

Table 10 Problems with sexual adjustment after radiation therapy

Problem	Percentage (%)
Uncomfortable/painful intercourse	79
Dry vagina	74
Feeling of shortened or narrowed vagina	79
Lack of information on sexual functioning	16
Feelings of being sad, disinterested, depressed	58
Fear of injury	32
Fear of recurrent cancer	42
Unpleasant vaginal discharge	16
Poor communication with sex partner	11
Feelings of being less feminine and/or desirable	32
Separation from sex partner	26
Lack of supportive person	11

Table 11 Rates of Amenorrhea after Pelvic Irradiation to 4.5 Gy, by patient age

Age, years	Rate of Amenorrhea (%)
<40	67
40–44	90
45–49	96
>49	100

This is supported by the experience with children of atomic bomb survivors, in whom genetic mutations were rarely seen. This suggests an all-or-none effect in which either the cell dies or damage is repaired.

7.1.2 Uterus/Cervix

The uterus is not usually considered to be a dose-limiting structure. Doses of up to 200 Gy at the surface can be delivered with brachytherapy without development of transmural necrosis. Areas of ulceration and necrosis are seen in hysterectomy specimens following brachytherapy but rarely result in significant symptoms. When lesions heal, they typically form areas of dense scarring.

7.1.3 Vagina

The vagina can tolerate relatively high doses of radiation, and the vaginal apex is more resistant to radiation than the distal vagina at the introitus. Severe complications such as necrosis have been seen following doses of greater than 140 Gy (Hintz et al. 1980). A dose of 175 Gy at the vaginal surface delivered with a single ovoid source and external irradiation is predicted to result in grade 3 complications (severe symptoms requiring frequent doses of medication) in 5 % of patients (Hintz et al. 1980; Au and Grigsby 2003).

Vaginal stenosis may have the greatest impact on sexual functioning. Table 12 lists the results of retrospective studies that have reported rates of vaginal stenosis following radiation therapy for cervical cancer. The mean reduction in vaginal length has been reported to be 1.5 cm following intracavitary radiation therapy for cervical cancer (Bruner et al. 1993). Stenosis has also been reported following intravaginal brachytherapy (Table 13). A randomized trial investigating 2 high-dose-rate regimens for intravaginal brachytherapy (6 fractions of 2.5 Gy prescribed to 5 mm versus 6 fractions of 5 Gy prescribed to 5 mm) found that the vaginal length was reduced by a mean of 2.1 cm when patients were treated with the higher-dose-per-fraction regimen (Sorbe et al. 2005). No difference was observed in the recurrence rates for these 2 regimens. The prescription depth is a critical parameter to consider when comparing fractionation schemes for vaginal brachytherapy. The dose is commonly reported to be prescribed to a 0.5-cm depth or to the vaginal surface. Less commonly, the dose may be prescribed to 1 cm. Given that the rectum may be 5 mm posterior to the posterior vaginal wall, rectal doses vary widely with these different fractionation schemes.

Vaginal stenosis can develop quickly after radiation therapy and can even develop during radiation therapy—reduction in vaginal length was reported during the course of intravaginal brachytherapy as measured by height of the vaginal dome above the pubic symphysis (Katz et al. 2001). In a study in which vaginal stenosis was identified prospectively, stenosis was first reported at a median of 7.5 months after irradiation (Brand et al. 2006).

Vaginal changes due to radiation can significantly impact sexual functioning. The causes for this are multifactorial:

Table 12 Rates of vaginal stenosis after radiation treatment of cervical cancer

Study	Treatment	Rates of vaginal stenosis		Dose relationships identified
Khor et al. (2007)	Radiation alone HDR brachytherapy	Grade 1 Mild	43.4 %	Associated with higher doses to bladder and rectum for patients with and without vaginal stenosis
		Grade 2 Moderate	1.9 %	
Brand et al. (2006)	Radiation alone 84 % Chemoradiation LDR brachytherapy	Grade 0 None. Flimsy adhesions easily broken down	58 %	No difference in median total dose to pt A
		Grade 1 Partial stenosis or shortening but less than complete occlusion	27 %	
		Grade 2 Complete occlusion. Telangiectasia with frequent bleeding	11 %	
		Grade 3 Radionecrotic ulcer	1.7 %	
		Grade 4 Fistula to bladder, bowel, or peritoneal cavity	2.3 %	
Hartman and Diddle (1972)	Radiation alone. 3000 R orthovoltage.	Grade 1 No stenosis	12 %	80–96 %
	6000 R to point A with radium implant.	Grade 2 Stenosis involving upper third	50 %	
		Grade 3 More than one third stenosis to complete stenosis	38 %	

HDR high-dose-rate; *LDR* low-dose-rate; *R* Roentgen

Table 13 Vaginal stenosis after intravaginal brachytherapy

Study	Treatment	Vaginal changes
Sorbe et al. (2005)	Vaginal cuff brachytherapy 2.5 Gy to 5 mm depth × 6 versus 5 Gy to 5 mm depth × 6	Mean reduction in vaginal length of 2.1 cm in patients treated with 5-Gy fractions. No change in patients treated with 2.5-Gy fractions.
Nori et al. (1994)	Vaginal cuff brachytherapy 7 Gy × 3 prescribed to 0.5 cm depth and external-beam radiation therapy to 40 Gy	Vaginal stenosis grade 1–2 in 2.5 % of patients. Vaginal necrosis in 0.5 %.

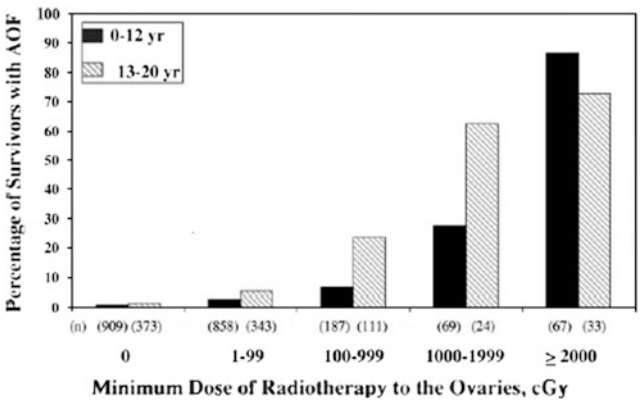


Fig. 5 Acute ovarian failure in childhood cancer survivors (with permission Sklar et al. 2006)

decreased estrogen levels, fibrosis, stenosis and shortening, and loss of lubrication from obliteration of vaginal glands all play a role. In one study, 48 % of women reported that they felt their vaginal dimensions were smaller 1 year following brachytherapy for cervical cancer (Jensen et al. 2003). In addition, telangiectases, which can bleed, may develop.

7.1.4 Vulva

The acute adverse effects of vulvar irradiation can be significant. Even doses of 45–50 Gy cause moist desquamation, which can be either patchy or confluent. In the long-term, radiation changes may result in significant fibrosis, atrophy, or telangiectases; less commonly, ulceration and necrosis *may* occur. Fibrosis and telangiectases have been reported to occur in 33–40 % of patients treated to 45–70 Gy (Grigsby

et al. 1995; Thomas et al. 1991). Vulvar necrosis occurred in 3 % of patients treated with 50–70 Gy in daily fractions of 1.5–1.8 Gy. Smaller doses per fraction (1.5–1.7 Gy) have been reported to decrease the likelihood of long-term vulvar damage (Grigsby et al. 1995; Thomas et al. 1989).

7.2 Dose Time Fractionation and Recommended Dose and Volume Constraints

7.2.1 Ovary

The long-term adverse effects of ovarian irradiation, ovarian failure and infertility, are often accepted as unfortunate but unavoidable consequences of pelvic irradiation. For there to be a significant chance of avoiding ovarian failure, the dose to the ovaries would have to be limited to less than 5–10 Gy in a very young woman and less than 4 Gy in a woman in her 30s. Such low doses might be achievable with oophoropexy or, if the ovaries were left within the pelvis, with an intensity-modulated radiation therapy approach. However, it would not be advisable to spare the ovaries left in situ in a woman with cervical cancer, both because the ovaries can harbor occult disease and because the ovaries are close to the target volume, including the pelvic lymphatics.

7.2.2 Uterus/Cervix

The uterus can be treated with radiation doses up to 200 Gy at the surface when limited small volume, as occurs adjacent to the tandem in cervical cancer.

7.2.3 Vagina

It is recommended that the vaginal apex receive not more than 120–140 cGy, with two-thirds of the dose delivered with intracavitary treatment. The lower two-thirds of the vagina should not receive more than 70–75 Gy unless higher doses are needed to treat tumor involving the distal vagina.

7.2.4 Vulva

Doses of up to 65 Gy may be necessary to control gross disease in patients with vulvar cancer. Moist desquamation is likely to occur in patients treated to 30 Gy. Fibrosis and telangiectases occur in approximately one-third of patients treated to definitive doses (Thomas et al. 1991; Manson et al. 2003), but more serious side effects, such as necrosis, are rare.

8 Special Topics

Potential options to avoid ovarian toxicity vary widely between patients depending on the risk of ovarian involvement with cancer, the types of cancer treatment, patient age, the time available before the start of treatment, the estrogen sensitivity of the tumor, and partner availability for fertilization (Sonmezer and Oktay 2004).

9 Prevention and Management of Adverse Effects

9.1 Ovary

Women with premature menopause can be treated with estrogen replacement. Women with an intact uterus should be treated with an estrogen/progesterone combination, and young women who have had a hysterectomy can be treated with unopposed estrogen. Estrogen/progesterone should be given continually rather than cyclically to avoid the possibility of hematometra which due to cervical stenosis. Estrogen replacement in postmenopausal women has been shown to increase the risk of breast cancer as well as cardiac disease, so in women with premature menopause, estrogen replacement should be stopped between 40 and 50 (Manson et al. 2003) (Table 1).

Although no agents have been developed to prevent ovarian damage due to radiation, several new approaches exist to conserve ovarian tissue in women who desire to preserve fertility. Embryos can be cryopreserved before radiation therapy when a woman has a male partner or is willing to use donor sperm. This technique has a higher rate of success than oocyte cryopreservation, which has a success rate of about 2 % per thawed oocyte (American Society of Reproductive Medicine 2008). Women undergoing pelvic irradiation would also require a surrogate to bear their biological child, as pregnancy after pelvic irradiation rare and successful embryo transplantation would be inadvisable in an irradiated uterus.

Ovarian transposition has been shown to protect the ovaries and can preserve the natural secretion of estrogen if doses are limited to less than 4 Gy (Le Floch et al. 1976). Successful pregnancies have been reported in women who underwent placement of the ovaries posterior to the uterus prior to treatment of Hodgkin's lymphoma with inverted Y-field irradiation (Terenziani et al. 2009). Women treated with whole-pelvic irradiation for cervical cancer can have the ovaries transposed into the abdomen before treatment. However, this approach is not commonly advocated for owing to reports of a 25 % rate of subsequent benign ovarian cysts, a 50 % incidence of ovarian failure, and reports of ovarian recurrences of cervical cancer, primarily in women with adenocarcinoma (Gershenson 2005).

9.2 Uterus/Cervix

No specific therapy is generally indicated for treatment of radiation toxicity to the uterus. Soft tissue necrosis can be

managed with antibiotics and gentle irrigation. If there is concern about tumor recurrence, biopsy should be attempted cautiously as biopsy can increase the risk that necrosis which can progress to fistula (Table 2).

9.3 Vagina

Vaginal dryness due to lower levels of estrogen after ovarian radiation can be treated with either systemic hormone replacement therapy or vaginal estrogen. We prescribe conjugated estrogens/medroxyprogesterone acetate tablets for women with an intact uterus. The elevated risk of endometrial cancer in women with higher levels of estrogen exposure has led to a concern that replacing estrogen in women treated for endometrial cancer could increase the risk of recurrence by stimulating growth of any residual estrogen-responsive cells. However, in a case–control study in which rates of recurrence were evaluated in women with a history of endometrial cancer treated with and without hormone replacement, recurrence rates were lower in women treated with hormones, suggesting that hormone replacement therapy is safe for women who are disease-free after treatment for endometrial cancer (Suriano et al. 2001) (Table 3).

Vaginal dilators and regular sexual intercourse are recommended to minimize vaginal stenosis after brachytherapy. A recent Cochrane review recommended the use of vaginal dilators, however this was a category 2C recommendation because of the low quality of the evidence demonstrating a benefit (Denton and Maher 2003). Although these interventions are often recommended, compliance is reported to be low, and increasing patient education may be important (Robinson et al. 1999).

9.4 Vulva

Positioning patients with vulvar cancer in the frog-leg position for radiation therapy decreases the dose to the inner thighs, which helps minimize discomfort. However, it is critical to ensure that adequate bolus is applied to the tumor. Regular Dumboro sitz baths help keep the affected area clean and facilitate healing. A topical lidocaine gel (2 %) or pyridium may alleviate discomfort with urination. Many patients undergoing treatment for vulvar cancer develop a progressive yeast infection midway through treatment; such infections respond to oral diflucan (Table 4).

10 Future Directions

New developments in ovarian and embryo cryopreservation (American Society of Reproductive Medicine 2008) offer women undergoing pelvic irradiation the opportunity to have a biological child. These approaches are associated with numerous challenges, such as ensuring that cryopreservation is done expeditiously not to delay the initiation of treatment and managing the costs of oocyte harvesting and preservation as well as ultimately surrogacy.

Attempts to reduce the toxicity of pelvic irradiation through use of more conformal dose delivery techniques have focused on reducing damage to the bowel and bone marrow (Jhingran 2006; Kouloulias et al. 2004). Intensity-modulated radiation therapy may be useful to reduce the dose to the gynecologic tract in the treatment of anal cancer. Radiation protectors may ultimately be useful in minimizing the toxicity of radiation therapy, but to date, there has been little investigation of the use of radiation protectors to minimize damage to the gynecologic organs. The radiation protector, keratinocyte growth factor, has proven useful for avoiding chemotherapy-induced mucositis in patients undergoing bone marrow transplantation but has shown little effect in patients treated with radiation for head and neck cancer (Keefe et al. 2008; Garden and Chambers 2007). Investigations of agents that protect normal tissue from the effects of radiation may ultimately help to minimize the toxicity associated with radiation to the gynecologic tract.

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Radiation Induced Rectal Toxicity

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Contents

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Abstract

- The incidence of late radiation-induced bowel toxicity has been reported to range from 5 to 20 %.
- Molecularly, NF-KB and COX-2 play important roles in the pathophysiology of radiation induced colitis.
- Acutely, radiation impairs the proliferative ability of the intestinal mucosa resulting in a deficit in cell re-population while the differentiated cells continue to shed.
- Chronic radiation injury to the bowel is manifested by a progressive vasculitis leading to thrombosis of small arteries and arterioles resulting in varying degrees of ischemia of the bowel wall.
- Bleeding is the most common symptom of chronic radiation proctitis compared to acute radiation proctitis where bleeding is relatively uncommon.
- The classic endoscopic findings of radiation proctitis include prominent telangiectasia, erythema, and friability.
- In patients receiving high dose rate (HDR) implants for gynecologic malignancies, a higher dose per fraction increases the rate of proctitis.
- Rectal bleeding was found to correlate with anorectal V55–V65 with V65 being the most significant parameter while stool frequency correlated with anorectal V40.

Abbreviations

BED	Biologically effective dose
BAT	B-mode acquisition and targeting
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
Cox-2	Cyclooxygenase-2
ERB	Endorectal balloons
GE	Gray equivalents
HDR	High dose rate
HBO	Hyperbaric oxygen
HIF1-alpha	Hypoxia-inducible factor-1alpha

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ICRU	International federation of gynecology and obstetrics
IG-IMRT	Image guided IMRT
IMRT	Intensity modulated radiation therapy
IL-1B	Interleukin-1b
LENT	Late effects of normal tissue
MRI	Magnetic resonance imaging
MAPK	Mitogen-activated protein kinase
NK-FB	Nuclear transcription factor kappa B
PAI-1	Plasminogen activator inhibitor type 1
SNP	Single nucleotide polymorphisms
3-DCRT	Three-dimensional conformal radiation
TDF	Time dose factors
TME	Total mesorectal excision
TNF	Tumor necrosis factor
TGF-beta1	Transforming growth factor beta1
VEGF	Vascular endothelial growth factor
RTOG/EORTC	Radiation therapy oncology group/european organization for research and treatment of cancer
R-FAS	Rectal function assessment score
SOMA	Subjective objective management and analytic

1 Introduction

Radiation therapy is integral to the management of pelvic malignancies including carcinomas of the prostate, bladder, rectum, anus, cervix, and uterus. Rectal tolerance is an important dose-limiting constraint in the treatment of these malignancies, especially prostate cancer. The incidence of any late radiation-induced bowel toxicity has been reported to range from 5 to 20 % (Garg et al. 2006).

The primary effect of radiation toxicity is alterations in the rectal mucosa. Early radiation-induced rectal damage includes mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscesses, and endothelial swelling in the arterioles which may progress to fibrosis of connective tissue and endarteritis of the arterioles resulting in rectal tissue ischemia, mucosal friability, bleeding, ulcers, strictures, and fistulae (Babb 1996). Late rectal toxicity is manifested by a progressive vasculitis leading to thrombosis of small arteries and arterioles resulting in varying degrees of ischemia of the bowel wall (Donner 1998). Molecular changes associated with acute and chronic radiation-induced bowel toxicity are being investigated to better understand the etiology and provide targets for future therapies which could ameliorate symptoms and improve quality of life.

Sophisticated treatment planning software has provided the means to further define rectal wall dose volume constraints enabling physicians and physicists the ability to design dose escalation studies which minimize rectal toxicity.

The Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Gross Anatomy (Normal)

The rectum and anus are the terminus of the digestive tract. The rectum, from the Latin *rectum intestinum* or straight intestine, begins at the terminus of the sigmoid colon approximately 12–14 cm cepahalad from the anal verge (Fig. 2). The rectum, a tube like structure with many layers, is normally empty until stool enters from the sigmoid colon and dilates near its terminus to form the rectal ampulla. The upper 1/3 of the rectum is covered by peritoneum. The rectum functions not only as a conduit organ but also as a reservoir of feces (Shafik et al. 2006). The rectum lies just anterior to the sacrum and posterior to the bladder and prostate in men, and vagina in women (Fig. 2).

The junction of the sigmoid colon and rectum is not well defined but is marked by anatomic changes that distinguish the transition between the two organs. First, externally there is a change in the peritoneal relationship, direction, and musculature. The sigmoid colon can be considered to start at the superior aperture of the lesser pelvis. It passes anteriorly to the sacrum to the left side of the pelvis and curves on itself turning to the right reaching midline at the 3rd sacral vertebrae extending downward losing its mesentery to transition into the rectum. It is covered entirely by peritoneum and innvervated by pelvic splanchnic nerves for parasympathetic innervations while lumbar splanchnic nerves provide sympathetic innervations via the inferior mesenteric ganglion. The rectum follows the sacrum extending inferiorly ending in the rectum. The upper third of the rectum is covered on its front and sides by peritoneum while the middle aspect of the rectum is only covered on the front by peritoneum and the lower third of the rectum is without peritoneum. The rectum contains three and sometimes more lateral curvatures corresponding to the transverse rectal folds. The rectum is without mesentery and haustra and has an almost complete outer longitudinal muscular coat instead of teniae. Second, internally there can be a change in the character of the lining mucosa with the fluffy, rugose mucosa of the colon giving way to the smooth mucosa of the rectum. This, however, may not be apparent in the non-distended bowel (Hollinshead 1974). The inferior part of the rectum is readily distensible and is known as the rectal ampulla. Caudally, the rectum extends to the

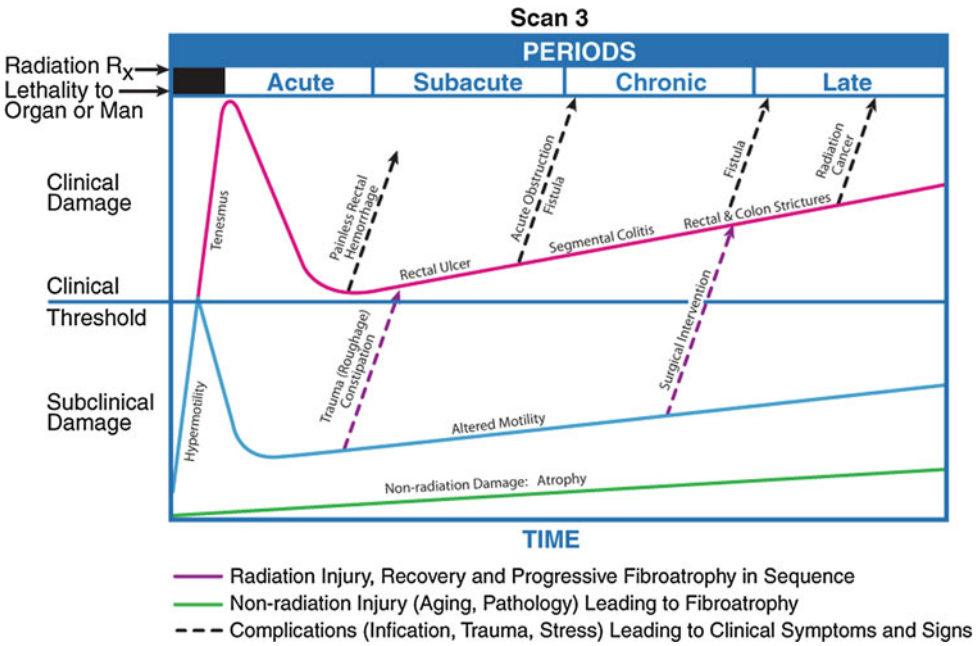

Fig. 1 Biocontinuum of adverse early and late effects (with permission from Rubin and Casarett 1968)

perineum, where the rectum turns sharply backward and downward through the pelvic diaphragm giving rise to the anal canal.

The rectum is surrounded by a filmy layer of connective tissue forming a tubular sheath called the rectal fascia. Superiorly, the rectal fascia becomes continuous with the subperitoneal connective tissue of the sigmoid. Transverse rectal folds project into the rectum and consist of mucosa, submucosa, and circular muscles and help to support rectal contents.

The arterial supply of the rectum comes primarily from the superior rectal artery with the inferior part of the rectum receiving blood supply from the middle rectal arteries. The venous drainage of the rectum follows the arterial supply. The lymphatics primarily drain superiorly as well paralleling the superior rectal blood vessels and emptying into the internal iliac lymph nodes. The lymphatics of the inferior third of the rectum are continuous with the lymphatics of the superior part of the anal canal and may drain into the superficial inguinal lymph nodes. The nerve supply of the rectum is through the rectal plexus which is a derivative of the inferior mesenteric plexus. Sensory fibers traveling in the lumbar splanchnic nerves are responsible for pain and the pudendal nerve is responsible for the control of emptying the bowel. Therefore the afferent and efferent side of the rectum receives its innervation through the pelvic splanchnic nerves which exit at approximately the second through fourth sacral nerves (Hollinshead 1974).

2.2 Histology and the Functional Subunit

The mucosa of the large intestines, including the rectum, has a simple columnar epithelium shaped into straight tubular crypts without villi as the majority of nutrient absorption occurs in the small intestines. The major function of the large intestines is to absorb water while the rectum is the repository of feces prior to evacuation. In addition, the mucosa of the large intestines is thicker than the small intestine, its crypts do not contain any Paneth cells, but it has more goblet cells. The proportion of goblet cells increases from the proximal colon to the rectum (Fig. 3).

Cell migration occurs, with epithelial cells dividing in the deeper half of the crypts and migrating to the surface. The crypts are separated by lamina propria composed of loose connective tissue infiltrated by white blood cells, capillaries, and thin strands of smooth muscle (Fig. 3).

The muscularis mucosa in the rectum is very thin only a few muscle fibers in thickness beneath the deep ends of the crypts. The muscularis externa consists of an inner circular and outer longitudinal smooth muscle band. The outer longitudinal band is collected into 3 flat bands known as the teniae coli. The rectum does not have an outer layer or serosa but has an adventitia.

3 Biology, Physiology, and Pathophysiology

3.1 Molecular Biology Mechanisms of RT-Induced Rectal Injury

The alimentary tract has the same embryological route of development involving all three germ layers of the developing embryo, therefore, it is hypothesized the mechanism for mucosal injury along the alimentary tract is the same or similar regardless of location (Yeoh et al. 2007; Keefe 2004; Keefe et al. 2004). Originally, it was thought that

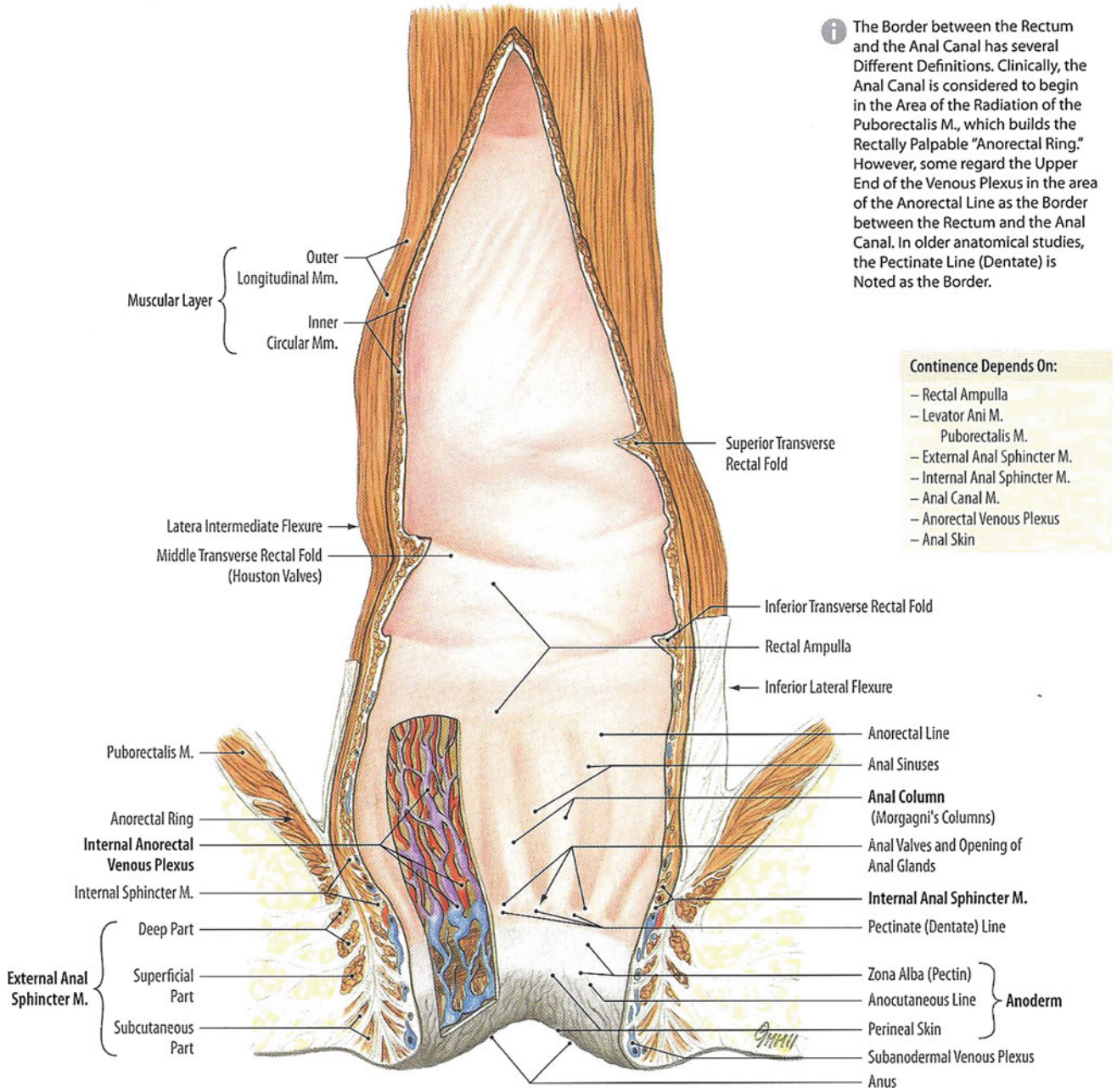

Fig. 2 Anatomy of normal rectum and rectal anal structure (with permission from Tillman 2007)

radiation induced toxicity via cytotoxic effects on the basal cells of the epithelium (Spijkervet et al. 1991; Stiff 2001). Further study, however, determined the primary damage response occurred in endothelial cells (Menendez et al. 1998; Maj et al. 2003; Paris et al. 2001; Garcia-Barros et al. 2003). Molecularly, NF-KB and COX-2 play important roles in the pathophysiology of radiation induced colitis (Yeoh 2004; Yeoh et al. 2006) (Fig. 4).

A four-stage model has been proposed by Sonis to describe the development of radiation-induced mucositis (Fig. 4) (Sonis 1998, 2004; Sonis et al. 2000, 2004). The four stage are initiation, upregulation, amplification/signaling, and finally ulceration. Although acute rectal toxicity of diarrhea and frequent stooling can be distressing to a patient while undergoing treatment, it is the late effects of radiation that are most problematic clinically, especially in a patient cured of their cancer. The majority of studies investigating radiation induced mucositis along the alimentary tract have focused on acute mucosal injury and its associated molecular changes. Since acute rectal symptoms predict for late rectal toxicity, acute molecular changes could be a proxy for late molecular changes. As discussed

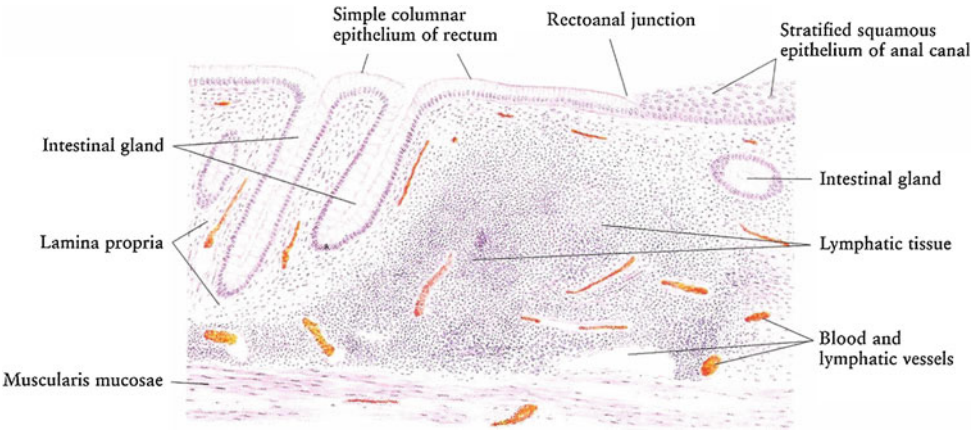

Fig. 3 Histology of normal rectum and rectal anal structure (with permission from Zhang 1999)

Fig. 4 The four stage model proposed by Sonis et al. outlining the molecular changes developing in the bowel acutely as a response to radiation (figure adapted from Logan 2007)

Initiation Phase

Radiation

Development of DNA and non-DNA Damage and generation of Reactive Oxygen Species (ROS)

Upregulation

Activation of Transcription Factors

NF-KB

NF-KB responsible for Upregulation of >200 genes

p53

Increased nuclear staining of p53 in colon crypts that were irradiated

Production of TNF, IL-1B, IL-6

Signal Amplification

Pro-inflamatory cytokines act via a positive feedback mechanism causing
Further activation of NF-KB and increased production of cytokines
Cox-2 upregulated and initiates an inflammatory cascade leading to activation of matrix metalloproteinases (MMP)

Ulcerative Phase

Healing

below, fibrosis and sclerosis of blood vessels, a histologic hallmark of late radiation change, were some of the distinct changes observed with accompanying increased expression of NF-KB within the blood vessel walls (Yeoh 2004). The acute radiation model is illustrated below.

3.1.1 Sonis Model

1. Initiation Phase

Radiation causes the creation of reactive oxygen species as well as direct DNA and non-DNA damage.

2. Upregulation and Message Generation Phase

Radiation-induced tissue damage as a result of the initiation phase results in the activation of a number of transcription factors including NF-KB. NF-KB is the "gatekeeper" functioning as the "on/off" switch in the pathogenesis of radiation-induced mucositis (Yeoh et al. 2006). Reactive oxygen species cause the degradation of IKB-a, which activates NK-KB moving from the cytoplasm to the nucleus to further activate genes playing a significant role in mucosal injury (Lee et al. 1998). NF-KB is responsible for upregulation of over 200 genes affecting mucosa integrity by inducing clonogenic cell death, apoptosis, and tissue injury (Logan et al. 2007; Sonis 2004). Apoptotic counts were also found to be increased in colon cells irradiated compared to nonirradiated colon cells (Yeoh et al. 2006, 2007). Staining of p53 was also increased in irradiated crypt cells compared to un-irradiated controls (Yeoh et al. 2007).

NK-KB activation results in the production of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1B (IL-1B), and interleukin-6 (Il-6) Logan et al. (2007; Sonis et al. 2000, 2004; Sonis 2004).

3. Signal Amplification

Cytokines produce earlier amplification of the primary signal or may activate NF-KB in other cells. TNF can work in a positive feedback loop causing further activation of NF-KB. Gene transcription occurs generating biologically active proteins mitogen-activated protein kinase (MAPK) and cyclooxygenase-2 (Cox-2). The inflammatory cascade is initiated leading to activation of matrix metalloproteinases further eliciting tissue damage.

4. Ulcerative Phase

Characterized by the clinically overt presence of an ulcer, breakdown of the mucosal barrier can lead to bacterial colonization and associated products that can stimulate further amplification of cytokine production and further tissue injury.

5. Healing

Following radiation, reepithelialization of the mucosa may occur due to signals from the extracellular matrix. The healing phase is probably the least well understood and studied with respect to mucositis pathobiology (Logan et al. 2007). The healed mucosa however has a persistently altered structure (based on both ultrastructural and histological studies) that compromises its ability to withstand further trauma or insults, a phenomenon originally observed by Rubin and Casarett in 1968 (Rubin and Casarett 1968).

Recently, plasminogen activator inhibitor type 1 (PAI-1) has been found to play a critical role in radiation-induced intestinal damage. Up-regulation of PAI-1 in the endothelium was found in mice as well as patients with radiation-induced damage (Milliat et al. 2008). A p53/Smad3-dependent mechanism was responsible for the increased PAI-1 expression. C-reactive protein, however, was not a prominent feature in uncomplicated chronic-radiation-induced toxicity (Khalid et al. 2007). The relationship between hypoxia expression and radiation-induced late rectal toxicity was studied in C57BL/6 N mice having 25 Gy delivered to the rectum in a single fraction. Expression of transforming growth factor beta1 (TGF-beta1), hypoxia-inducible factor-1alpha (HIF1-alpha), vascular endothelial growth factor (VEGF) and endothelial cell marker CD31 increased significantly with the formation of fibrosis induced by radiation compared to unirradiated controls (Liu et al. 2008). Maximum expression of TGF-beta1, HIF-1alpha, and VEGF was found 14, 30, and 90 days after irradiation, respectively, consistent with the dynamic change of fibrosis.

3.2 Cellular Dynamics and the Radiation Response

Acutely, radiation impairs the proliferative ability of the intestinal mucosa resulting in a deficit in cell repopulation while the differentiated cells continue to shed. The continued cell loss without repopulation results in tissue hypoplasia. The lamina propria is then infiltrated by a plasma cells, neutrophils, and eosinophils. Crypt abscesses and sloughed epithelial cells could also be present. Radiation could also cause crypt disintegration with disorganization and loss of goblet cells. The muscularis mucosa at the base of the lamina propria can be fibrosed and disorganized with leukocyte infiltration (Yeoh et al. 2005). Telangeictatic vessel formation and fibrosis and sclerosis of the blood vessels were principal features in the submucosa with increased density and thickening of the collagenous fibers making up the submucosa (Yeoh et al. 2005). The circular and longitudinal muscle layers can be fibrosed with a neutrophil infiltration into the muscle layers. The fat layer surrounding the rectum showed evidence of fibrosis and sclerosis of the blood vessels with telangiectatic vessels present (Yeoh et al. 2005). The degree of goblet cell damage is proportional to the radiation dose. Yeoh et al. found

less goblet cell degeneration further away from the area of the primary tumor that had received a lower radiation dose (Yeoh et al. 2005). Mucin secreted by the goblet cells is also affected with a mixed borderline to normal pattern of mucin differentiation the further away from the tumor compared to sialomucins predominate with little sulfomucin apparent characteristic of an abnormal mucin pattern closer to the primary area of irradiation. This corresponds to the goblet cell composition changing from more acidic to more neutral (Yeoh et al. 2007). Tissue hypoplasia with the cellular reaction is responsible for the decreased intestinal function and decreased stool caliber leading to a more watery stool or mucoid diarrhea (Zimmermann and Feldmann 1998).

Chronic radiation injury to the bowel is manifested by a progressive vasculitis leading to thrombosis of small arteries and arterioles resulting in varying degrees of ischemia of the bowel wall (Donner 1998). Figure 5a is a photomicrograph showing fibrin thrombi in a vessel in a patient with late radiation-induced rectal toxicity. The arteritis and submucosal fibrosis can lead to structuring and obstruction. Severe ischemia can lead to necrosis, deep ulceration, and fistula formation. Telangiectasis and neovascularity form later as a result of a network of collateral small vessels which are superficial and fragile, susceptible to trauma resulting in bleeding. The abnormal blood supply to the mucosa results in regenerating crypts and may lead to distortion and atypia of the epithelial cell lining resembling dysplasia (Donner 1998). The lamina propria can become fibrotic. Collagen can become deposited below the surface epithelium leading to ulceration, mucosal sloughing, and fistulization. Trauma to the fragile neovasculature results in chronic low grade rectal bleeding leading to iron deficiency anemia (Buchi and Dixon 1987).

The ability of the mucosa to regenerate is impaired resulting in a thin and vulnerable mucosa with atypical epithelial cells. Small abscesses can be found in the deep crypts with large foam cells seen beneath the intima considered to be evidence of radiation vascular injury. The submucosa becomes thickened and fibrotic containing large, bizarre-formed radiation fibroblasts with the muscularis propria exhibiting focal areas of fibrosis or involvement of deep fissures or penetrating ulcers (Fig. 5b). The serosa can develop diffuse hyaline changes with fibroblasts, telangiectasia or small vessels, and ischemic changes in larger vessels resulting in an opaque, grayish, and thickened tissue surrounding the intestinal wall (Zimmermann and Feldmann 1998).

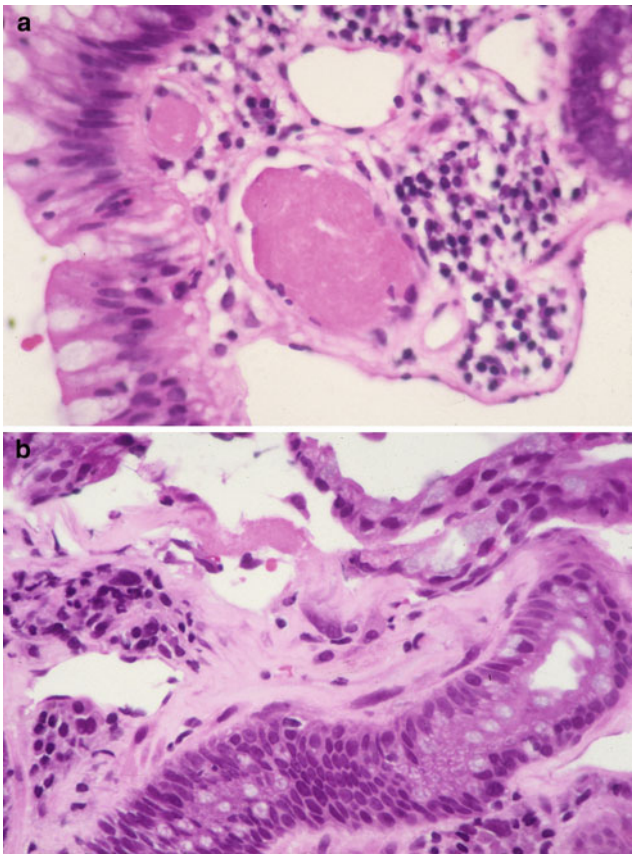

Fig. 5 **a** Photomicrograph of a fibrin thrombi in a small blood vessel characteristic of chronic radiation proctitis. **b** Photomicrograph showing submucosal fibrosis in the rectum of a patient with chronic radiation proctitis (courtesy of Dr. Harry Cooper, Department of Pathology, Fox Chase Cancer Center)

3.3 Physiology and Pathophysiology

The rectum is not only a conduit organ but also a reservoir (Shafik et al. 2006). The pelvic splanchnic nerves, responsible for emptying the bowel, increase the peristaltic activity of the rectum and with the help of increased abdominal pressure move the feces out of the rectum. Voluntary muscle activation of the muscles around the anal canal restrains bowel movements. If the increase in abdominal pressure is great enough, voluntary contraction of the external anal sphincter may also be initiated but cannot be maintained for long time periods. This reflex activity depends upon the presence of a part of the rectum; if the rectum is entirely removed, the passage of gas or feces can be resisted only by the rather incompetent voluntary contraction of the external anal sphincter. Patients with coloanal anastomosis may have incontinence but patients with the lower 2 cm of the rectum remaining can have good control of the passage of gas and feces (Hollinshead 1974).

Diarrhea can be a result of an enteroenteric or enterocolonic fistula, stricture formation resulting in stasis and bacterial overgrowth, and from direct injury of the colonic mucosa with a collagenous colitis-type syndrome interfering with absorption of fluids (Donner 1998). The pathophysiology of abnormal bowel function was studied in 30 randomly selected women treated with radiation for carcinoma of the cervix. Bile acid, vitamin B12 and lactose

absorption were less in patients receiving radiation. Bile acid absorption was below the control range in 14 of 30 patients and dietary calcium intake was lower in those patients with lactose malabsorption Yeoh et al. (1993). In addition, gastric emptying and whole gut transit were inversely related to stool frequency. Either bowel frequency, bile acid absorption, vitamin B12 absorption was outside the control range in 19 of 30 patients (Yeoh et al. 1993). Stool weight was also greater and whole-gut transit faster 1–2 years after patients received both pelvic and abdominal radiation (Yeoh et al. 1993).

The pathophysiology of incontinence is not well understood. Although patients may be incontinent, they may not exhibit any change in the internal or external sphincter (Petersen et al. 2007). Yeoh et al. found no significant change in the thickness of the internal or external anal sphincter 6 weeks after radiation (Yeoh et al. 1998). The clinical correlates of incontinence can be differentiated into two groups, core factors and associated factors. Reduced anal resting tone is considered as a core factor of incontinence. Further clinical signs of radiation-induced incontinence are a reduction in squeeze pressure and decrease in rectal wall stretch (Petersen et al. 2007; Yeoh et al. 1998; Berndtsson et al. 2002).

Two of the most important factors in the development of fecal incontinence are connective tissue remodeling of the rectum and diminished neural function of the continence organ. Smooth muscle hypertrophy and myenteric plexus damage may contribute to the reduction in rectal volumes at sensory threshold, constant sensation and maximal tolerance, and in rectal compliance (Varma et al. 1985, 1986). Lumbosacral plexopathy has been implicated in fecal incontinence after pelvic radiotherapy (Iglicki et al. 1996; Georgiou et al. 1993). In addition, a significant change in the density of the nerves in the internal anal sphincter was seen as early as 6–12 months after radiotherapy reflecting myenteric plexus injury (Da Silva et al. 2003). Further strengthening the argument in favor of nerve damage, Kushwaha et al. found an appreciable decrease in the electrosensitivity of the rectal wall in 31 patients receiving radiotherapy for prostate or bladder cancer (Kushwaha et al. 2003). Recently, causes of fecal and urinary incontinence were studied in cadavers. Cadaver total mesorectal excision (TME), surgery demonstrated that, especially in low tumors, the pelvic floor innervation can be damaged (Wallner et al. 2008).

A number of patient-associated factors have been linked to a higher rate of radiation proctitis including young age, previous abdominal surgery, hypertension, vasculopathy, diabetes, and hemorrhoids (Tagkalidis and Tjandra 2001; Potish et al. 1979; Gilinsky et al. 1983; Lanciano et al. 1992). Other patient factors include inflammatory bowel disease, connective tissue disorder, previous acute radiation proctopathy, and ataxia-telangiectasia gene (Garg et al. 2006).

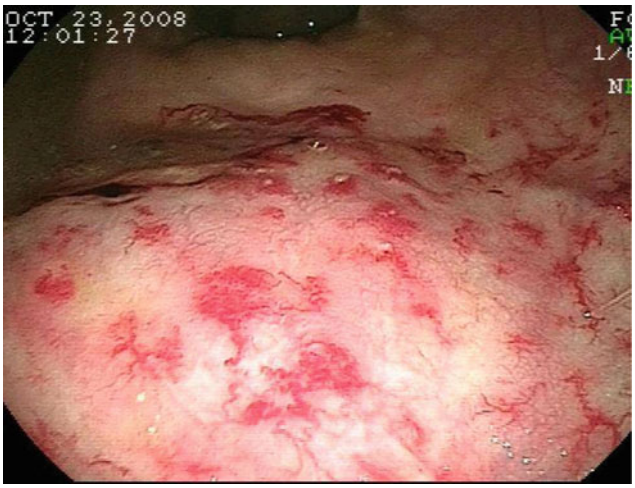

Fig. 6 An endoscopic view of the rectum showing multiple telengectasias of the rectum as a result of radiation

4 Clinical Syndromes

4.1 Detection (Symptoms)

Acute proctitis can occur in the latter half of fractionated radiation regimens and are often expressed with symptoms of diarrhea and accompanied by pain depending on the severity of the mucositis (Figs. 5 and 6, Tables 1 and 2).

Chronic radiation proctitis typically occur anywhere from 8 to 13 months after completion of treatment (Tagkalidis and Tjandra 2001) (Fig. 5a). Bleeding is the most common symptom of chronic radiation proctitis compared to acute radiation proctitis where bleeding is relatively uncommon. Other symptoms of chronic radiation proctitis include mucous discharge, urgency, fecal incontinence, diarrhea, and pain (Zimmermann and Feldmann 1998). Constipation can occur in the presence of a stricture most notably in the sigmoid colon region usually occurring as a result of an intracavitary implant in the treatment of cervical cancer or endometrial cancer. Fibrosis can also be seen following RT (Fig. 5b).

The Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC), Late Effects of Normal Tissue (LENT) and the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 are the three most widely used scoring systems use to grade late toxicity.

The removal of the separation between acute and late radiation effects was made when CTCAE v3.0 was adopted. An event is defined and graded relative to the time the evaluation was performed but CTCAE v3.0 does not separate criteria by acute or chronic. The CTCAE v3.0 criteria classify symptoms along the GI tract and not by anatomic region.

Table 1 LENT SOMA. Clinical syndromes

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Subjective				
Tenesmus	Occasional urgency	Intermittent urgency	Persistent urgency	Refractory
Mucosal loss	Occasional	Intermittent	Persistent	Refractory
Sphincter control	Occasional	Intermittent	Persistent	Refractory
Stool frequency	2–4/day	4–8/day	>8/day	Uncontrolled diarrhea
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective				
Bleeding	Occult	Occasionally >2/week	Persistent/daily	Gross hemorrhage
Ulceration	Superficial ≥ 1 cm^2	Deep ulcer	Perforation, Fistulae	
Stricture	>2/3 normal diameter with dilatation	1/3–2/3 normal diameter with dilatation	<1/3 normal diameter	Complete obstruction
Management				
Tenesmus & stool frequency	Occasional, ≥ 2 antidiarrheals/week	Regular, >2 antidiarrheals/week	Multiple, >2 antidiarrheals/day	Surgical intervention/ Permanent colostomy
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Bleeding	Stool softener, iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention/ Permanent colostomy
Ulceration	Diet modification, stool softener	Occasional dilatation	Steroids per enema, hyperbaric oxygen	Surgical intervention/ Permanent colostomy
Sphincter control	Occasional use of incontinence pads	Intermittent use of incontinence pads	Persistent use of incontinence pads	Surgical intervention/ Permanent colostomy
Analytic				
Barium enema	Assessment of lumen and peristalsis			
Proctoscopy	Assessment of lumen and mucosal surface			
CT	Assessment of wall thickness, sinus, and fistula formation			
MRI	Assessment of wall thickness, sinus, and fistula formation			
Anal manometry	Assessment rectal compliance			
Ultrasound	Assessment of wall thickness, sinus, and fistula formation			

Table 2 Late injury to the rectum/anus may be broadly, and somewhat arbitrarily, segregated into categories as shown

	Focal	Global
Subclinical	1. Telangiectasia 2. Asymptomatic stricture via endoscopy or radiographs 3. Thickened bowel wall by imaging	1. Asymptomatic abnormalities in anorectal manometry
Clinical	1. Bleeding, ulceration 2. Stricture	1. Incontinence 2. Constipation

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

The LENT SOMA system provides a means to categorize and grade toxicities (Table 1) (Rubin et al. 1995). An alternative way to segregate endpoints are provided in Table 2.

Fecal incontinence after pelvic radiotherapy is poorly understood and potentially underreported occurring in perhaps 3–53 % of patients (Putta and Andreyev 2005). The underreporting may be due to patient's embarrassment and associated failure to report incontinence and because prospective studies often fail to properly assess incontinence as a specific endpoint using validated and reproducible methodologies. Patients with prostate cancer may have a lower incidence of incontinence compared to patients with gynecologic, bladder, rectal, or anal cancer because of

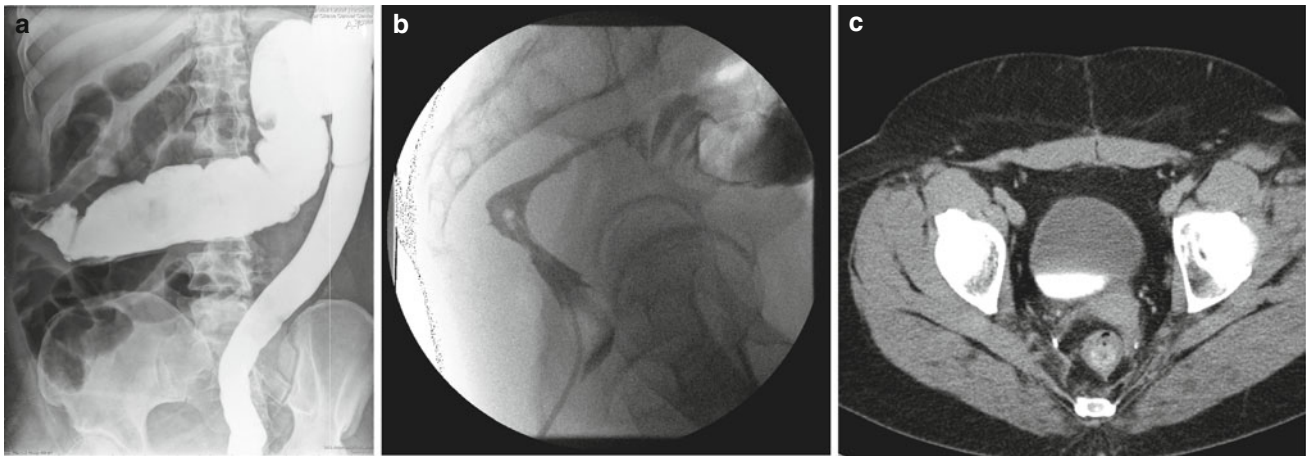

Fig. 7 **a** A barium enema of a patient who received post-operative radiation for adenocarcinoma of the rectum. The mucosal pattern is obliterated resulting in a smooth featureless tubular appearance of the rectum. **b** A stricture in the upper rectum as a result of radiation. **c** A CT image showing a thickened rectal wall in a patient having undergone a low anterior resection and postoperative radiation for an adenocarcinoma of the rectum

potentially lower dose volume parameters involving the anal sphincter. Most studies assessing anorectal function are generally not adequately controlled or powered, do not adequately assess anorectal function, and often fail to follow patients for extended time. Thus, the reported data are limited and suspect (Putta and Andreyev 2005).

4.1.1 Endoscopy

Flexible endoscopy is becoming the most frequently used diagnostic examination to treat and manage radiation proctitis. Flexible sigmoidoscopy or colonoscopy can be used to visualize the colon and assess for other etiologies of rectal bleeding or diarrhea. The classic endoscopic findings of radiation proctitis include prominent telangiectasia, erythema, and friability (Gilinsky et al. 1983; Reichelderfer and Morrisey 1980). A distinct margin can be detected between the normal rectal mucosa and the area affected by radiation. A typical endoscopic picture of radiation proctitis is shown in Fig. 6. Patients suspected of having a radiation reaction should *not* be biopsied. The trauma of the mucosa can lead to infection and/or a poorly healing wound.

4.1.2 Functional Tests

Anorectal manometry is a common and widely used test to assess anorectal function (Sun and Rao 2003). Continuous fluid-inflation procometrograms have been used to evaluate the symptoms of chronic radiation proctitis in patients who received radiation. Significant reductions in rectal volumes at sensory threshold, constant sensation and maximal tolerance, and in rectal compliance are seen in patients treated with radiotherapy compared to age- and sex-matched controls who did not receive radiation (Varma et al. 1985).

4.2 Diagnosis: Imaging

4.2.1 Barium Enema

Double contrast barium enema, while standard in the past, has been replaced in the diagnosis of chronic proctitis by flexible sigmoidoscopy. Characteristic features of chronic radiation injury to the rectum seen in a barium enema include (Gilinsky et al. 1983) (Fig. 7a, b):

1. Loss of distensibility of the rectum and/or sigmoid
2. Fixed stenoses and stricture of various lengths and degrees of narrowing
3. Shortening of the rectum and/or sigmoid, loss of normal rectal curves, and increase of retrorectal (presacral) space
4. Mucosal pattern changes, including irregularities, pseudo-polypoidal protrusions, various degrees of obliteration of mucosa, sometimes resulting in a smooth, featureless tubular appearance of the rectum
5. Irregularities of contour varying from tiny serrations representing shallow ulcerations to ragged marginations similar to those associated with malignancy
6. Sinuses into the pelvic tissue and fistulae to the bladder, vagina, and small bowel.

Figure 7a is a typical barium enema of a patient with radiation proctitis showing the smooth featureless tubular appearance of the rectum. Figure 7b shows a stricture of the rectum.

4.2.2 Computed Tomography/Magnetic Resonance Imaging

Computed tomography (CT) can be helpful in the diagnosis of radiation proctitis. CT scans can show a thickened rectal wall and dilated proximal loops of bowel (Chen et al. 2003).

CT and magnetic resonance imaging (MRI) are more sensitive in identifying changes in the surrounding tissue compared to barium enemas. MRI is more sensitive, however, in identifying early radiation changes (Rubin et al. 2002). T2-weighted images show increased signal intensity of the submucosa and inner muscle layer with a normal appearance of the outer muscle layer. The outer muscle layer of the rectum will develop increased signal with time on T2-weighted images. (Rubin et al. 2002) Fig. 7c is a CT scan of a patient who received postoperative radiotherapy for rectal cancer with radiation proctitis.

5 Radiation Tolerance: Predicting RT-Induced Rectal Injury

Radiation proctitis comprises a spectrum of symptoms ranging from rectal bleeding, mucus discharge, incontinence and fecal leakage. The TD 5/5 (probability of 5 % complication in 5 years) and TD 50/5 (probability of 50 % complication within 5 years) from Rubin and Casarett's original work (1968) was updated by Emami and Lymen et al. with volume of tissue incorporated into the analysis. The toxicity endpoint selected for rectal toxicity was severe proctitis, necrosis, fistula, or stenosis. A volume effect did not exist for 1/3 and 2/3 of the organ volume for the TD 5/5 and TD 50/5 if the volume irradiated was 100 cm^3 (Emami et al. 1991). The whole organ TD 5/5 and 50/5 was 6000 cGy and 8000 cGy, respectively (Emami et al. 1991). Unfortunately, because of the paucity of data, the clinical judgment of the physician on the normal tissue task force was used to generate these values.

A clearer picture of rectal tolerance has emerged with dose escalation trials for prostate cancer and improved radiation therapy treatment planning systems with the ability to calculate dose volume histograms. The greatest literature identifying risk factors for chronic radiation toxicity originates from reports of cervical and prostate cancer patients treated with radiation. The literature is sparse, however, detailing risk factors for chronic radiation toxicity for patients with rectal cancer treated with pre or postoperative radiation. This may be a result of the relatively lose doses used with pre and postoperative treatment. Large radiation treatment volumes and techniques were, however, mentioned as risk factors for late rectal toxicity (Glimelius et al. 2003).

5.1 Dose Time Fractionation

5.1.1 Cervix Cancer

Severe bladder and rectal complications occurred when the external beam dose was greater than 50 Gy in patients with Stages IIIA B cervical cancer treated with external beam radiation and 2 intracavitary implants (Stryker et al. 1988). It was recommended the whole pelvis dose should not exceed 40–45 Gy when combined with 2 intracavitary implants. There is controversy, however, if time dose factors (TDF) are able to predict late normal tissue reactions in patients with cervical cancer. TDF did not correctly predict late normal tissue reactions with increasing complication rates noted in patients receiving increased dose per fraction of external beam (Deore et al. 1992). Ogino et al. however, found both TDF and biologically effective dose (BED) values to significantly correlate with grade 4 rectal toxicity. Grade 4 rectal toxicity was not seen with a TDF < 130 or BED < 147 (Ogino et al. 1995). Ferrigno et al. reported patients with a cumulative BED > 110 Gy had a higher but not statistically significant rectal complication rate (Ferrigno et al. 2001). A 19.6 % rate of late rectal sequelae was noted when the cumulative BED was <110 compared to 36.4 % when the cumulative BED was >110 Gy (Chen et al. 2000). In another study, late rectal complications $\geq$Grade 2 were 5.4 % with a BED < 125 Gy compared to 36.1 % with a BED $\geq$125 Gy (Hyun Kim et al. 2005). Rectal dose in comparison to point A has also been reported to be a prognostic factor for patients with late rectal complications. Late rectal complications were noted in 9/13 patients when the rectal dose was greater than the prescribed dose to point A compared to 7/30 when the rectal dose was less than the prescribed dose (Clark et al. 1994). A greater rate of late rectal complications was also noted if the percent intracavitary dose to point A was 80 % or more (Shin et al. 1999) (Fig. 8a).

With High dose rate (HDR), the dose per fraction was shown in multivariate analysis to be a significant factor influencing proctitis rate. Patients treated with 7.2 Gy for 3 fractions had a greater proctitis rate compared to patients receiving 4.8 Gy for 5 fractions (Wang et al. 2004). Higher complication rates were noted when the intracavitary fractional dose was $\geq$3.2 Gy or with a total intracavitary dose of $\geq$20 Gy or more (Shin et al. 1999).

5.2 Dose/Volume Constraints

Table 3 depicts the dose recommendations for patients with cervical cancer undergoing external beam radiotherapy and intracavitary implants. Most data from these studies were collected prior to the 3D-CRT era. These studies combine external beam radiation therapy and HDR intracavitary doses; the intracavitary fractionation schedules were variable. In addition, the late rectal endpoints were measured with different toxicity scales. Koom et al. correlated DVH parameters from 3D-CRT gynecologic brachytherapy planning with the rectosigmoid mucosal changes observed on flexible sigmoidoscopy (Koom et al. 2007). The degree

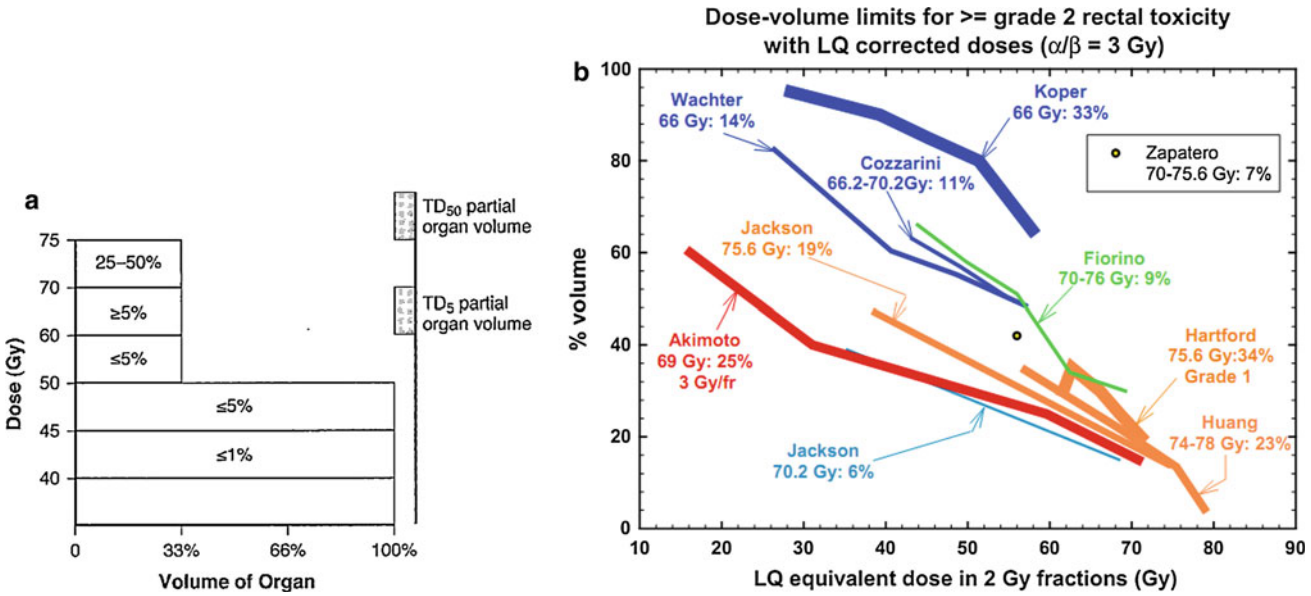

Fig. 8 **a** Dose–volume histogram for late effects seen in the gastrointestinal tract, illustrating the relationship between volume and tolerance doses. The right y-axis indicates the tolerance dose ranges for the TD_5 and TD_{50} for partial organ volume (POV) irradiation. (Modified from Rubin et al. 2001 with permissions) **b** Dose–volume histogram thresholds found to be significantly associated with Grade ≥2 rectal toxicity. Thicker lines indicate higher rates of rates of overall toxicity (percentages are indicated on the graph along with the physical prescription dose). Threshold doses are expressed as linear-quadratic equivalent doses delivered in 2-Gy fractions, calculated using $\alpha/\beta = 3$ Gy. The associated linear-quadratic equivalent prescription doses are coded by spectrum from lowest (*blue*), to highest (*red*). Volumes shown in the graph are based on the full length of the anatomic rectum. Curves for Huang and Wachter were adjusted downward by 15 % and by 50 % for Hartford, to account for the different definitions used for rectal volume. Dose–volume data from multiple centers converge at the high dose range, implying that these values are more consistently associated with toxicity. Abbreviations: LQ = linear quadratic (with permission from the Quantec review, Michalski et al. 2010)

Table 3 Dosimetric recommendations for the rectal wall to limit injury in patients irradiated for cervical cancer

Study	Dosimetric Recommendations
Ferrigno et al. (2001)	A higher but not statistically significant complication rate noted with a BED > 110 Gy
Ogino et al. (1995)	Grade 0 toxicity- Mean BED 126 Gy s.d. 35.3 Gy
Chen et al. (2000)	BED < 110 Gy 19.6 % late rectal complication rate BED > 110 Gy 36.4 % late rectal complication rate
Kim et al. (2005)	BED < 125 Gy 5.4 % late rectal complication rate BED ≥ 125 Gy 36.1 % late rectal complication rate
Huang et al. (2004)	BED < 100 Gy and external beam parametrial dose of <54 Gy

BED Biologically effective dose; s.d.-standard deviation

of mucosal change was related to DVH parameters and International Federation of Gynecology and Obstetrics (ICRU) rectal point ($ICRU_{rp}$) (Koom et al. 2007). The endpoint of visual mucosal change is not part of conventional toxicity scales and is of unclear clinical significance (Fig. 8b, Tables 3 and 4).

Table 4 shows the rectal dose constraints for external beam radiotherapy in the treatment of prostate cancer derived from studies using 3D-CRT. The rectal dose constraints are grouped by the reported-associated symptom. The studies that considered incontinence or fecal leakage only reported on 1 volume data point, V40 while the other endpoints were related to a broader array of dose/volume parameters.

5.2.1 Prostate Cancer

Several studies report a relationship between rectal/prostate dose/volume parameters and the incidence of late rectal toxicity (Fiorino et al. 2003, 2008; Huang et al. 2002; Peeters et al. 2005a, b; Pollack et al. 2002; Sohn et al. 2007; Storey et al. 2000; Vargas et al. 2008; Vargas et al. 2005, 2007). A variety of dose/volume metrics, and clinical endpoints have been considered. Some of the studies used ≥ grade 2 rectal bleeding while others use fecal incontinence and others use unspecified toxicity. In addition, all of the studies did not use the same toxicity scoring scale. Some used the RTOG/EORTC, some used LENT/SOMA, and others CTCAE v3.0. van der Laan et al. found late toxicity grading differed

Table 4 Dose/volume constraints for the rectum suggested in patients receiving external beam radiation therapy for prostate cancer

Study	V40	V50	V60	V65	V70	V75
Rectal bleeding						
Fiorino et al. (2008)		<55 %	<40 %		<25 %	<55
Peeters et al. (2006)				<30 %		
Incontinence/Fecal leakage						
al-Abany et al. (2005)	<40 %					
Fiorino et al. (2008)	<65–70 %					
Unspecified late rectal toxicity						
van der Laan et al. (2008)	<65 %	<55 %	<45 %		<20 %	
Storey et al. (2000)					<25 %	
Pollack et al. (2002)					<25 %	
Huang et al. (2002)			<41 %		<26 %	<16 %
Quantec Summary[a] Michalski et al. (2010)		<50 %	<35 %	<25 %	<20 %	<15 %

[a] Values expected to be associated with a rate of Grade ≥2 late rectal toxicity of <15 % and the probability of Grade ≥3 late rectal toxicity of <10 %, for prescriptions up to 79.2 Gy in standard 1.8- to 2-Gy fractions

depending upon the grading system used with the predictive value of the various dose–volume parameters lowest with the RTOG/EORTC grading system as compared to the LENT/SOMA and the CTCAE v3.0 scoring systems (van der Laan 2008). Dose to the different anatomic regions also can influence the measured toxicity. Heemsbergen et al. found the strongest correlation for dose received by the superior portion of the rectum, which often is the volume receiving the highest dose. 70–80 % of the anorectal region and bleeding and mucous loss while soiling and fecal incontinence had the strongest association with dose to the lower 40–50 %.(Heemsbergen et al. 2005) Rectal bleeding was found to correlate with anorectal V55–V65 with V65 being the most significant parameter while stool frequency correlated with anorectal V40. (Peeters et al. 2006) al-Abany et al. reported a statistically significant correlation between radiation to the anal sphincter region and risk of fecal leakage in the interval between 45–55 Gy and a statistically significant correlation between radiation to the rectum and risk of defecation urgency, diarrhea, or loose stools in the interval between 25 and 42 Gy(al-Abany et al. 2005).

The recent Quantec review summarized the dose/volume/outcome data from several studies involving patients treated with external beam for prostate cancer (Michalski et al. 2010). The DVH's that were suggested to best segregate patients into 'high' versus 'low' risk of rectal bleeding are shown in the Fig. 8. There is much variation in the apparent volume thresholds at dose $<\approx 60$ Gy. However, there appears to be much inter-study agreement in the 60–75 Gy dose range, suggesting perhaps that the volumes exposed to these higher doses are the most critical determinants of rectal bleeding. Additional information is provided in the colon section of "Stomach, Small and Large Intestines".

Table 5 Chemo therapy agents and associated GI toxicities

Agent	Late effect
5-Fluorouracil	Enteritis
5-Fluorouracil + mitomycin C(+RT)	Late benign esophageal stricture
5-Fluorouracil + MeCCNU(+RT)	Fistulas, perforation
Actinomycin D(+RT)	Enteritis
Bleomycin D(+RT)	Esophagitis
Cisplatin(+RT)	Enteritis
Cyclophosphamide(+RT)	Esophagitis
Doxorubicin(+RT)	Esophagitis
Methotrexate	Enteritis
Procarbazine	Enteritis

RT = radiation therapy
Modified from Rubin P: The Franz Buschke Lecture:Late effects of chemotherapy and radiation therapy: a new hypothesis, Int J Radiat Oncol Biol Phys 1984; 10:5–34, with permission from Elsevier Science

6 Chemotherapy Tolerance

Chemotherapy alone does not appear to produce significant late GI complications with any frequency, despite the well-documented acute toxicity caused by a long list of agents (Table 5) (Mitchell 1992). Drugs, such as 5-flurouracil (5-FU), produce diarrhea and, occasionally, small bowel toxicity (Fata et al. 1999). More severe late effects, such as GI bleeding, generally have been seen only in combined-modality therapy, which has led to severe acute complications, particularly in the small bowel (Minsky et al. 1995; Bosset et al. 1997) (Table 5).

6.1 Colorectum

The absence of predictive parameters for late intestinal events was demonstrated in the catastrophic complications that occurred in a carefully piloted Eastern Cooperative Oncology Group (ECOG) study using split-course radiation (60 Gy in 10 weeks: 20 Gy in 2-week courses x 3 with 2-week rest intervals) and adjuvant 5-FU, and maintenance chemotherapy (5-FU and MeCCNU [semustine]) for 1 year (Danjoux and Catton 1979). Although no undue acute toxicity occurred with the administration of either radiation therapy of chemotherapy, late fistulization and necrosis occurred in 29 % of patients 6 months to 2 years after al therapy ceased. Generally, 5-FU alone added to 45–50 Gy is well tolerated, but the addition of mitomycin C raises grade III toxicity to 25 % (Cummings et al. 1991), and a similar addition of cisplatin in cancer of the cervix leads to an 18 % large bowel complication rate (Grigsby and Perez 1999).

7 Special Topics

7.1 Cervix Cancer

Stage

Patients with stage IIB-IVA had a greater risk of developing late rectal sequelae but this may be more a function of higher dose delivered to these patients compared to lower stage patients (Chen et al. 2000).

Age

Age has been found to be a predictor of a higher rate of rectal toxicity. Age > 60 was the only factor to predict late grade 3 rectal toxicity in a multivariate analysis of 54 patients with cervical cancer treated with external beam radiation therapy and intracavitary implant (Kim et al. 2008). Age >70 was one of 3 factors to predict in a multivariate analysis for an increased risk of developing late rectal sequelae (Chen et al. 2000).

Surgery

The risk of fistula formation was doubled in 234 patients with stage IB cervix cancer undergoing adjuvant extrafascial hysterectomies after radiation. An increased rate of GI toxicity was also seen in black and non-Hispanic white women as compared to Hispanic women (Eifel et al. 1995).

Consequential late effects

Late effects occurring *due to* an acute effect are termed consequential. There are some data to suggest that the severity of acute reaction is related to the development of a late effect, but the causality is unclear. For example, Wang estimated proctitis rates rates to be 28, 48, and 71 % in patients without diarrhea, moderate diarrhea, and sever diarrhea, respectively (Wang et al. 1998). On Cox multivariate analysis, the severity of acute diarrhea was the only factor that significantly correlated with the development of late radiation proctitis. The severity of the diarrhea, however, did not correlate with the severity of the proctitis.

Body-Mass Index

In a study of 3,489 women undergoing radiation therapy for stage I or II cervical cancer, those with a BMI < 22 had an increased rate of gastrointestinal complications compared to those with a BMI > 22. In addition, women with ≥ 1 pack/day of smoking were also found to have increased rectal complications (Eifel et al. 2002).

Table 6 Patient-related factors that could increase the risk for radiation proctitis

Young age
Ataxia-telangiectasia gene
Pelvic node dissection
Connective tissue disorder
Hypertension
Cardiovascular disease
Hemorrhoids
Inflammatory bowel disease
Previous abdominal surgery
Peripheral vascular disease
Diabetes
Tumor stage

Adapted from Garg et al. (2006)

7.2 Patient Related Factors

A number of patient related factors associated with the developed of radiation proctitis have been reported in an review of radiation proctitis by Garg et al. (2006), including young age, Ataxia-telangiectasia gene, prior pelvic/abdominal surgery, connective tissue disorder, hypertension, hemorrhoids, inflammatory bowel disease, peripheral vascular disease, diabetes, and advanced tumor stage. Similarly, the recent Quantec review noted that the risk of rectal bleeding was reported to be associated with diabetes, inflammatory bowel disease, advanced age, androgen deprivation therapy (perhaps a surrogate for tumor stage/size), rectum size, prior abdominal surgery, and severe acute rectal toxicity. This later finding suggests that late effects might, in part, be in consequential (i.e., resulting from a severe acute reaction). If follows therefore that aggressive treatment to lessen the severity of an *acute* effect might lessen late effects as well (Table 6).

The increased risk in the patients with a large rectum appears to be related to inconsistencies between the planning CT and the anatomy at the time of the treatment. It has

been suggested that the rectal movement post-planning causes the rectal doses to be 'higher-than-believed based on the planning CT'. It is thus reasonable to consider checking the accuracy/consistency of the rectal position in patients with a large rectum on their planning scan. Table 6 details possible patient related factors in the development of radiation proctitis.

7.3 Brachytherapy

Rectal morbidity can occur in patients undergoing prostate seed implants, with or without external beam radiotherapy. Ohashi et al. investigated rectal morbidity in a group of 227 consecutive patients with localized prostate cancer treated with I-125 implants alone or in combined with external beam. The overall rate of RTOG grade ≥2 rectal bleeding was 4.4 %. Multivariate analysis revealed maximal rectal dose to be correlated with rectal bleeding (Ohashi et al. 2007). A rectal dose >160 Gy correlated with grade 2 rectal morbidity, and all patients receiving >160 Gy had external beam radiotherapy (Ohashi et al. 2007). Shah et al. using the CTCAE v3.0 found the percent of the rectal wall volume receiving 25 % of the prescribed prostate dose >25 % (%V25 > 25 %) and the percent of the rectal wall receiving 10 % of the prescribed dose >40 % (%V10 > 40 % predicted worse late diarrhea and maximum toxicity, respectively (Shah and Ennis 2006). The rectal wall volume receiving at least 100, 200, or 300 % of the prescription dose was also related to rectal bleeding in an analysis of 161 intermediate risk prostate cancer patients randomized to implantation with (Henriksson et al. 1992) Pd (90 versus 115 Gy) with 44 versus 20 Gy external beam (Sherertz et al. 2004).

The study instrument was also found to be a factor in identifying patients with rectal toxicity. Merrick et al. found the multifactorial Rectal Function Assessment Score (RFAS) to elucidate fine gradations in bowel function of a severity less than RTOG grade 3 morbidity and only the minimum dose received by 5 % of the rectum (D5) to correlate with rectal morbidity in multivariate analysis (Merrick et al. 2003).

8 Prevention and Management

8.1 Prevention

8.1.1 Device

Three-Dimensional Conformal Radiation/IMRT/Proton Beam

An evidence-based review of the available literature found three-dimensional conformal radiation (3-DCRT) reduced late GI toxicity in patients with prostate cancer, compared to conventional radiation (Morris et al. 2005). Anorectal function after radiotherapy for prostate cancer, however, was found to be independent of technique, two-dimensional versus three-dimensional radiotherapy (Yeoh et al. 2009).

Intensity modulated radiation therapy appears to further reduce the incidence of radiation-induced late rectal toxicity. Zelefsky et al. reported that IMRT significantly reduced the risk of gastrointestinal toxicity compared to patients treated with 3-D CRT despite the use of higher doses in the IMRT group (Zelefsky et al. 2008). More recently, proton beam radiotherapy has been investigated as a means to reduce toxicity in patients receiving radiotherapy for prostate cancer. Rectal wall volumes receiving 10–80 Gray Equivalents (GE) were significantly reduced with proton beam therapy compared to IMRT (Vargas et al. 2008). Clinical trials comparing this new technology to IMRT, however, have not been performed and until recently, there have only been two operational proton beam therapy facilities in the US.

Image Guidance

The ability of B-mode acquisition and targeting (BAT) system ultrasound to reduce acute and late rectal toxicity was evaluated in 42 sequential patients with prostate cancer treated with 70 Gy. Patients treated without the BAT ultrasound has significantly more acute toxicity and a trend to more late toxicity compared to patients treated with the BAT ultrasound (Bohrer et al. 2008). A reduction in grade 2 RTOG rectal toxicity was found when Image Guided IMRT (IG-IMRT) versus IMRT alone in patients with prostate cancer (Chung et al. 2009). The reduction in toxicity appeared to result from the use of smaller margins around the prostate in the IGRT patients.

Endorectal Balloon

Endorectal balloons (ERB) have also been found to reduce late rectal mucosal changes detected after 3-D CRT and IMRT. (van Lin et al. 2007; Teh et al. 2005; D'Amico et al. 2006) van Lin et al. reported ERB's significantly reduced the rectal wall volume receiving >40 Gy and late rectal toxicity rate (van Lin et al. 2007). Teh et al. reported 6.9 and 1.7 % Grade 2 and 3 late rectal toxicities, respectively, in men treated with a daily 100-cc ERB and IMRT (Teh et al. 2005). A 10 % estimate of Grade 3 rectal bleeding at 2 years was reported by D'Amico et al. after a 60-cc ERB was used with 3D-CRT. Vargas and colleagues reported that either an ERB or water instilled into to rectum can reduce the dose the rectal wall receives with proton radiotherapy (Vargas et al. 2007). Selected patients appeared to have a small but significant advantage with an ERB over the water instillation, but they concluded that water alone was well tolerated and a reasonable option for most patients.

8.1.2 Medication

Amifostine

Amifostine, a thiol derivative, acts as a free radical scavenger with its sulfhydryl compound. Intrarectal amifostine (WR 2721) reduces rectal toxicity in patients undergoing radiotherapy for prostate and gynecologic malignancies (Kouloulias et al. 2004; Simone et al. 2008; Kouvaris et al. 2003; Kouloulias et al. 2005; Liu et al. 1992). In patients receiving RT for prostate cancer, the addition of 1500 mg of amifostine in a 40-ml aqueous enema solution reduced late rectal toxicity compared to patients who did not receive the amifostine (Kouloulias et al. 2004). Similarly, two grams of amifostine given in a rectal suspension to patients with prostate cancer receiving radiotherapy improved acute and late bowel quality of life scores compared to patients who received 1 gm of amifostine (Simone et al. 2008).

Sucralfate

Sucralfate is a nonabsorbable basic aluminum salt used to treat gastric ulcers. Sucralfate appears to reduce microvascular injury by stimulating angiogenesis. Since late radiation injury may be mediated by the microvasculature, sucralfate was hypothesized to potentially prevent late radiation change (Szabo et al. 1991). The ability of oral sucralfate to prevent late radiation-induced rectal toxicity has been tested in four trials. Overall, three of these are negative (and one is positive. Patients were tested in a double-blind, placebo-controlled randomized trial in patients with prostate cancer receiving radiation. There was no difference in RTOG grade 2 or worse late toxicity at 2 years, bowel frequency, mucus discharge, or fecal incontinence between the two groups (Kneebone et al. 2004). Another randomized trial, however, suggested that sucralfate reduced the rates of rectal toxicity at 12–14 months after radiotherapy while yet another found no benefit 10–12 months after RT (Henriksson et al. 1992; Martenson et al. 2000). Finally, the Trans-Tasman Radiation Oncology Group did not find intra-rectal enemas reducing rectal toxicity after radiotherapy (O'Brien et al. 2002).

Misoprostol

Misoprostol is a prostaglandin E_1 analog that has been used in the treatment and prevention of nonsteroidal anti-inflammatory agent-induced gastric and duodenal ulcers (Graham et al. 1993, 1988). A double-blinded randomized phase III trial of 100 patients with prostate cancer treated with radiotherapy were randomized to either misoprostol rectal suppositories or placebo. The study found misoprostol rectal suppositories did not decrease the incidence and severity of radiation-induced acute proctitis and may have increased the incidence of acute bleeding (Hille et al. 2005). There was, however, one small randomized study of misoprostol suppositories in 16 patients which showed a potential preventative effect but this study used a nonvalidated scoring system (Khan et al. 2000).

Probiotics

Nuclear transcription factor kappa B (NK-FB) has been shown to play a key role in the development of radiation-induced mucositis (Yeoh et al. 2005). The mechanism of action of one probiotic, *L. casei* DN 114-001, is to modulate the pro-inflammatory pathways including the blockade of ubiquitylation of the alpha-subunit of the inhibitor of transcriptional activator NK-KB that prevents its degradation by the proteasome and ultimately the transcription of the dependent pro-inflammatory genes by intestinal epithelial cells (Tien et al. 2006). *Lactobacillus acidophilus* was shown in a randomized trial of 24 patients, to reduce bowel movements in 11 patients with gynecologic cancer randomized to the *Lactobacillus acidophilus* as compared to the control group (Salminen et al. 1988). The incidence of diarrhea was significantly reduced in the group receiving the intervention as compared to the control group, $p < 0.01$. However, Giralt et al. reported on 85 patients with gynecologic cancer treated with radiation, and randomized to ± a probiotic drink consisting of liquid yogurt containing *L. Casei* DN-114 (Giralt et al. 2008). There were no differences in the incidence of diarrhea, but a significant effect on stool consistency was reported ($p = 0.04$) (Giralt et al. 2008). Conversely, the probiotic preparation VSL #3 appeared to reduce radiation-induced diarrhea in a randomized trial in 429 patients with sigmoid, rectal, or cervical cancer undergoing adjuvant radiation after surgery (Delia et al. 2007).

8.2 Management

8.2.1 Hyperbaric Oxygen

Hyperbaric oxygen has been used to treat the effects of radiation (Marx 1983; Feldmeier and Hampson 2002; Bouachour et al. 1990). Approximately 21 studies evaluating the use of hyperbaric oxygen have been published to date. The atmospheres absolute ranged between 2.0–2.5 with the majority of dives lasting 90 min (Clarke et al. 2008). Treatment sessions ranged from 3 to 80 with a reported overall improvement of 25–100 % (Clarke et al. 2008). Clarke et al. conducted a randomized double-blind crossover trial of hyperbaric oxygen 2.0 atmospheres absolute for 30 sessions or sham treatment with 1.1 atmospheres absolute for 30 sessions. They reported patients receiving hyperbaric oxygen experienced a significantly improved healing response compared to sham-treated patients with an absolute risk reduction of 32 % (Clarke et al. 2008).

8.2.2 Laser Coagulation

Argon laser therapy has been used to alleviate the symptoms of rectal bleeding in patients suffering from radiation proctitis; Table 7 for summary. Overall, laser therapy appears effective. Most reports note that patients either improve or have few recurrences of bleeding.

8.2.3 Sucralfate

Small retrospective single institution cohort studies have reported a benefit to sucralfate in the treatment of radiation proctitis. Sasai reported decreased long term bleeding in 3 patients given oral sucralfate (Sasai et al. 1998). Kochhar et al. reported 70.8 % of 26 patients treated with rectal sucralfate had no further bleeding (Kochhar et al. 1999). However, a larger randomized placebo controlled trial did not find any effect on grade $\geq$2 rectal bleeding, bowel frequency, mucus discharge or fecal incontinence (Kneebone et al. 2004). This study was highlighted in the previous section on prevention. Rectal sucralfate was compared to oral sulfasalazine and rectal steroids in a prospective randomized, double blind trial in 37 patients with radiation proctitis. Both groups experienced significant improvements in posttreatment symptoms compared to pretreatment symptoms. The patients receiving the sucralfate enemas had significantly better clinical responses, although endoscopic responses were not statistically different (Kochhar et al. 1991).

8.2.4 Vitamins

The oxidative stress of radiation on the rectum has been thought to play a part in the development of radiation proctitis so it has been hypothesized antioxidants such as vitamins C and E could be used in the treatment of radiation proctitis. Twenty patients with prostate or gynecologic malignancies treated with radiation and experiencing symptoms were given a combination of 400 IU of vitamin E TID and 500 mg of vitamin C TID. A significant reduction in the symptom index for bleeding, diarrhea, and urgency was noted compared prior to treatment. Pain, however was not improved with vitamin treatment (Kennedy et al. 2001). Nineteen patients with significant symptoms of radiation proctitis were randomized to oral palmitate (vitamin A) or placebo in a double-blinded randomized controlled trial. The primary goal of the study was relief of symptoms of chronic radiation proctopathy. Seven of ten patients randomized to vitamin A were found to have a response while only 2 of 9 patients randomized to placebo responded, $p = 0.057$ (Ehrenpreis et al. 2005). All five of the placebo nonresponders who crossed over to vitamin A treatment responded.

8.2.5 Short Chain Fatty Acids

Short chain fatty acids are the main energy source of colonic epithelium. Their use may be impaired in patients with radiation proctitis. Nineteen patients were randomly assigned to short chain fatty acid enemas containing 60 mM sodium acetate, 30 mM sodium propionate, and 40 mM sodium butyrate or placebo for 5 weeks and patients followed for 6 months (Pinto et al. 1999). After 5 weeks, patients receiving fatty acid enemas had a significant decrease in the number of days with rectal bleeding and an improvement of endoscopic score compared to patients receiving the placebo. After 6 months, the differences seen at the 5 week period decreased, however, to a degree that there were no differences between patients receiving the enema and those receiving placebo. Changes in the histologic parameters did not significantly change in either group and although patients receiving short chain fatty acid treatment did not experience worse symptoms, the placebo treated patients gradually improved and the differences seen between the two groups were no longer observed (Pinto et al. 1999). al-Sabbagh et al. also reported an improvement in 4 patients who received short chain fatty acid enemas (al-Sabbagh et al. 1996). Butyric acid enemas were compared to placebo enemas in a randomized, double-blind cross-over trial in 15 patients with radiation proctitis. There was a nonsignificant improvement in total symptom score in the patients receiving the short chain fatty acid versus the placebo (Talley et al. 1997).

8.2.6 Miscellaneous

The ability of *L.rhamnosus* (Antibiophilus) to treat radiation proctitis has been evaluated in a double-blind, randomized study in 206 patients. Patients receiving Antibiophilus had an improvement in the number of bowel movements and feces consistency compared to controls (Urbancsek et al. 2001).

Seven patients with radiation proctitis were treated with endoscopic cryotherapy with cessation of bleeding noted in all 7 patients (Kalloo and Kantsevoy 2001). There was no mention, however, of any late damage from the cryotherapy.

The active component of sulfasalazine, 5-aminosalicylic acid, was tested in 4 patients. One of the 4 noted a transient improvement while the other 3 did not (Baum et al. 1989). Loperamide-N-oxide was tested in a double-blind randomized trial in 18 patients with chronic radiation enteritis. Patients receiving loperamide-N-oxide had reduced frequency of bowel action, slower small intestinal and total gut transit, more rapid gastric emptying, improved absorption of bile acid and increased permeability to 51Cr EDTA (Yeoh et al. 1993). This medication, however, is not available in the United States. Metronidazole in combination with corticosteroid enemas and mesalazine (5-aminosalicylic acid) was compared to corticosteroid enemas and mesalazine alone in 60 patients with rectal bleeding and diarrhea. Rectal bleeding and mucosal ulcers were significantly lower in patients who received metronidazole at 1, 3,

Table 7 Laser therapy for late rectal bleeding

Study	Patients	Type of malignancy	Laser type	RT Dose (range)	# of Laser procedures (range)	Recurrence or Outcome
Taylor et al. (1993)	14	N/R	Argon	N/R	Median 3	10 (71 %)
Fantin et al. (1999)	7	Prostate Endometrial	Argon	68.4 (24–72) Gy	Median 2	0
Kaassis et al. (2000)	16	Prostate Endometrial	Argon	N/R	Mean 3.7	1
Taieb et al. (2001)	11	Prostate Endometrial Rectal	Argon	N/R	Mean 3.2 (1–5)	2/11 bleeding greatly reduced
Viggiano et al. (1993)	47	N/R	Nd:Yag	N/R	N/R	N/R
Taylor et al. (2000)	23	Prostate Endometrial	Nd:Yag	N/R	Median 2 (1–5)	2 patients developed rectal ulcers after treated treatment; 65 % Improved; 30 % No Change; 5 % worse

N/R- Not reported

and 12 months after therapy (Cavcic et al. 2000). Diarrhea and edema was also decreased at the same time points.

Formalin instillations into the rectum were used in 20 patients with gynecologic malignancies, 18 cervical cancer and 2 endometrial, who failed other topical therapy. Hemorrhage immediately ceased after 4 % formalin instillation in 17 patients with an overall success rate of 90 % (Luna-Perez and Rodriguez-Ramirez 2002). Five patients, however, had moderate pelvic pain, one developed rectosigmoid necrosis requiring surgery, and two patients developed a rectovaginal fistula requiring a colostomy (Luna-Perez and Rodriguez-Ramirez 2002). Other less-conventional methods of treating radiation proctitis, including hormone therapy and intrarectal Maalox®, have been reported as case reports. Surgery has been used when less invasive treatments have failed (Thompson and Levitt 2000; Kimose et al. 1989; Pricolo and Shellito 1994; Yegappan et al. 1998).

9 Future Directions

9.1 Single Nucleotide Polymorphisms

The predictive ability of single nucleotide polymorphisms (SNP) in candidate genes to predict tumor response and toxicity has been investigated in a number of cancers including prostate cancer. A significant association with toxicity was found for the SNP LIG4 (T > C, Asp(568)Asp), ERCC2 (G > A, Asp(711)Asp), and CYP2D6*4 (G > A, splicing defect) in 83 patients with prostate cancer undergoing 3-D CRT (Damaraju et al. 2006). In another study, the -509 T/T genotype was found to be associated with a significant increase risk of developing late rectal bleeding, 55 versus 26 %, $p = 0.05$, compared to the C/T or C/C genotype in 141 patients with prostate cancer treated with radiotherapy (Peters et al. 2008). Patients with the SOD2 rs4880 T/C (Val16AIa) genotype had a significant increase in grade 2 late rectal bleeding, 8 versus 0 %, $p = 0.02$, compared to patients with either the C/C or T/T genotype (Burri et al. 2008). In addition, patients with the combination of the SOD2 rs4880 C/T genotype and the XRCC3 rs861539 T/C (T'HR241Met) genotype experienced a significant increase in grade 2 late rectal bleeding, 14 versus 1 %, $p = 0.002$, compared to patients without these genotypes (Burri et al. 2008).

10 History and Literature Landmarks

The first report of radiation induced rectal damage was in 1897. Walsh reported on several instances of what is now regarded as the acute effects of radiation after prolonged exposure of several regions of the body with Roentgen rays (Walsh 1897). Buie and Malmgren coined the term "factitial" to describe the unintended radiation injury to an organ after radiation for a malignancy (Buie LAaM 1930). Warren and Friedman reported on 38 cases of radiation lesions in the gastrointestinal tract in 1942 (Warren et al. 1942). They reported radiation-induced lesions could be grouped by location and type including ulcers, fistulae, and strictures. The location of the lesions varied from in close proximity or distant to the neoplasm. Radiation-induced damage could be focal or involve long segments of intestine uniformly. Radiation changes were found in the connective tissue,

Table 8 Landmark articles of radiation induced rectal damage

Author	Topic
Walsh (1897)	First to describe deep tissue effects of exposure to Roentgen ray
Warren et al. (1942)	Early review of radiation proctitis in 38 patients
Rubin and Casarett (1968)	First text to systematically describe clinical radiation pathology
Gilinsky et al. (1983)	Oft quoted article describing the natural history of radiation proctitis
Yeoh et al. (1993, 1993)	Described the pathophysiology of radiation-induced enteritis
Emami et al. (1991)	Related dose and volume to predict normal tissue toxicity
Gunderson and Martenson (1989)	Modified the gastrointestinal tract radiation tolerance
Sonis (1998)	Described a four-stage model for radiation mucositis
Liu et al. (2008)	Found increased expression of TGF-beta1, HIF-1 alpha, VEGF, and endothelial cell marker CD31 associated with radiation induced fibrosis
Rubin et al. (1995)	Overview of late effects normal tissues (LENT)
Garg et al. (2006)	Recent review article on Radiation Proctopathy

blood vessels, mucosa, and muscle. They reported the diagnosis of radiation-induced damage could be made by primary criteria; hyalinization of the connective tissue, abnormal fibroblasts, telangiectasia, and hyaline degeneration of vessel walls, and secondary criteria; endothelial abnormalities, phlebosclerosis, changes in muscle fibers, and epithelial alterations.

Rubin and Casarett's Clinical Radiation Pathology was published in 1968 (Rubin and Casarett 1968). In this work, Rubin and Casarett introduce the theory of radiation damage being described as acute, subacute, chronic, and late. Irradiated tissues recover after radiation with persistent subclinical damage that could transform into clinical damage after further injury or infection. Gunderson et al. modified the TD5/5 and TD 50/5 for rectal ulcer stricture in 1988 to 55–60 Gy and 75 Gy, respectively (Gunderson and Martenson 1989). A more recent listing of articles describing the effects of radiation on rectal function is listed in Table 8.

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Musculoskeletal System: Growing Endochondral Bone, Mature Osseous, Muscle (Striated), and Soft Tissue Mesenchyme

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Contents

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Abstract

- Most radiation therapy fields include bone and/or soft tissue.
- Damage to bone and connective tissue is frequent after radiation therapy, particularly in the growing tissues of children.
- The growing less differentiated cells in bone and muscle tissues of children undergo apoptosis and cell depletion after even low doses of RT, causing hypoplasia and bone shortening.
- Limb-length discrepancy and other manifestations of impaired development are common late effects of radiation therapy to children.
- Craniofacial deformities, slipped capital femoral epiphysis, valgus and varus deformities, and bone necrosis are other sequelae of irradiating children and demonstrate the variety of possible adverse treatment effects.
- Bone necrosis and pathologic fracture are the most severe effects after bone irradiation in adults.
- Irradiating muscle and other connective tissue can result in fibrosis and loss of range of motion in joints.
- The TD 5/5 for bone necrosis is probably about 65 Gy at 1.8–2.0 Gy per fraction.
- The TD 5/5 for severe soft tissue fibrosis is probably about 55 Gy at 1.8–2.0 Gy per fraction.
- Pathologic fracture after radiation therapy usually requires surgical intervention.
- Fibrosis can sometimes be reversed with pentoxifylline and vitamin E.

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Abbreviations

ALL	Acute lymphoblastic leukemia
AVN	Avascular necrosis
BMP	Bone morphogenetic protein
CSI	Craniospinal irradiation
CTC	Common toxicity criteria
DSB	Double-strand breaks
EORTC	European Organization for Research and Treatment of Cancer
ECM	Extracellular matrix
FGF2	Fibroblast growth factor 2
GH	Growth hormone
HO	Heterotopic ossification
IRS	Intergroup rhabdomyosarcoma study
MRIs	Magnetic resonance images
MSC	Mesenchymal stem cells
nAChR	Nicotine acetylcholine receptors
ORN	Osteoradionecrosis
PTH	Parathyroid hormone
RT	Radiation therapy
RTOG	Radiation therapy oncology group
RIF	Radiation-induced fibrosis
TBI	Total-body irradiation
TGFBeta1	Transforming growth factor beta 1
TNF alpha	Tumor necrosis factor alpha
SI	Sacroiliac
SOMA-LENT	Subjective, objective, management, and analytic-late effects normal tissue
SMPs	Skeletal muscle precursors

1 Introduction

Many cancer survivors who receive radiation therapy (RT) are at risk for developing serious musculoskeletal late effects. This complication is more severely manifested in children, but adults are also at risk for various quality-of-life-limiting treatment sequelae. It is important to understand the causes of therapy-related late effects on bone or muscle that can affect cancer survivors' quality of life. The musculoskeletal system receives RT for one of two main reasons: intentional dose delivery to muscles and/or bones to treat malignant lesions or the unavoidable inclusion of these structures in a radiation field used to treat an adjacent neoplasm. The effects of RT on musculoskeletal structures depend on the type of bone, the extent of surgical interventions before or after RT, the quality of the X-ray beam, the total dose, dose fractionation, age, and comorbid conditions of the patient as well as co-existing trauma or infection. Although the late effects are never easy to treat, if they are anticipated and recognized early, it may be possible to prevent some of the more serious consequences of treatment from developing while still curing the underlying malignant disease. Biocontinuum of adverse early and late effects is shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

2.1.1 Endochondral Bone

Evidence shows that skeletal development and volume depend on interacting genetic, racial, anthropometric, nutritional, and lifestyle factors that contribute together to the acquisition of peak bone mass, usually by the end of normal adolescence and puberty (Sheth et al. 1996). Hormones appear to play a leading role in developing and preserving skeletal health.

The human body consists of long, short, flat, and irregular types of bones. In the adult skeleton, which is divided into axial (skull, vertebrae, pelvis, sternum, and the ribs) and appendicular (limbs) parts, there are about 200 distinct bones. The long bones (e.g., femurs, tibias, and humeri) are found in the limbs and create a system of levers to allow locomotion (See Fig. 2 for anatomy of a long bone). The short bones compose the part of the skeleton mainly intended for strength and many limited motions. The flat bones (e.g., skull, scapula, sternum, and ribs) protect certain cavities, are composed of two thin layers of compact tissue, and enclose only a small amount of cancellous tissue. The irregular or mixed bones (e.g., vertebrae, sphenoid, and maxillary) are also composed of outer dense layers and filled with spongy cancellous tissue. Their diversity in shape and composition allows these bones to implement various essential locomotive and structural functions in the body.

2.1.2 Striated Muscle

Muscles are also widely distributed thorough the body and are connected with bones, cartilage, ligament, and skin either directly or through structures called tendons or aponeuroses. Muscles vary in form and size and can be elongated, broad, or flattened. They are classified as skeletal, cardiac, or smooth. Their function is to produce force and cause motion either for locomotion of the organism itself or movement of internal organs. Cardiac and smooth muscle contraction (such as peristalsis) occurs without conscious thought, but is essential for survival. Skeletal muscles or "voluntary muscles" respond to conscious control and are used to move the body and maintain posture. Skeletal muscle constitutes a large percentage of total body mass and varies by age and gender. Both cardiac and skeletal muscles are striated, but this chapter will confine itself to skeletal muscle.

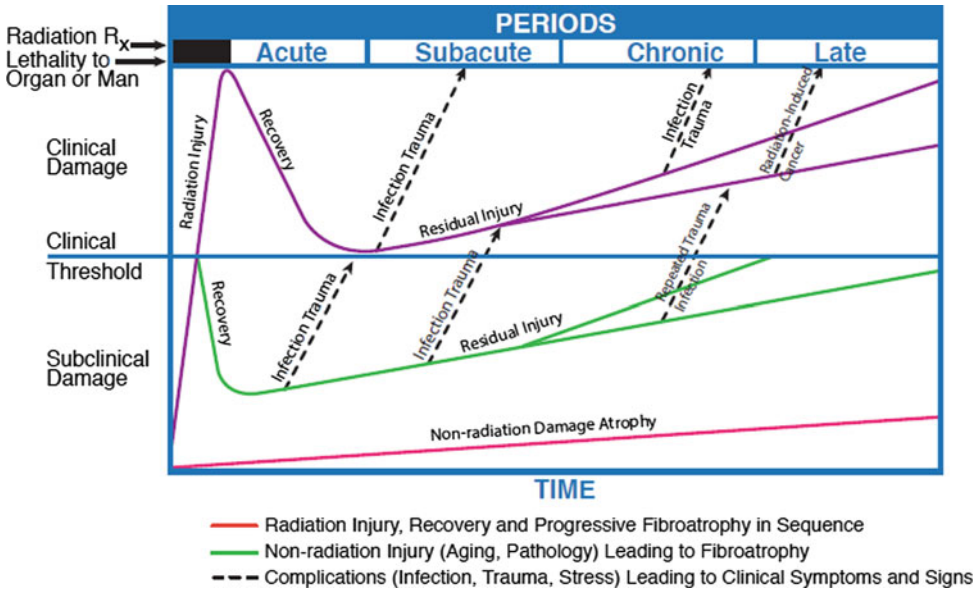


Fig. 1 Biocontinuum of adverse and late effects for the skeletal muscle (with permissions from Rubin and Casarett 1968)

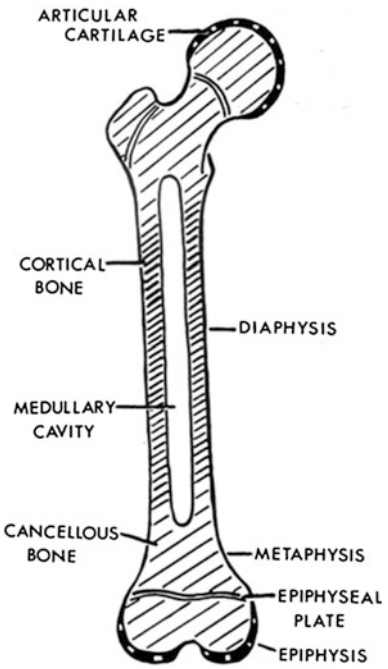


Fig. 2 Schematic of a growing long bone. The shaft of the bone is called the diaphysis, which contains the medullary cavity filled with bone marrow. The two expanded ends are the epiphyses. The epiphysis at each end extends from the articular cartilage to the epiphyseal growth plate. The metaphysis is the region between the epiphyseal plate and the diaphysis (with permission from Salter 1983)

2.1.3 Joints

The bones in the skeleton are connected by joints, some of which, like the facial bones, are immovable. These are joined with a thin layer of ligament or cartilage. In a joint where only slight motion is required, the bones are connected by tough and elastic fibro-cartilage. In a movable joint, the ends of the adjoining bones are usually covered with cartilage and held together by strong bands or capsules of fibrous tissue called ligaments. Movable joint surfaces are also at least partially covered with a fluid-secreting synovial membrane. Based on their function, joints are classified as synarthrotic (permitting little or no mobility), amphiarthrotic (permitting slight mobility), and diarthrotic (permitting a variety of easy movements). Joints can also be classified based on their anatomy or on their biomechanical properties. Joints allow movement and provide mechanical support.

2.2 Histology

2.2.1 Endochondral Bone

The long bones of the appendicular skeleton are composed of a middle portion of the shaft called the diaphysis and two enlarged rounded ends called epiphyses. The diaphysis is made up of cancellous bone and contains a medullary cavity filled with bone marrow and fat. The external layer of cancellous bone contains red bone marrow where the production of blood cellular components takes place. The cortical bone forms the outer layer of long bones and is the densest part of the bone, providing the main structural support of the human skeleton. The metaphysis, a small part of the bone between the epiphysis and the diaphysis where longitudinal growth of the bone occurs, contains the epiphysial growth plates. The outer layer of the bone, the periosteum, consists of dense connective tissue. Unlike osseous tissue, the periosteum has nociceptor nerve endings, which are nerve fibers that respond to noxious stimuli including pain.

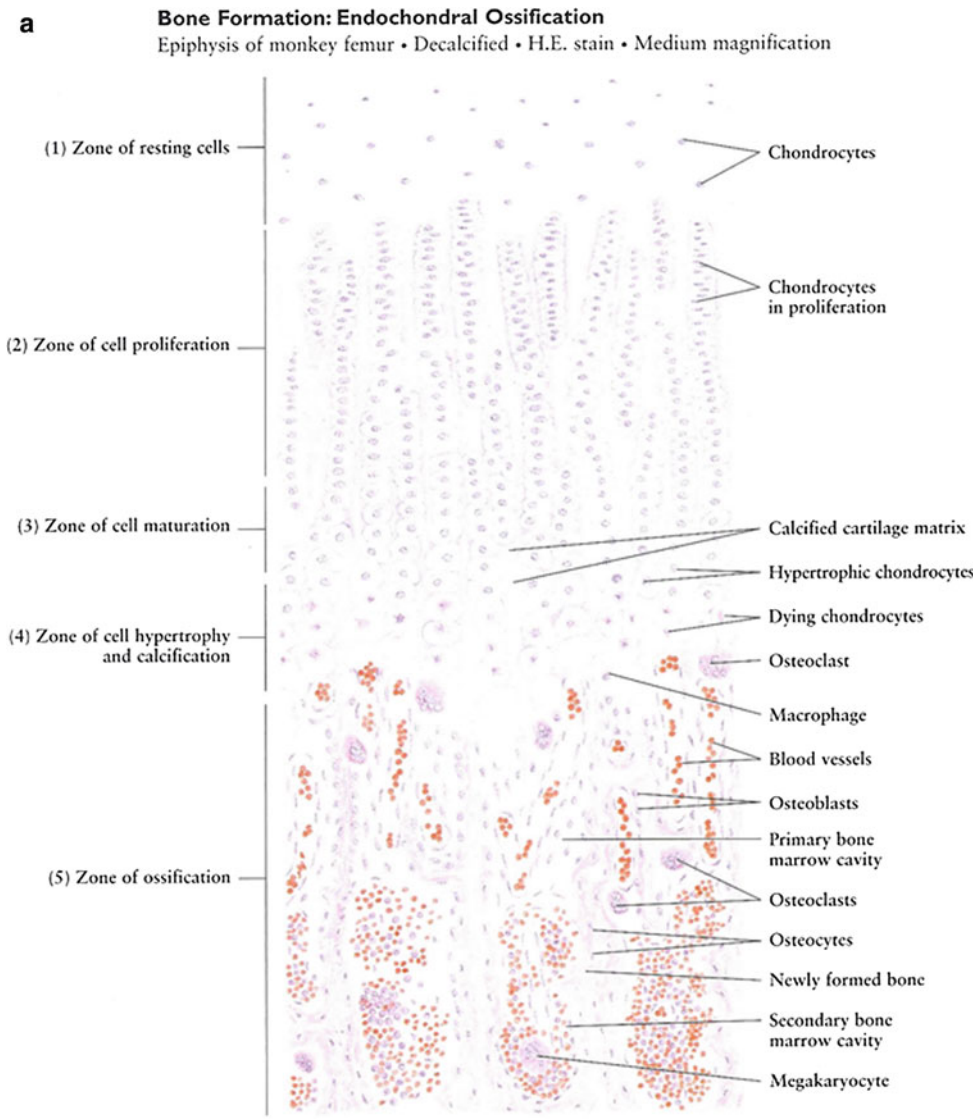


Fig. 3 **a** Bone formation: endochondral ossification. **b** Intramembranous bone formation. **c** Skeletal muscle (with permission from Zhang 1999)

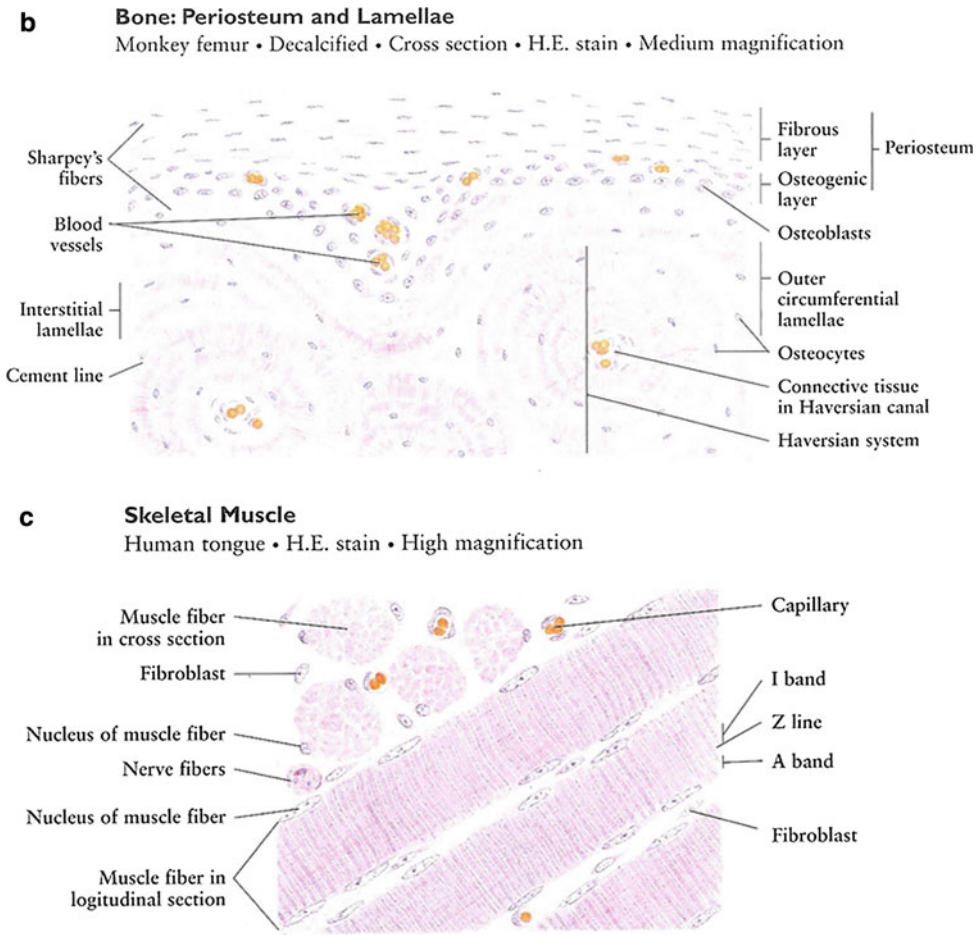
The main histological functional subunit for both compact and cancellous bone tissue is a circularly appearing structure called the Haversian system or osteon. It contains a centrally located Haversian canal and concentrically arranged rings called lamellae. The osteocytes in their lacunae are also arranged concentrically and connected by canaliculi containing fibrils that allow the osteocytes to communicate with each other.

Long bones are formed by endochondral ossification. Ossification centers appear within a cartilaginous matrix in predictable order and timing during fetal and postnatal life. Some bones are ossified from a single center (e.g., the bones of the wrist and ankle), while others are ossified from several separate foci. At varying times after birth, secondary ossification centers develop in the cartilaginous end of the bone. Longitudinal growth of a long bone comes from the growth plate. The growth plate can be divided into five zones: (1) a *zone of reserve* containing resting chondrocytes; (2) a *zone of proliferation* containing chondrocytes undergoing mitosis; (3) a *zone of hypertrophy* containing hypertrophic chondrocytes secreting phosphatase; (4) a *zone of calcification* containing dead chondrocytes and calcified cartilage; and (5) a *zone of ossification* containing osteoprogenitor cells differentiating into osteoblasts (Fig. 3a, b). Although the reserve cells may serve a nutritional or storage function, their role is not well understood. It has been suggested that these cells may be recruited to repopulate the proliferative zone following damaging insults such as irradiation.

2.2.2 Striated Muscle

Striated-muscle tissue is derived from the mesodermal layer of embryonic germ cells (McKinnel and Rudnicki 2005). Muscle cells contain contractile filaments called myofibrils, which are composed of sarcomeres, which move past each other and change the size of the cell. Actin (thin myofilament) and myosin (thick myofilament) are the main parts of

Fig. 3 (continued)



sarcomeres and are responsible for forming cross-bridges for contracting and stretching (Fig. 3c). The myofibrils are contained with muscle cells (myoblasts and myotubes). Differentiated-muscle cells (myotubes) proliferate slowly, if at all. Skeletal-muscle cells are arranged in discrete muscles and individual muscles are connected by tendons to processes of the bony skeleton.

Skeletal muscle is divided into subtypes: Type I, slow oxidative or "red" muscle, is dense with capillaries and rich in mitochondria and myoglobin; Type II, "white fibers," is less dense in mitochondria and myoglobin. Cardiac and skeletal muscles are striated, but anatomically different.

2.2.3 Joints

The layer of compact bone which forms the end of the long bone (the articular surface), and to which the cartilage is attached, is called the articular lamella. It is extremely dense and lacks Haversian canals. Cartilage is divided into hyaline cartilage, fibrocartilage, and yellow or elastic white fibrocartilage. Hyaline cartilage is covered with epichondrium, a dense connective tissue, except over the end of the articular lamella. White fibrocartilage consists of a mixture of white fibrous and cartilaginous tissue. It can form interarticular plates (menisci), connecting fibrocartilage (between vertebrae and other less mobile joints), circumferential fibrocartilage surrounding margins of certain joints (glenoid cavity of the shoulder), and stratiform fibrocartilage.

Ligaments consist of bands of connective tissue linking together articular bones and are mainly composed of white fibrous tissue. They are very flexible to allow freedom of movement, but simultaneously extremely strong. Another component of the joint structure is the synovial membrane, which is a thin, delicate layer of connective tissue. It secretes a thick, viscous liquid called synovial fluid that lubricates the joint, producing less friction with movement. Beneath the synovium is a layer of loose connective tissue with few cells called the subsynovium.

3 Physiology and Biology

3.1 Endochondral Bone Functional Subunits

Bone provides both a supportive and a protective function in the human body. Three primary types of cells produce and maintain bone tissue: osteoblasts, osteoclasts, and

osteocytes. Osteoblasts are derived from osteoprogenitor cells, the progeny of mesenchymal stem cells (MSC). Osteoblasts secrete osteocalcin and alkaline phosphatase producing a mineral matrix of collagen. Clinical markers for osteogenesis and bone repair are serum alkaline phosphatase and serum osteocalcin. Once an osteoblast becomes completely encased within the matrix it becomes an osteocyte, though it still participates in minor bone remodeling. Osteocytes occupy a space called a lacuna and communicate with each other using long cytoplasmic filaments that traverse the bone in tiny canals called canaliculi. Neither osteoblasts nor osteocytes are mitotically active. Osteoclasts are derived from granulocyte-monocyte progenitor cells within the bone marrow. They are also nonmitotic and are responsible for bone resorption. Clinical markers of bone resorption are: urine hydroxyproline, urine pyridinoline cross-links, and serum N-telopeptides.

Several hormones have a clear influence on bone formation and remodeling, including growth hormone (GH), parathyroid hormone (PTH), calcitonin, thyroid hormones, androgens and estrogens, and cortisol. Vitamin D acts directly on osteoblasts to secrete IL-1, which stimulates osteoclasts to increase bone resorption.

3.2 Muscle Functional Subunits

Striated muscle contains bands composed of thick and/or thin myofilaments, which are the histologic functional subunit. Myofilaments are made from various forms of proteins (F-actin, myosin, tropomyosin, troponin, and titin), each responsible for the formation of cross-bridges, which produce the contracture and stretching functions of the striated muscles. This process is triggered from impulses coming from a neuromuscular junction transmitting signal via nicotine acetylcholine receptors (nAChR), ultimately causing interdigitation of the myofilaments. Several pharmacological agents (tubocurarine, vecuronium, etc.) as well as botulin toxin can disrupt the neuromuscular junction and paralyze muscles.

3.3 Bone Modeling

The concept of bone modeling is a complex dynamic process that needs to be defined logically to understand the radiation effects across the age spectrum from child to adolescence to mature adult. The dysplastic alterations are a function of the segment in a bone, the type of bone and the age at the time of irradiation. The anatomic-physiologic correlations are shown histologically with vectors of bone growth and modeling (see Fig. 4a, b for the anatomic-histologic correlation present in the ends of growing long bones).

- *Epiphyseal segment or epiphysis*. The epiphysis grows in the form of a hemisphere from the subarticular cartilage zone; thus the term hemispherization is used. It is recognized that the ultimate shape of any epiphysis is rarely a true hemisphere, but nevertheless the term allows us to visualize its growth pattern.
- *Physeal segment or growth plate*. By cellular division, the cartilage disk increases its length interstitially and increases in diameter by apposition. Thus, the normal tendency is toward expansion in this segment. The simplest and most appropriate term for this segment is growth (Latin for *physis*).
- *Metaphyseal segment*. The normal tendency in this zone is toward a reduction in shaft caliber by internal and external absorption. The term "constriction" is deeply entrenched in the literature but is not descriptively accurate. The vascular erosion and osteoclastic absorption are not constrictive but are reductive in caliber. If one were to select a new term for these processes, it would be "funnelization". It preserves the image of these absorptive activities at the ends of the shaft, which allow for progressive narrowing of caliber and the resultant concave shape of the metaphysis as one passes from the end toward the middle of the shaft.
- *Diaphyseal segment*. There is a tendency in the middle of the shaft to maintain a certain structural balance between the flaring, growing ends. To maintain this balance, the diameter of the diaphysis increases in width as the tubular bone grows in length. Proliferation of osteoblasts on the periosteal surface exceeds osteoclastic endosteal absorption, in that the cortex thickens and the marrow cavity widens as the tubular bone matures. The term "cylindrization" is applied to the vectors of the diaphyseal growth, which is such as to ensure a cylindrical shape to the shaft. The irregular shape of the cylinder is due to muscle pull.

3.3.1 Skeletal Growth and Modeling

To more fully understand normal skeletal growth, there are three basic considerations: (i) amplification or actual increases in size of bone, (ii) polarity or direction of growth, and (iii) time or scale of measurement. (see Fig. 4c for a depiction of the kinesis of skeletal development relative to other organ systems, and Fig. 4d for variations in polarity and amplification in various bones).

- *Kinesis* is not a steady process and varies as a function of age. Increments in bone growth occur in three phases:
  - 1–6 years gradual growth
  - 6–12 years steady state
  - 12–18 years rapid growth spurt
- *Amplification* is the concept that the bone showing the greatest growth potential shows the greatest change because it magnifies the same defect to a greater degree.

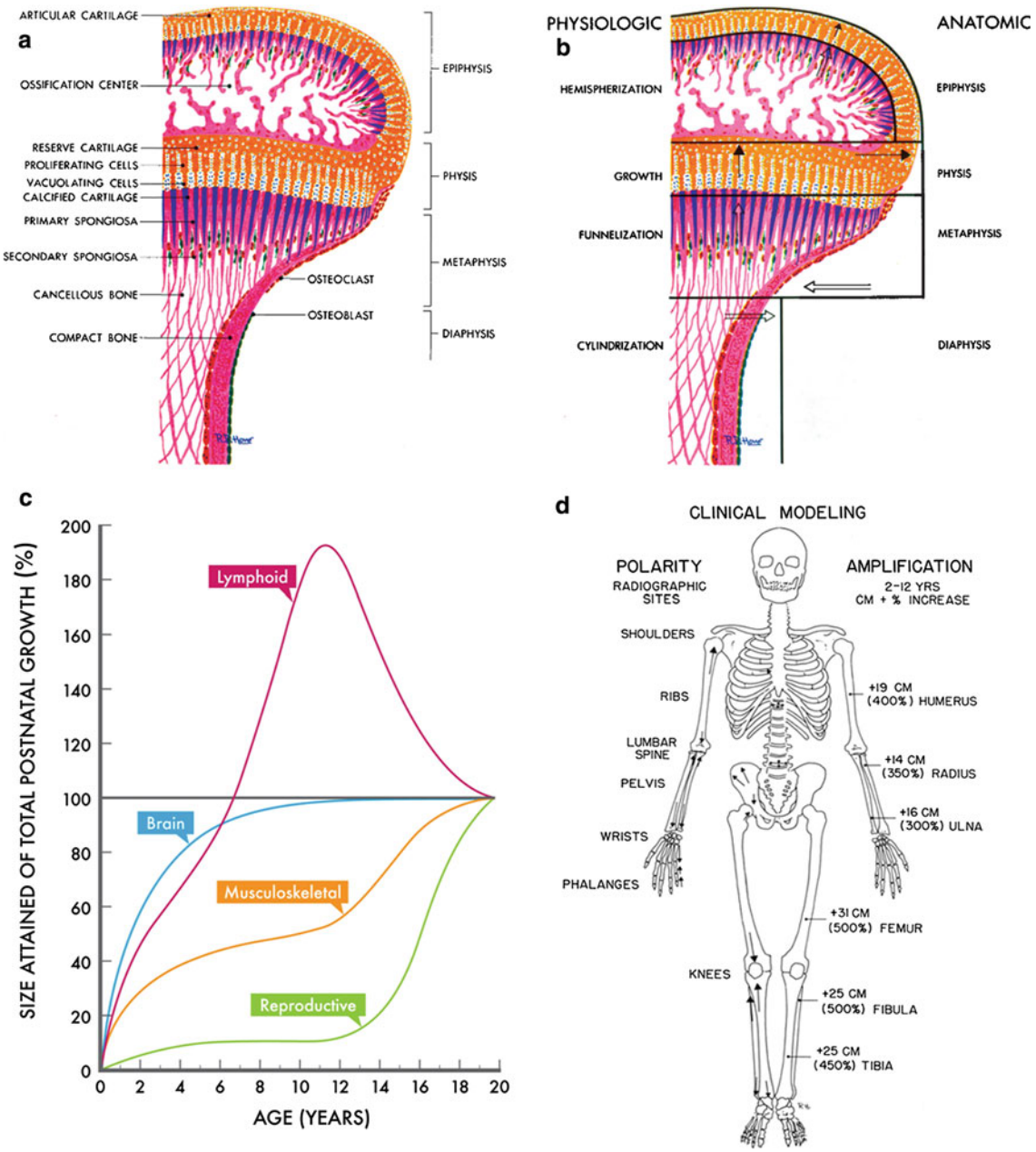


Fig. 4 Bone modeling. **a** Anatomic-histologic correlation of the end of a growing long bone: epiphysis, physis, metaphysis, and diaphysis. **b** Bone modeling at the same end of a growing long bone. (with permissions from Rubin 1964). **c** Post natal growth curves according to age and organ size. (Adapted and recreated from Tanner JM 1962) (Biopediatric chapter F2). **d** Polarity and amplification of skeletal growth and modeling. Arrows indicate polarity of growth, and percentages quantify the amplification from birth to adulthood (with permissions from Rubin 1964)

- *Polarity* is the concept that tubular bones grow in a differential pattern, with one end predominating over the other. The maximal direction of longitudinal growth is its polarity.

3.3.2 Classification of Bone Types

Each bone in skeletal growth is shaped or modeled as a function of its capacity for either endochondral and/or intramembranous growth depending on the anatomic location and its ultimate function as to support, protection and movement.

3.3.3 Orientation by Anatomic Region and Bone Type

There are eight anatomic regions:

- *Head*. Skull, facial bones, and mandible
- *Neck*. Cervical vertebrae (C1–C7), hyoid bone, and clavicle

- *Thorax*. Ribs, thoracic vertebrae (T1–T12), sternum manubrium, and pectoral girdle
- *Abdomen*. Lumbar vertebrae (L1–L5) and pelvic girdle (false pelvis)
- *Back*. Vertebrae composing the spine—cervical (C4–C7), thoracic (T1–T12), lumbar (L1–L5), and sacral (S5–S1)
- *Pelvis*. Sacrum (S1–S5), coccyx, and true pelvis
- *Upper limb*. Pectoral girdle, arm, forearm, and hand
- *Lower limb*. Pelvic girdle, thigh, leg, and foot.

The five types of bone shapes are long, short, irregular, flat, and special bones. Most bones are a mixture (^{m}) of endochondral growth and intramembranous bone formation. Some are mainly endochondral (^{e}) or intramembranous (^{i}) bone formation.

- ^{m}*Long*. Upper—humerus, radius, ulna; lower—femur, tibia, and fibula
- ^{e}*Short*. Metacarpal, metatarsal, and phalanges
- ^{m}*Irregular*. Vertebrae
- ^{m}*Flat*. Ribs, scapula, and pelvis
- ^{i}*Special*. Skull, face, and mandible^{m}

The skeletal anatomic regions can be divided into five basic bone types for the purposes of presentation. Each site is presented diagrammatically to indicate sites of maximal bone growth and modeling.

3.4 Biology

3.4.1 Molecular Mechanisms of Radiotherapy-Induced Musculoskeletal Injury

3.4.1.1 Endochondral Base and Bone

In most tissues, damage from radiation is related to both DNA damage and an apoptotic protective function regulated partially by p53. In bone, however, p53 does not usually play much of a role, even in apoptosis. In the growth plate, dividing chondrocytes are very sensitive to the damaging effects of RT. Even low doses produce significant apoptosis, resulting in cell depletion and decreased growth from that plate. The radiation of a child's growth plate causes growth abnormalities and bone shortening described in more detail later. The exact regulators of apoptosis in the growth plate are not well described, but, oddly enough, p53 has no role in this apoptosis since it is not present in growth-plate chondrocytes (Midgley et al. 1995). Whatever the mechanism, it also affects osteocytes near the growth plate. In fact, as a response to RT, apoptosis of osteocytes occurs and increases with decreasing distance to the growth plate (Stevens et al. 2000). Osteocytes in adults, as well as osteocytes in children that are located distant from the growth plate, do not exhibit apoptosis in response to RT. In these, p53 accumulates after RT, but upstream signaling does not occur, resulting in no apoptosis (Midgley et al. 1995). Brg 1, an ATPase enzyme, may be partially responsible for this lack of apoptosis in mature-bone osteocytes, as may Bcl-2, an anti-apoptotic gene. Studies of mature-bone cells show Bcl-2 to be present in developed bone osteocytes absent from any cells in the growth plate. This absence of Bcl-2 is observational at this time, but may prove to be significant.

Since osteocytes are nonmitotic, their resistance to apoptosis is not likely to result in severe cellular damage. However, the resistance of osteocytes to apoptosis is overcome in long-term hypoxic conditions, particularly in the presence of high-dose steroids; therefore, a vascular compromise from RT may induce enough hypoxia to create necrosis of the femoral circumstances (Tsuji et al. 2006).

3.4.1.2 Striated Muscle

Undifferentiated muscle cells are as sensitive to RT damage as the chondroblasts in the growth plate, but their manifestation is different. In muscle cells, RT causes double-strand breaks (DSB) that activate DNA damage sensors, or signal transducers and effectors that determine the life or death of the cell (Latella et al. 2004). In contrast to osteocytes and chondrocytes, p53 plays an important role in muscle cells. This reaction is mediated at a checkpoint (Chk1 or Chk2) to allow either DNA damage repair or, if the damage is too severe to be safely repaired, cause the cell to undergo apoptosis. Ataxia-telangiectasia-mutated (ATM) phosphorylates Chk2 and this modification create an activating signal response to DNA damage in myoblasts. If P53 is phosphorylated at conserved residue mouse serine 18 and human serine 15 [Ser15(h)/18(m)], apoptosis is triggered (Latella et al. 2004). However, in differentiated cells, p53 is not phosphorylated; the p53 does accumulate in the differentiated cells, but it does not correspond to increased p53 transcriptional activity, so apoptosis does not occur (Latella et al. 2004). Obviously, this mechanism is displayed by terminally differentiated muscle cells to prevent cell depletion in undifferentiated muscle cells with a limited capacity to self-regenerate. Radioresistance is also present because these cells do not divide, thus DNA damage does not lead to cell death at the time of division.

Differentiated cells, the myotubes, are prone to developing late radiation fibrosis, which is volume, dose, and fraction-size dependent. Different molecular mechanisms are responsible for the two effects. Late radiation fibrosis is probably caused by the release of downstream fibrogenic cytokines such as fibroblast growth factor 2 (FGF2) and transforming growth factor beta 1 (TGFBeta1). Fibrosis is worsened by inflammation, and RT is thought to produce aberrant proinflammatory cytokines, including tumor necrosis factor alpha (TNF alpha). This cytokine causes neovascular necrosis at low doses of radiation and mature vascular necrosis at higher doses. It also helps recruit and activate macrophages into injured tissue, increasing the

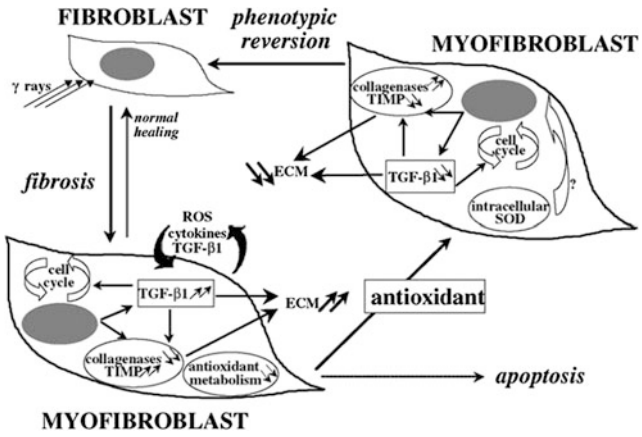


Fig. 5 Main radiation-induced fibroatrophic process (RIF) actors and possible cell phenotype reversion after antioxidant treatment. [with permissions from Delanian and Lefaix (2004)]

release of FGF2 and TGFBeta1. FGF2 attracts fibroblasts and induces mitosis, while TGFBeta1 incites fibroblast proliferation and premature end-differentiation, which leads to the extracellular matrix accumulation of glycoprotein production (Fig. 5) (Okunieff et al. 2004).

3.4.1.3 Joints

There is little information on the molecular cause of radiation damage to tendons and other structures of the joint.

4 Pathophysiology

4.1 Endochondral Base and Bone

The growth plate is the most sensitive structure to radiation damage. Early changes after RT include loss of chondrocytes. Near the growth plate, osteoblasts, and endothelial cells that invade the cartilage columns and produce bone exhibit pyknotic, hyperchromatic nuclei, and focal necroses (Farjardo et al. 2001). With longer followup, growth plates will show the typical pathology of mature bone, with osteoid and bone matrix replacing the chondrocytes of the immature growth plate. Thrombi from platelet-fibrin groupings can be visible in the microvasculature. There will be less new osteoid and vacant osteocytic lacunae may be visible (Farjardo 1982). This is true in mature bone as well (Fajardo et al. 2001). Years after treatment, atrophy and fibrosis of the marrow spaces will be present, replacing normal bone marrow (Fajardo et al. 2001). Eventually, fibrosis of the periosteum and endosteum will evolve. The histologic picture will be that of a cellularly depleted bony matrix. However, at times, new bone will start to form around the damaged bone (See Fig. 6a, b for the effects of radiation on the growth of different components of long bones).

Sometimes osteoradionecrosis (ORN) results from high doses of RT. In addition to empty lacunae and pyknosis of osteocyte nuclei, Haversian vessels may show endothelial cell injury with the platelet-fibrin thrombi noted above. Demineralization of the bone by osteocytes begins at some point, evolving into a necrotic zone with a yellow–gray color seen under the microscope (Farjardo et al. 2001). Bone marrow changes may range from a hypoplastic and fatty marrow to fatty acid crystals and masses of amorphous calcium soaps (Chang et al. 1993).

The primary late effect damage to mature bone is ORN, with its accompanying loss of strength and increased risk of fracture. ORN is usually found at the site of a fracture.

4.2 Muscle

Though myotubes are nondifferentiating and resistant to genotoxic stress, stem cells and myoblasts are not. The stem cells are the most sensitive to the effects of RT. Studies on myoblasts also show significant apoptotic cell death from small doses of radiation (Olive et al. 1995). The depletion of stem cells and myoblasts from the cell pool causes significant decreases in muscle growth and size in children. Myotubes are relatively resistant to the effects of radiation. Only massive doses will produce cell death, though aggressive RT will cause late fibrosis.

The histology of radiation-induced fibrosis (RIF) varies depending on the stage of fibrosis: (a) In *the initial pre-fibrotic stage*, chemokines attract leukocytes to the injury site, giving the histologic appearance of chronic nonspecific inflammation (Delanian and Lefaix 2004), resulting in increased vascular permeability and edema. Collagen degradation fragments attract the local connective and epithelial tissue cells as well as blood. Necrosis of the endothelium with thrombosis can cause necrosis of the microvessels with local ischemia. Loss of this barrier probably causes connective cell exposure to foreign stimuli, triggering fibroblastic activation (Lefaix and Daburon 1998). (b) Later, in the *constitutive organized phase*, the injured irradiated tissue histologically appears to be primarily composed of fibroblasts and extracellular matrix (ECM). In some areas, there is a high density of myofibroblasts (activated fibroblasts) in a disorganized matrix; the rest of the tissue appears to be primarily regions of densely sclerotic ECM. (c) The constitutive organized phase evolves to a *late fibroatrophic phase*, during which, histologically, almost all fibroblasts are gone and the tissue is almost entirely a dense ECM. These irradiated areas are fragile and poorly vascularized, and can undergo reactivated inflammation after even a mild insult (Delanian and Lefaix 2004) (Fig. 5).

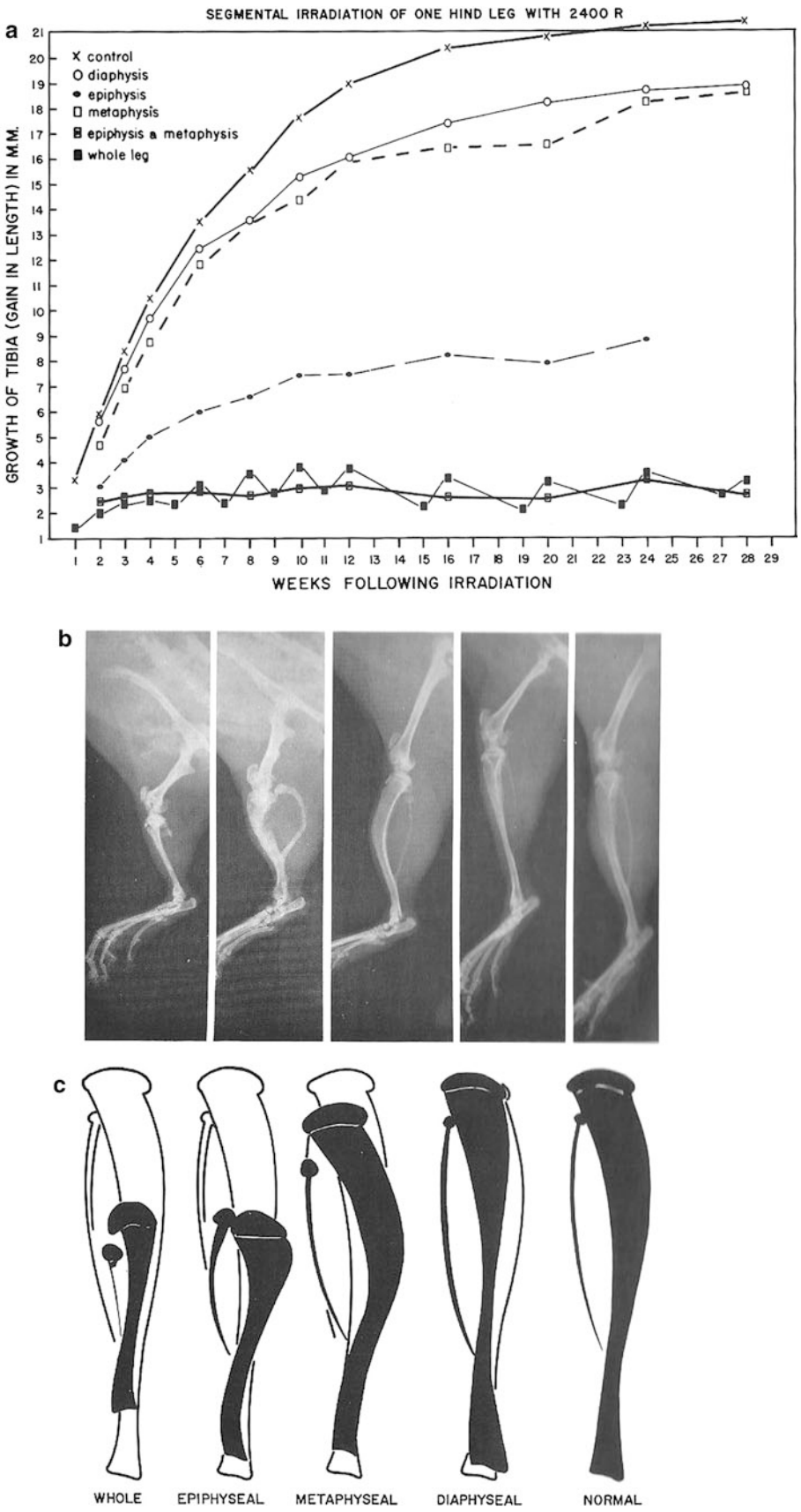


Fig. 6 **a** Reduced bone growth after segmental irradiation in long bone. **b** The radiographic correlate to **a**. **c** is a schematic showing the impaired bone as the filled-in structure (from Rubin and Casarett 1968)

Fibrosis in muscle increases with time. The evolution of the muscle tissue from contracting, flexible myotubes to the late fibroatrophic phase, which is primarily a dense ECM with few functioning cells, produces significant function results. The muscles become firm and less pliable and lose strength and flexibility, resulting in a loss in range of motion. There can also be pain from motion, particularly in the morning with first use. If the fibrosis affects the lymphatic and vascular drainage, there can also be lymphedema with swelling and enlargement of the extremity. Note that bone deformity alters the musculature (Fig. 6b).

4.3 Joint

The most useful data on the histologic response of joint cartilage come from arthritic radiosynovectomies of animals. After injection of Re-188 intraarticular microspheres to doses of either 0.3 or 0.6 miCi, histologic specimens did not show any significant changes in the cartilage, even a year after therapy (Wang et al. 2001). However, after as little as 12 weeks, sclerosis of the subsynovium was noted after the injection of either dose (Wang et al. 2001). There is little data on the histologic response of ligaments to RT.

Radiation has been used to sterilize tendons for transplant, and has been found to reduce the tensile strength, elastic modulus, strain, and toughness of transplanted tendons. These reductions were dose dependent for strength and toughness. There was an average of 36 and 55 % loss in tensile strength at 25 and 50 kGy compared to unsterilized controls (Seto et al. 2008). This reduction is thought to be caused by reduced crosslink density and collagen fragmentation. Since these large single-fraction doses are not used in vivo, it is not clear how much of an effect fractionated RT has on the ligaments of the joint. However, it is probable that some degree of loss of strength and flexibility occurs, though it may not be clinically significant. Note that joint abnormality results from deformity in bone modeling.

4.4 Bone Dysplasia due to Radiation-Induced Errors in Modeling

In general, the severity of the radiation effect varies directly with the dose, and fractionation or protraction of the dose has been found to lessen the degree of effect. In regard to the importance of the relative radiosensitivity of osteogenic elements or processes in determining the ultimate outcome of radiation effects in growing bone, it should be emphasized that the damage to the moderately sensitive fine vasculature of the marrow, cartilage, or bone and its capability for recovery play a large role in determining the degree of recovery of bone growth processes after irradiation. Since the nondividing reserve chondroblasts of the growing physeal cartilage plate are relatively radioresistant, they can initiate the regeneration of a growing cartilage plate in the event of survival or regeneration of adequate vasculature, even after severe damage to the proliferating and growing chondroblasts and devitalization of other parts of the growth plate. This may be associated with splitting off of the devitalized portion of the plate adjacent to the metaphysis, and displacement of this separated portion of the growth plate toward the diaphysis as longitudinal bone growth is resumed and progresses.

The severity and time of appearance of, and the time and degree of recovery from, the histopathologic effect of irradiation in the zones of endochondral bone growth are dependent upon both dose and age at the time of irradiation, and so is the degree of stunting of bone length. Some of the factors responsible for this dependence are the greater radiosensitivity of the more rapidly proliferating chondroblasts associated with phases of rapid skeletal growth, and the greater potential for stunting of bone length in bones that are far from attaining their full length at the time of irradiation.

4.5 Recovery/Regeneration

4.5.1 Endochondral Base and Bone

Bone shows a high capacity for repair after damage and fracture. After the initial damage takes place, inflammatory cells infuse from blood-secreting transforming growth factor β (TGF-β) to activate MSC in the bone marrow to produce osteoprogenitor cells and ultimately osteoblasts. Initially, a soft tissue callus called procallus forms around the ends of the fractured bone and osteoblasts begin to deposit immature woven bone characterized by an irregular arrangement of collagen. Mesenchymal cells in the procallus start to form hyaline cartilage, which will undergo endochondral ossification and develop into a bony callus. Bone remodeling will eventually change woven bone into mature lamellar bone.

MSCs can also differentiate into chondrocytes, adipocytes, and stromal cells. In the past decade, there has been considerable interest in the capacities of MSCs to increase tissue repair in humans. There have been reports on the infusion of MSCs in patients with osteogenesis imperfecta (Horwitz et al. 1999). All patients had increases in total-body bone mineral content, increases in growth velocity, and reduced frequencies of bone fracture.

Another interesting area of research is osteoinductive protein therapy using bone morphogenetic proteins (BMP)-2 and -7, which have been shown to stimulate new bone formation. Despite early promising laboratory results, it has not proven useful in clinical practice, particularly after radiation damage (Wurzler et al. 1998).

4.5.2 Muscle

Skeletal muscle repair/regeneration is very limited. Adult skeletal muscle fibers and cells do not undergo mitosis. If injury happens, satellite cells residing beneath the basal lamina of skeletal muscle fibers act as precursors for a little muscle growth and repair, proliferating and fusing to form new skeletal fibers. This satellite cell pool contains a distinct population of skeletal muscle precursors (SMPs) that can function as muscle stem cells. The efficacy of myogenic stem-cell transplant for treating muscle degenerative disease and other injuries is the subject of active laboratory research (Cerletti et al. 2008).

Since RT causes significant depletion of stem cells and myoblasts from the cell pool, it substantially limits the repair capacity of muscle (Olive et al. 1995). It remains to be seen if future stem-cell research will have any impact on patients with muscular toxicities as a consequence of RT.

5 Clinical Syndromes

Developing a grading system for bone and muscle toxicity was complicated by how these organ systems encompass anatomically and functionally diverse sites, and because changes only became evident with long-term follow-up. Furthermore, it was clear that it was necessary to assess not only the effects of RT alone, but also the combined effects of RT with surgical resection, cytotoxic drugs, and other therapeutic interventions. The radiation therapy oncology group (RTOG), building upon clinical experience on toxicity, initiated an active effort to establish criteria and scoring for late effects. In early 1981, RTOG started to include late-effects monitoring in its protocols. The European Organization for Research and Treatment of Cancer (EORTC) used its own toxicity scoring. The National Cancer Institute created the common toxicity criteria (CTC) in 1990, but in this system mainly included acute toxicities (CTC 2008) (http://ctep.cancer.gov/reporting/ctc.html). One of the pivotal publications on this topic came from Eifel et al. (1995) who proposed a late-effects scoring system for bones. It was built on both laboratory evidence and clinical observations in children experiencing various forms of bone late effects. This groundbreaking work laid a foundation for the musculoskeletal scoring system later included in the RTOG Toxicity scoring as well as the subjective, objective, management, and analytic-late effects normal tissue (SOMALENT) systems developed as a result of the EORTC and RTOG joining its subcommittees aimed at standardizing toxic-effects criteria (LENT SOMA Tables 1995). (Tables 1, 2 and 3 LENT SOMA tables).

5.1 Detection and Diagnosis

5.1.1 Radiation Effects on Growing Bone

The most commonly reported skeletal side effects on growing bone are growth retardation secondary to the impact of RT on the growth plate, but deformities, changes in bone composition, osteoradionecrosis, and fractures can also occur. Both external-beam RT and brachytherapy are responsible for these adverse long-term effects.

5.1.1.1 Growth Retardation

Retardation of bone growth is frequent from RT to the bones of a growing child. Irradiation of the vertebral bodies and long bones of the leg produce the most serious effects. The extent of this growth retardation strongly depends on the patient's age and bone age as well as on RT-beam quality, field size, dose distribution, dose per fraction, and the total dose (Probert and Parker 1975; Rubin et al. 1962; Willman et al. 1994).

Although RT was tried in the treatment of many different childhood malignancies in the early part of the last century, most patients succumbed to the disease and thus long-term followup results were sparse. However, adding postoperative RT to patients with Wilms' tumor or neuroblastoma finally yielded a substantial group of long-term survivors to study. Since most of these survivors received abdominal RT, some of the best early reports on bone sequelae were from the spinal dose, where its deleterious effect on growth has been well documented (Schriock et al. 1991; Shalet et al. 1987; Paulino et al. 2000a). Young children treated with orthovoltage irradiation to a high dose and large volumes suffered the most significant loss of height. Despite obvious clinical evidence, models for predicting linear growth deficits have not been perfected. Silber et al. (1990) created a model of expected stature loss by age at treatment for three dose levels for a hypothetical male patient receiving radiation from T10–11 to L4–5. Hartley et al. (2008) from St. Jude's Children's Hospital (Memphis, TN) have proposed a model for patients treated with craniospinal irradiation (CSI) in CNS tumors. By measuring the height from magnetic resonance images (MRIs) of both individual and grouped vertebral bodies before and after CSI, they found that slower growth was observed in older patients, girls, and patients treated with high-dose CSI (36–39.6 Gy). Although longitudinal modeling of spinal growth after CSI was feasible in this retrospective study, there is clear need for prospectively verified quantitative modeling methods for helping clinicians predict the magnitude of spinal growth impairment.

Table 1 Muscle/soft tissue: LENT-SOMA

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Function	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack
Objective				
Edema	Present/asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Mobility and extremity function	Present/asymptomatic	Symptomatic	Secondary dysfunction	No mobility, frozen
Fibrosis	Detectable	≤20 % of muscle	>20–50 % of muscle	>50 % of muscle
Atrophy	≤10 %	>10–20 %	>20–50 %	>50 %
Contraction		≤10 % linear field	>10–30 % linear field	>30 % linear field
Management				
Pain	Occasional nonnarcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Edema		Compression	Medical intervention	Surgical intervention
Mobility and extremity	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy or medical intervention	Surgical intervention
Fibrosis	Occasional physiotherapy	Intermittent physiotherapy		Surgical intervention
Atrophy		Intermittent physiotherapy		Surgical intervention
Muscle/soft tissue: LENT A				
Analytic				
MRI	Development of investigational testing suggested			

Radiation to the long bones also produces limb shortening when the irradiated long bone is compared with the matching untreated extremity, particularly in younger children. In addition to the effects of radiation, growth changes can be caused by direct invasion of a tumor to the epiphyseal plate. When an entire bone is exposed to radiation, impaired periosteal bone formation may result in abnormal narrowing of the shaft. Growth abnormalities are detected in most children treated for extremity sarcomas like Ewing tumor or soft tissue tumors adjacent to these bones (Paulino 2004).

As a result of RT, there is retardation of chondrogenesis and osteogenesis with the premature closure of epiphyseal plates and termination of bone growth, causing permanent deficits in bone length (DeSmet et al. 1976; Goldwein et al. 1993). The site and volume of irradiation are an important predictor of subsequent growth changes. Anderson et al. (1963) reported that 80 % of humeral bone growth comes from the proximal growth plate, 70 % of femoral growth comes from the distal epiphysis, and approximately 60 % of tibial growth from the proximal growth plate (Table 4). Altogether, about 65 % of leg growth occurs at the knee, explaining why any irradiation of the knee that includes both the proximal tibial and the distal femoral epiphyses cause the most severe leg-length discrepancies (Gonzalez et al. 1981). The degree of growth disturbance in long bones is dose dependent as well as age dependent. Limb-length discrepancies are most symptomatic in the lower extremities because they can significantly affect gait (Fig. 7a). Failure to correct even minor leg-length discrepancies can cause joint damage in the hip and secondary spine problems like scoliosis. Consideration to these effects is essential in radiation therapy planning (Craft et al. 1997).

5.1.1.2 Craniofacial Deformities

In the pediatric population, growth retardation from radiation can also cause severe deformities in the craniofacial bones. Most are cosmetic, but some are functional. Clinical and laboratory evidence has shown that RT to young children causes permanent, cumulative, and progressive damage to the facial and cranial skeleton. Microcephaly, micrognathia, and other growth abnormalities are reported in children receiving cranial and external-beam RT to orbital tumors like retinoblastomas and rhabdomyosarcomas (Fig. 7b). Raney et al. (1999) reported that 77 % of children treated to the head and neck on intergroup rhabdomyosarcoma study (IRS) I and II had one or more of

Table 2 Growing bone LENT-SOMA

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Abnormal gait	Slight	Noticeable limp	Severe limp	Unable to walk
Disfigurement	Slight, not cosmetically significant	Mild cosmetic deformity	Moderate cosmetic deformity	Severe disfigurement
Objective				
Extremities	Mild curvature or length discrepancy <2 cm	Moderate curvature or length discrepancy 2–5 cm	Severe curvature or length discrepancy >5 cm	Epiphysiodesis, severe functional deformity
Spine Sit/ standing height	Mild disproportion	Moderate	Severe	
Scoliosis	<5°	5–10°	>10–20°	>20°, interfering with cardiopulmonary function
Kyphosis/ lordosis	Mild radiographic changes	Moderate accentuation	Severe accentuation	
Femoral heads	Mild valgus/varus deformity	Moderate valgus/varus deformity	Mild slipped capital femoral epiphysis/epiphyseal widening	Severe slipped capital femoral epiphysis >60°;avascular necrosis
Flat/facial bones	Slight changes, not cosmetically significant	Mild cosmetic deformity	Moderate cosmetic deformity	Profound hypoplasia or functional problem
Management				
Extremities		Minimal shoe lift	Moderate shoe lift	Surgical intervention
Scoliosis			Brace	Surgical intervention
Femoral heads			Pinning	Hip replacement
Flat/facial bones				Surgical intervention
Analytic				
Measure growth	No growth retardation	Growth retardation ≤1 percentile	Growth retardation >1 percentile	Growth arrest
Radiograph/CT	Assessment of bone integrity			

these problems. Hypoplasia or asymmetry of tissues was recorded in 30 % of survivors; 5 % of them underwent reconstructive surgery. Other studies using anthropometric and descriptive methods have documented alterations in the skull shape and size (Estilo et al. 2003; Donaldson et al. 1973; Meadows and Silber 1985; Denys et al. 1998). As in other sites, it is difficult to accurately assess the risk of these deformities and they depend on multiple factors.

5.1.1.3 Spinal Deformities

Vertebral end plate changes are often responsible for spinal deformities such as scoliosis and kyphosis in patients treated to the chest and abdomen. Since the initial description of a radiation-induced scoliosis with orthovoltage beams, numerous reports have followed corroborating this data (Riseborough et al. 1976; Rubin et al. 1995; Halperin 1996; Paulino et al. 2000a). Scoliosis risk is increased in children who have undergone laminectomy. Its severity is also thought to be linked to asymmetrical radiation of vertebral bodies and the inhomogeneous growth that results. Other types of deformities like kyphosis, accentuated lordosis, and bone hypoplasia may also occur (Fig. 7c). The severity of these changes is commonly worsened during the pubertal growth spurt (Heaston et al. 1979).

5.1.2 Radiotherapy Effects on Mature Bone

Complications in the mature skeleton are dependent on the patient's age, general health, systemic therapy, and the

Table 3 Mature bone (excluding mandible) LENT SOMA

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasion and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Function	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete fixation, necrosis
Objective				
Fracture			Partial thickness	Full thickness
Mucosa soft tissue			Sequestration	
Skin over bone	Erythema	Ulcer	Sinus	Fistula
Joint movement	<10 % decrease	>10–30 % decrease	>30–80 % decrease	>80 % decrease
Management				
Pain	Occasional nonnarcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Function	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy or medical intervention	Surgical intervention
Joint movement	Occasional physiotherapy	Intensive physiotherapy	Corrective surgery	
Analytic				
Imaging: density	Assessment for osteosclerosis and osteoporosis			
X-ray	Assessment of bone and joint integrity including linear fracture and displaced fracture			
Arthrography	Assessment of joint integrity			
Arthroscopy	Evaluation for joint abnormalities			

Table 4 Fractionated external beam radiation doses associated with a 5 % risk at 5 years (TD 5/5) and a 50 % risk at 5 years (TD 50/5), for musculoskeletal late effects

Late Effect	TD 5/5	TD 50/5
Hypotrophy in growing muscle	No threshold dose; proportional to dose	No threshold dose
Soma grade 3–4 fibrosis	55 Gy	70 Gy
Osteoradionecrosis	65 Gy	75 Gy
Chondronecrosis	60 Gy	70 Gy
Pathologic fracture	50 Gy	65 Gy
Deformities (scoliosis, hypoplasia)	No threshold dose	No threshold dose
Significant limb shortening	No threshold dose; proportional to dose up to 40–50 Gy	No threshold dose

individual radiation parameters of dose, dose per fraction, and beam quality. Although changes in bone composition such as coarsening of trabecular architecture and cortical irregularity are observed in irradiated bone, tumor infiltration can cause similar radiographic pictures, and it is important to distinguish the two. Mature bone is more resistant to damage than growing bone, however, and most effects are secondary only to high doses of RT.

5.1.2.1 Radiation Osteitis

Radiation osteitis is a term used to describe potentially reversible changes such as periostitis, bone sclerosis, and increased fragility. On radiographs, the bone will appear mottled, demonstrating both osteopenia and sclerosis, and show areas of coarse trabeculation. Changes are seen at different time intervals and depend on the type of bone irradiated. These changes may be the initial manifestations of damage such as ORN that can appear much later. Despite that radiation osteitis was early described as an RT effect (Ewing 1926), this condition is not readily distinguishable from other types of bone damage and the term is not commonly used in the modern medical literature.

5.1.2.2 Osteopenia and Osteoporosis

The causes of low bone density in the mature skeleton are similar to those in children. However, many patients with breast and prostate cancer are at high risk for osteopenia because of the hormonal therapy they receive as part of their cancer treatment. Women with gynecologic cancer can lose

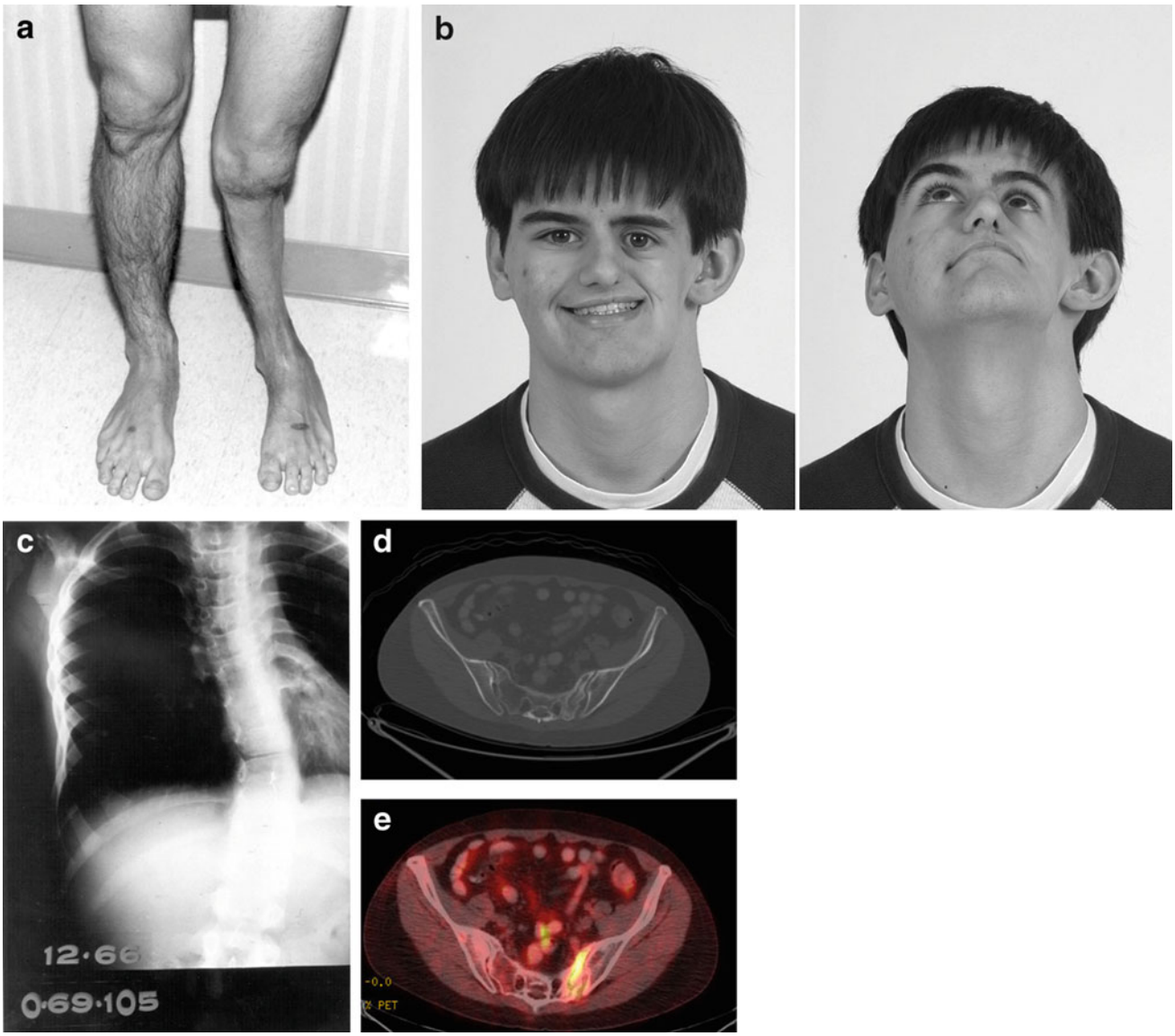


Fig. 7 **a** An 18-month-old boy was treated postoperatively with 50 Gy in 25 fractions for a primary rhabdomyosarcoma of the *left* calf. His leg is shown 16 years after treatment. The muscles are extremely hypoplastic: the distal leg is shortened and alopecic. An epiphysiodesis was performed on the other leg to prevent the occurrence of too large a limb-length discrepancy. **b** An adolescent survivor of pediatric head-and-neck cancer, treated with radiotherapy (add dose and dose per fraction), with resulting radiation-induced craniofacial bone growth inhibition, deformities, and muscle hypoplasia. [with permissions from Gevorgyan et al (2007)]. **c** A 2-year-old girl was treated with orthovoltage irradiation to the abdomen and spine (dose unknown) for a neuroblastoma in 1960. Two years after treatment, mild scoliosis developed. Progression of kyphoscoliosis occurred over the next 7 years. **de** Pathologic Fractures. A 64-year-old postmenopausal female treated for grade three follicular lymphoma to 30.6 Gy at 1.8 Gy/fraction with AP-PA fields. The patient developed a pelvic insufficiency fracture 1 year after completing radiotherapy without trauma or other injury. Computed tomography scan images in the bone window demonstrating mixed sclerotic and hypodense area (**d**) and positron emission tomography showed diffuse linearly oriented FDG activity within the sacral ala with maximum SUV uptake of 4.5 (**e**)

normal hormone functions due to RT damage to their ovaries and also develop osteoporosis.

5.1.2.3 Pathologic Fractures

Changes in bone structure may precede the development of spontaneous fractures after irradiation and must be recognized early (Bonarigo and Rubin 1967). Long-bone fractures are the most serious, particularly those of the femoral neck, often occurring after RT for the treatment of gynecological malignancies in older women who are osteoporotic (Konski and Sowers 1996). With any fracture after RT, tumor involvement has to be excluded. Radiation dose may impact the risk of fracture. In patients with breast cancer treated with radiation to the chest wall, Overgaard

(1988) found that a large dose per fraction had a significantly higher incidence of late bone damage and spontaneous rib fracture (19 %) than standard doses per fraction (6 %). Bell et al. (1991) reported that removing the cortical bone at the time of tumor excision for extremity soft tissue sarcomas significantly increased the risk of later long-bone fracture.

Fractures of the pubic rami and sacral insufficiency fractures are also reported in patients receiving pelvic RT after menopause (Moreno et al. 1999) (Fig. 7d, e). The sacral ala, adjacent to the sacroiliac (SI) joint, is the most commonly involved site because it is weight bearing (Fig. 7d, e). Use of high-dose steroids and rheumatoid arthritis is known to increase the risk in patients treated with RT (Finiels et al. 1997). A vertical sacral ala fracture can be diagnosed with computed tomography or MRI (Blomlie et al. 1996). Again, these patients are predominantly postmenopausal and usually have underlying osteoporosis secondary to a lack of estrogen.

Fracture Healing

Pathologic fracture healing will most often require irradiation; however, radiation therapy is a double edged sword. Even modest radiation doses will impair the healing mechanisms which are a combination of an *anchoring callous* (endochondral) and a *sealing callous* (intramembranous) *bone formation.* Thus, pinning the fracture site long bones is essential since modest doses of irradiation *(20cGy × 10)* will inhibit endochondral bone formation (anchoring callous) but allows for intramembranous bone to proceed (Bonarigo and Rubin 1967).

5.1.2.4 Osteoradionecrosis

ORN is a rare complication defined as irradiated bone that fails to heal over a period of 3 months without a residual or recurrent tumor (Epstein et al. 1987). In the literature, its incidence varies, ranging from 0.9 to 35 % (Sulaiman et al. 2003; Vissink et al. 2003) following high doses to bone. ORN may occur many years after RT in the persistence of suboptimal wound healing. Differentiating osteoradionecrosis from tumor recurrence can be difficult. It is most commonly reported in the mandible in patients undergoing RT for head-and-neck tumors. ORN is often asymptomatic and more frequently encountered by imaging. Patients also can present with chronic exposure of necrotic bone or osteosynthetic devices, mucosal necrosis, ulceration, or persistent pain. On the plain radiograph of the mandible, ORN appears as ill-defined cortical destruction without sequestration. Despite advances in RT and increased attention to predisposing factors, ORN of the mandible has not been totally eliminated. Prevention of ORN is important since the condition may be chronic, progressive, and lead to a serious pathologic fracture.

5.1.2.5 Chondronecrosis

Chondronecrosis is rare in adult patients and has been primarily reported in patients receiving a high dose of RT (60–70 Gy). It usually occurs in the thyroid cartilage after the treatment of head-and-neck cancer. The overall symptomatic incidence is very low, but the subclinical incidence may be much higher at standard doses for head-and-neck cancer (Keene et al. 1982).

5.1.3 Striated Muscle

5.1.3.1 Radiotherapy Effects on Growing Muscle

Muscles are present in almost every RT treatment except the focal treatment of brain lesions. In general, high doses and large volumes are necessary to produce significant sequelae in mature muscle, but growing muscle is much more sensitive to the effects of radiation (Gerstner et al. 1954).

Hypotrophy and Atrophy

Children commonly lose full muscle development after RT treatment. Age, dose, dose per fraction, and the volume treated affect the degree of these sequelae. Even with the most conformal techniques, muscles can still receive a substantial dose. One of the most common and clinically recognizable muscle late-effects in children is hypotrophy or atrophy. An obvious result is the loss of function in spinal muscles after treatment for Wilms' tumor and neuroblastoma, or facial muscle atrophy in young children treated for head-and-neck sarcomas (Fig. 7a, b, c, d, e). Long-term survivors treated with head-and-neck RT are reported to have a 77−100 % incidence of mild-to-severe radiation damage of soft tissues and bones (Raney et al. 2000; Paulino et al. 2000b). Clinical observations suggest that radiation at an early age induces this risk and it becomes more pronounced as the child continues to grow.

Hypotrophy or atrophy is partially a vascular effect, but it is probably primarily due to depleted undifferentiated stem cells and myoblasts in the young child from apoptosis secondary to radiation damage (Rubin and Casarett 1968; Olive et al. 1995). Since fewer muscle cells are present after RT, even strenuous exercise cannot completely compensate for the underdevelopment of these muscles. However, except for those muscles treated to very high doses in very young children, the functional impact of these sequelae is less than the cosmetic impact.

5.1.3.2 Radiation Effects on Mature Muscle

Fibrosis

Fibrosis is the most common radiation injury to mature muscle, and can lead to several sequelae, including stiffness and pain in the muscle, induration, and loss of range of motion (Rowin et al. 2006). At times, the fibrosis can produce lymphedema, particularly if it involves the

subcutaneous region in addition to a large portion of the muscle compartments of an extremity. This injury can occur and become a fibrous tunicate if the entire circumference of the limb is irradiated. Optimally, a medial strip should be spared to allow for lymphatic drainage of limbs.

The functional results of muscle injury have been studied primarily in adult patients treated for sarcoma with surgery, chemotherapy, and RT (Stinson et al. 1991; Davis et al. 2002). RT for soft tissue sarcoma of the limb conventionally involves irradiation of the entire transverse cross-section of the affected anatomical compartment (Barnett et al. 2005). Studies have shown that the functional outcome after RT to the limb is related to the RT volume and the size of the unirradiated corridor (Alektiar et al. 2000; Karasek et al. 1992; Gillette et al. 1995). The total dose and dose per fraction of RT used is also a significant factor in determining range of motion, muscle power, and limb function (Keus et al. 1994). Posttreatment function is paramount in the management of soft tissue sarcoma.

Trismus

Trismus is a specific type of fibrosis characterized by an inability to fully open the mouth. When the masticator muscles and the temporomandibular joint are included in the irradiated field, musculoskeletal fibrosis can cause trismus and mandibular dysfunction. It has been reported in about 5–10 % of children treated for head-and-neck malignancies (Vissink et al. 2003; Ozyar et al. 2005). Since doses are lower in rhabdomyosarcoma of the head and neck, trismus is less common in rhabdomyosarcoma than in nasopharyngeal carcinoma (Paulino et al. 2000b).

Trismus is most common as a complication of RT of primary head-and-neck cancers in adults. The data suggest that the dose delivered to the pterygoid muscles may be directly correlated to the incidence of this complication (Teguh et al. 2008).

Nichol et al. (2003) found significant hypotrophy when they measured and compared masticator and pterygoid muscle volumes before and after RT for patients treated to the head-and-neck area.

5.1.4 Imaging

Radiological images are complementary to a clinical examination when evaluating musculoskeletal structures (Mitchell and Logan 1998). A radiograph in two planes is well established as the starting point of the evaluation of acute bony injury. This allows assessment of alignment, structural integrity, and presence of any displaced fragments. However, many bony injuries are occult on plain X-rays, and soft-tissue visualization next to the bone is poor. Skeletal radiographs with multi-planar X-rays are valuable for identification of pathological processes, including fractures, deformities, growth stunting, pathological malformations like osteomas, as well as lytic or blastic lesions. They are also helpful for defining bone age in children when making decisions on interventions with growth hormone supplementation. If plain X-rays are not diagnostic, bone scintigraphy is more sensitive in identifying occult and coexistent fractures. Scintigraphic tracer uptake occurs early in response to injury, which often allows fracture identification earlier than plain radiography at sites in which radiography has known limitations. Despite these early changes, it has been recognized for some time that initially the skeletal scintigram may be normal and can give false-negative findings in early fracture, especially in the axial skeleton.

A bone scan can be helpful for picking up pathological lesions in the bone, including osteoblastic formations, which are mostly associated with malignancies. Conventional skeletal scintigraphy also has the advantage of covering the entire skeleton in a format that allows quick review, and at an acceptable radiation exposure of 3–5 mSv. A dual-emission X-ray absorptiometry scan (DEXA) is helpful for measuring bone density and is a standard test for patients at high risk for low bone mineral density, osteopenia, and osteoporosis.

Computer tomography imaging is a more sophisticated, three-dimensional anatomical body imaging and quite valuable for musculoskeletal system evaluation. Bones are well visualized, including both cortical and marrow spaces. The CT can pick up smaller fractures in bones sometimes missed on plain X-ray. It can also identify pathological formations, like osteomas, bone cysts, and tumors. Irregularities in bone growth like stunting, deformities, and kyphoscoliosis of the spine are usually better assessed with CT, especially with thin slice and high resolution imaging tools and also capacity for three-dimensional image reconstructions. Hybrid SPECT/CT, which combines scintigraphy and multidetector CT, has improved sensitivity and diagnostic confidence. A new nuclear medicine modality, Fig. 7d, e PET/CT can show hard to diagnose postradiation pelvic insufficiency fracture.

Magnetic resonance imaging (MRI) appeared superior in detecting fracture that only involved the trabeculae, whereas CT appeared superior at detecting cortical fractures. Fat-suppressed MRI sequences, such as STIRs are likely to be most useful, in assessing bone edema, and hence sites of trabecular disruption.

The MRI is an invaluable tool and provides high-quality anatomical images not only of bone, but also muscles, ligaments, joint spaces, and other soft tissue structures. The MRIs are an invaluable tool for identification of abnormal soft tissue formations, like seen in soft tissue tumors of both malignant and benign type. T2 and fat-suppressed sequences are quite helpful in showing both acute inflammatory soft tissue changes in muscles, connective tissue spaces, subcutaneous, and cutaneous tissues, but also chronic

pathological processes like fibrosis of soft tissue commonly seen after irradiation. The radiologist can usually distinguish between treatment-related pathology and de novo formations like tumors of bone and soft tissues.

All of the imaging modalities should be incorporated in both diagnostic steps and treatment planning decisions.

6 Radiation Tolerance: Predicting RT-Induced Musculoskeletal Injury

Clinical experience on tolerance doses and the effects of fraction size is mainly derived empirically; however, some prospective data are available on various doses and fractionations, namely hypo- and hyperfractionation for a variety of clinical indications. In this section, we will review the existing data on single- and multiple-fraction dose effects on skeletal structures and muscles.

6.1 Radiation Dose Time Fractionation

As described in the pathophysiology section, mature bone and cartilage are resistant to direct damage. However, growing bone is more sensitive. For both single and fractionated RT, the dose data mainly rely on laboratory research. Experimental animal models suggest a fairly continuous dose–effect relationship for growing bone between doses of about 5–40 Gy and an α/β ratio for growing bone of approximately 4–5 (Eifel and Sampson 1990). The most sensitive cells are the growth plate chondrocytes. Surviving chondroblasts can repopulate the physis to some extent after low-dose RT, allowing some further growth, but higher doses cause more irreversible damage, closing the growth plate rapidly, and ending growth.

6.1.1 Single Fraction

Clinical tolerance dose information from single-fraction RT is quite limited. In children who received single doses of 0.5–5 Gy of external-beam RT delivered for benign conditions like adenitis and enlarged thyroid, growth retardation in mandibular and spinal bones was detected in comparison with an untreated control group (Adkins 1966).

In recent years, single-fraction RT has been used in the prophylaxis of heterotopic ossification (HO). HO induction is due to bone debris as a result of hip replacement surgery, and initiates osteoblasts, ergo they are very radiosensitive (Pellegrini 1992). The most common dose is 7 Gy of megavoltage external-beam radiation delivered to the affected joint area. Outcomes of these patients, who are mostly adults, suggest that there is no appreciable risk of either acute or long-term complications for the structures exposed to this relatively large dose (Balboni et al. 2006). Metastatic bone lesions are also treated with single large doses (8–10 Gy) to palliate pain. Pain relief is good and there appears to be no significant risk of complications. Of note, these patients usually have terminal disease and long-term followup data are sparse (Roos et al. 2005; Hartsell et al. 2005). Single doses of 8 Gy or less appear to have very little risk of significant musculoskeletal sequelae.

Animal experiments suggest that doses of 15 Gy do not cause microscopic changes, but changes did accompany dose increases. These changes take months to develop, with little change at 1 month, but 2–4 months after 20–50 Gy there was marked degeneration and vacuolization with loss of capillaries (Gillette et al. 1995).

6.1.2 Multiple Fractions

Despite many animal experiments and clinical observations, tolerance doses for bone, cartilage, and muscle in humans are not clearly established. Total dose and fractionation appear to impact late toxicities, but dose thresholds are hard to determine, partially because the volume treated has a significant role as well. Table 4 summarizes fractionated RT dose-effects based on accumulated clinical data.

6.2 Recommended Dose/Volume Constraints

The volume irradiated has a substantial impact on the extent of musculoskeletal toxicity. Sparing normal tissues, particularity the epiphyseal plate, joint space, and unaffected muscle, without compromising tumor coverage, may dramatically alter the degree of late effects and should be a significant consideration in treatment planning. Modern therapies directed toward more targeted and conformal treatments reduce the volume of bone and other connective tissues irradiated to a high dose (Wolden et al. 2005; McDonald et al. 2008). These conformal techniques, along with new technologies such as proton and heavy-ion therapy, hopefully will diminish the extent of late effects such as craniofacial deformities (Yock et al. 2005).

6.2.1 Growing Bone

Dose data on epiphyseal growth arrest are incomplete. Some authors report that permanent bone-growth arrest can be observed after total doses as low as 12 Gy delivered to the growth plate (Dawson 1968). Growth abnormalities are detected in almost all children treated for extremity sarcomas with conventional fractionation to doses of 40–55 Gy (Gonzalez et al. 1981; Gonzalez and Breur 1983; Paulino 2004; Craft et al. 1997). Every attempt should be made to lower the dose to the growth plate without affecting the therapeutic value of the radiation course, which means using sophisticated planning techniques such as IMRT or proton therapy. Doses below 20 Gy produce less damage

than higher doses. Hyperfractionated RT may also decrease the extent of growth abnormalities. Data from Bolek et al. and the treatment of Ewing tumor of bone indicate that fractions of 1.2 Gy twice daily to between 50.4 and 63.2 Gy produce less musculoskeletal late effects than would be expected from similar doses using fractions of 1.8–2.0 Gy once a day (Bolek et al. 1996).

Available data today would imply that there is no threshold dose and that any dose of RT will affect the growth plate. But what dose is clinically significant? Clearly, bone maturity at the time of treatment plays a critical role in the extent of growth change. Probert and Parker (1975) studied the standing and sitting height after radiation; patients receiving more than 35 Gy of spinal dose had a sitting height more than two standard deviations below the mean for their age, while a dose less than 25 Gy still caused changes but to a lesser degree. The authors concluded that doses exceeding 20 Gy irreversibly affected vertebral body growth in children. A potential problem in interpreting this data is that many of the patients in these series were treated for CNS tumors, and therefore underwent full craniospinal irradiation that also affected growth hormone secretion. Various degrees of deformities are also reported at similar dose levels (range, 20–35 Gy), without a definite dose threshold (Mayfield et al. 1981; Paulino and Flower 2005).

Silber et al. (1990), from the data at Children's Hospital of Philadelphia, created a model that tries to predict growth deficits from spinal irradiation based on the vertebral bodies treated, the total dose at normal fractionation, and the age of the child. From this data, significant deficits would not be expected below 20 Gy (Fig. 8).

Several figures in this chapter show the effect of age and dose on growing bone and muscle. There is mild hypoplasia of the bones and muscles. The bone-growth deficit is not detectable, but there is mild muscle hypotrophy. However, the same dose (using a once-a-day fractionation scheme) to the left distal extremity in an 18-month-old boy resulted in extreme growth deficits of both muscle and bone. Modern surgical management allowed the leg to still be functional 16 years after treatment, however. These examples show that the degrees of growth abnormalities depend upon dose and age at treatment.

6.2.2 Mature Bone

The primary risks of irradiating mature bone are osteoradionecrosis and subsequent pathologic fracture. Total-dose and fractionation data for these risks of bone fracture are also limited and confounded by multiple interrelated factors. In the mandible, the TD 5/5 (that is, the dose at which there is a 5 % probability of a complication within 5 years) is approximately 60–65 Gy and the TD 50/5 (the dose at which there is a 50 % probability of a complication within 5 years) is approximately 75 Gy in edentulous patients (Cooper et al.1995). The size of the tumor did not impact

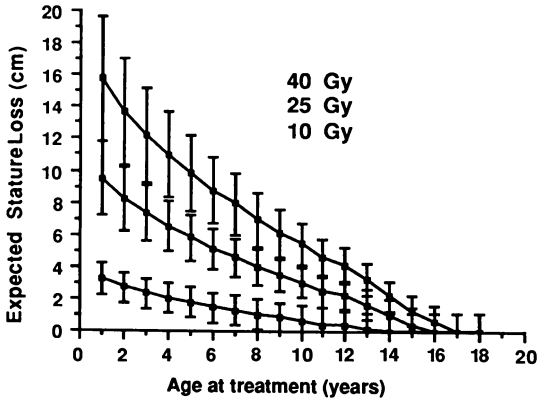


Fig. 8 Model to predict growth deficit from vertebral body irradiation according to total radiation dose following fractionated therapy (with permission from Silber et al. 1990)

the risk, implying no volume effect of the radiation field. Dental extractions after RT increase the risk. Xerostomia likely increases the risk as well. There are no data to suggest that xerostomia effects the risk of mandibular fractures, however. The TD 5/5 and TD 50/5 for undamaged long bones are probably higher. The TD 5/5 and the TD 50/5 for the femoral head have been estimated to be 52 and 65 Gy, respectively (Rubin and Casarett 1968, Emami et al. 1991). Overgaard (1988) in his series on rib pathological fracture in breast cancer survivors estimated that the TD 5/5 was 52 Gy while the TD 50/5 was 68 Gy. Patients treated with a hypofractionated regimen had a much higher risk of this complication. Add more in about what degree of hypofractionation is associated with what risk of complication.

The risk of this complication obviously depends on the bone involved, its vascular supply, and the stress on that bone, among other factors.

6.2.3 Mature Cartilage

Clinically significant radiochondronecrosis is rare. Most cases are detected in the thyroid cartilage after treatment for head-and-neck cancer. The TD 5/5 is probably around 70 Gy and the TD 50/5 about 80 Gy (Rubin and Casarett 1968; Emami et al. 1991).

6.2.4 Growing Muscle (Hypotrophy and Atrophy)

As with growing bone, there is no clear dose threshold or dosimetric modeling system for RT effects on developing muscles. Again, doses less than 20 Gy are likely to produce insignificant late effects except in children younger than 3 years old. And, again, the higher the dose, the more profound are the late effects. Doses in the range of 10–30 Gy can certainly cause some degree of muscular hypoplasia in children. Higher doses are associated with substantially more severe changes like asymmetry and hypotrophy (Raney et al. 2000; Paulino et al. 2000a).

6.2.5 Mature Muscle (Fibrosis)

Adult muscle tissue is quite radioresistant. The clinical data on muscle damage secondary to ionizing radiation are sparse. In adults, fibrosis is usually not observed unless doses exceed 50–60 Gy (Alektiar et al. 2000; Gillette et al. 1995). As with the skeletal system, hyperfractionation may reduce the severity of late effects (Bolek et al. 1996). The TD 5/5 for severe fibrosis in adults, as studied in the treatment of adult sarcomas, is probably about 55 Gy for moderate to large fields. The TD 50/5 is probably 65–70 Gy (Alektiar et al. 2000, Gillette et al. 1995).

7 Chemotherapy

Chemotherapy is not thought to produce significant late effects with regard to the musculoskeletal system. However, in animal models, the use of chemotherapy has reduced the shear strength of the physis (Van Leeuwen et al. 2003), which would theoretically predispose patients to developing slipped capital femoral epiphysis. This finding has not been studied in humans.

The use of corticosteroids alone or combined radiation therapy can augment osteonecrosis of the femoral head.

8 Special Topics

8.1 Surgery

Organ-sparing procedures have been commonly performed in recent years and combined surgery and RT is often required to achieve good local control. If the periosteum is stripped, the risk for radiation late effects, especially fracture, increases. The surgical removal of parts of muscles or bone can lead to severe functional deficits, and the damage from RT can cause additional dysfunctions. In many instances, the physical disabilities produce serious psychological and social consequences. For example, the risks of conservative surgery and preoperative or postoperative RT to the leg or arm need to be considered in the treatment of extremity sarcomas, but if amputation is the alternative, those risks may be well worth taking. Every patient needs an individualized treatment plan.

8.2 Slipped Capital Femoral Epiphysis

RT has been shown to increase the risk for epiphyseal plate injury to such a degree as to cause slipped capital femoral epiphysis. Most of the reported cases have been in children who were treated at a very young age and received a relatively high dose of irradiation (Wolf et al. 1977; Libshitz and Edeikin 1981; Silverman et al. 1981). RT can cause injury to the blood vessels and deplete the physis growth plate cells, causing structural weakening. The stress of weight bearing causes fissures that coalesce to a fracture in the growth plate. As the slip progresses, an increasing angulation occurs between the epiphysis and the remainder of the femur. The weight and epiphysis is displaced due to a rotational slip and tilt, often made possible by a compression fracture in the posterior part of the metaphysics. In children who have had hip irradiation, slippage may occur without other predisposing factors like obesity. The incidence peaks at a much earlier age (age 9–10 years) compared to children who get it for nonmalignant conditions.

8.3 Pathologic Fracture

Children are at high risk for pathologic fracture after receiving RT to bones. This complication can be seen in weight-bearing bones after treating Ewing tumor of bone or soft tissue sarcoma near bone (Paulino 2004; Wagner et al. 2001). Sometimes persistent cancer may be hard to diagnose, and cause a pathologic fracture, particularly in Ewing's tumor of bone where it is not easy to evaluate the tumor status after radiation therapy. If the bone is biopsied trying to ascertain the presence of residual tumor, the incidence of fracture increases.

8.4 Avascular Necrosis

Avascular necrosis (AVN) of the femoral head has been reported as a complication of hip irradiation in children who have received doses exceeding 30 Gy (Libshitz and Edeikin 1981). High cumulative corticosteroid doses administered during the therapy strongly predispose children to AVN, and dexamethasone seems to be more toxic than prednisone (Burger et al. 2005). Age greater than 10 years at diagnosis has been recognized as an important risk factor (Mattano et al. 2000), indicating that the rapidly growing and maturing bones of adolescents are more susceptible to developing AVN. Outside steroid use and other factors like immobilization or the malignancy itself may contribute as well. AVN may be asymptomatic or may result in joint swelling, pain, and limited range of motion. In some patients, AVN may cause joint damage and articular collapse. MRI is the best technique to detect early stages of AVN.

8.5 Valgus and Varus Deformities

RT delivered to the metaphysis of the long bones is responsible for valgus and varus deformities. The data from

modern RT techniques indicate that in limb-sparing sarcoma treatment a conformal RT dose distribution to the target causes asymmetric dose delivery to the bone itself. This coupled with brachytherapy, which can also expose a limited portion of the bone to the therapeutic dose, can lead to a higher risk of valgus and varus deformities, as shown by authors from St. Jude (Fletcher et al. 2004). Valgus and varus deformities by themselves may also make the irradiated hip more vulnerable to subsequent stress and severe functional limitations requiring major surgical interventions.

8.6 Osteopenia and Osteoporosis

Osteopenia and osteoporosis are systemic skeletal disorders characterized by low bone mass and disturbances of the microarchitecture of the bone tissue and produce an increased risk of fractures. Osteoporosis is observed in many pediatric cancer patients at different phases of their therapy and is also recognized during their followup period. The cause of osteopenia in pediatric cancer patients is multifactorial. Infiltration of bone marrow by cancer cells, cancer therapy (particularly at an older age), and prolonged administration of pharmacologic doses of glucocorticoids can all contribute to this complication.

There are two possible mechanisms for explaining RT effects on bone density: (1) a direct effect through the interaction of the ionizing radiation with the bone structure itself, and (2) an indirect impact through the disruption of endocrine function and its regulatory control of bone metabolism. Several studies have reported loss of bone density due to hormonal deficits in patients treated with cranial irradiation or total-body irradiation (TBI) for acute lymphoblastic leukemia (ALL) as well as central nervous system tumors (Vassilopoulou-Sellin et al. 1999). Data on the direct relationship between local RT and reduced bone density in children are not well established. In fact, recent data suggest that RT does not routinely decrease bone density when corrected for weight bearing or mechanical effects. The pathogenesis for the known increased risk of pathologic fracture in irradiated bones is likely multifactorial, including possible alterations in bone remodeling that can result in stable, or even increased bone density (Dhakal et al. 2011). Endocrine deficits are the main cause of osteoporosis secondary to RT, most commonly a loss of growth hormone after receiving cranial RT. Sex hormones also have a profound anabolic effect on bone metabolism and sex-hormone deficiencies can contribute to osteopenia and osteoporosis in both young adults and older individuals (Holmes and Shalet 1996). RT delivered to the pelvic area can result in the suppression of ovarian function and secondarily cause osteopenia (Hamre et al. 1987).

9 Prevention and Management

9.1 Prevention

9.1.1 Endochondral Bone Formation

Patients who have had spinal irradiation should be followed closely for spinal abnormalities. The evaluation of spinal sequelae should include the region of curvature, the magnitude of the curve, the deviation from vertical, the degree of shoulder asymmetry, the position of any rib humps or rib flare, and the type and degree of any gait abnormality. Usually, the best way to examine the back is with the patient bent over with straight knees and the arms touching the toes. At each visit, measurements should be taken of the standing and sitting heights. While spinal shortening does occur from the direct effects of irradiation, it is not correctable and, except for an ultimate decrease in height, does not usually cause major problems unless spinal curvature develops. Anteroposterior and lateral films of the entire spine should be performed to screen for this condition. It is also important to inform patients of the expected height deficit. As part of the followup, standard scoliosis X-rays should be done to detect early scoliosis or kyphoscoliosis every 1–2 years until skeletal maturity. Films should still be taken every 1–2 years thereafter if some curvature is already present. It is rare to develop curvature after skeletal maturity if none were present before, so patients without spinal problems at skeletal maturity probably do not need radiographs unless a problem develops.

The most common method for measuring spinal curvature is the Cobb technique. The two end vertebrae of the curvature, the ones most tilted from the horizontal on the upright film, are selected. A line is drawn along the upper end plate of the upper end vertebra and along the lower end plate of the lower end vertebra. The angle of intersection of the perpendiculars from these lines is the angle of the curvature. It is extremely important to perform these measurements carefully and accurately. In the event of a double curvature, both should be measured. Since progression of any defect may be more important than the occurrence of the defect, the amount of curvature should always be measured from the same two vertebrae to ensure accurate comparison (Winter 1990). Paravertebral neuroblastomas erode and invade vertebrae, ribs, and when ablated, post irradiation, lead to severe kyphoscoliosis. Unlike Wilm's tumor, the scoliosis tends to be milder since normal vertebrae are irradiated (Nakissa et al. 1985).

9.1.2 Mature Bone

The only mature bone effect that can potentially be prevented is a pathologic fracture. Most fractures occur within a year or two after RT, which produces temporary bone

resorption that heals with time. It is important to stress to the patient that even moderate stress to the treated bone should be avoided, particularly to the long bones of the leg. When there is more than 50 % cortical destruction from the tumor in any circumferential portion of the bone, when the tumor involves the femoral neck, or when pain from the tumor does not improve with RT, prophylactic surgery of the femur (pinning of the femur) should be considered.

9.1.3 Muscle Fibrosis

The only sure way to minimize fibrosis is to keep the high-dose volume of radiation to a minimum. Although some fibrosis occurs at any dose, severe fibrosis is generally limited to doses of 55 Gy or more with conventional fractionation. Surgery increases the fibrosis in irradiated tissues. In most cases, late effects from RT involve both the muscles and the bones of an anatomic region. While it is preferable to prevent major problems, this cannot always be done, and moderate to severe sequelae develop. Whether or not surgery is required, a good exercise program is a necessary part of management. Range-of-motion exercises should progress slowly to weight bearing and then muscle-strengthening exercises. The battle with sequelae may be lif-long, and a proper exercise program is one of the few means of combating the progression of damage or regaining previously lost function. Caution must be emphasized when recommending vigorous exercise regimens for patients who have received high doses of doxorubicin, since cardiac decompensation may result.

9.1.4 Lymphedema

With limb extremity irradiation, it is important to avoid irradiation of the entire limb circumference. The medial portion of the upper and lower extremities allows for lymphatic drainage, thereby lymphedema is avoided.

9.1.5 Joints

Since stiffness, pain, and loss of range of motion in the joints can occur after RT, it is important to emphasize exercise, with range-of-motion exercises being the most important. Bicycling, swimming, walking, and running are also beneficial. It is easier to prevent contractures in the muscles around the joint and stiffness in the ligaments of the joint than to reverse it once it occurs.

9.2 Management

9.2.1 Endochondral Base and Growing Bone

The only proven treatment for growth arrest of bone and its consequences is surgery. Of the common deficits that develop, scoliosis and leg-length discrepancies often require intervention.

Table 5 Recommended treatment for categories of leg-length discrepancies

Leg-length discrepancy (cm)	Treatment
0–2	None required
2–6	Shoe lift, epiphysiodesis
6–15	Leg lengthening
>15	Prosthetic fitting

with permission from Mosely (1990)

Scoliotic curve progression beyond 30° (or curves over 20° with rapid progression) generally requires bracing. Curves greater than 40°, particularly in skeletally immature patients, should be instrumented and fused.

Table 5 shows the recommended treatment for categories of leg-length discrepancies (Mosely 1990). Small differences (0–2 cm) usually require no intervention. Greater differences require an orthopedic evaluation. Differences of 2–6 cm can be corrected with a shoe lift or a contralateral epiphysiodesis, an operation creating a premature fusion of an epiphysis in the contralateral limb to arrest growth, thereby preventing further exaggeration of the deficit. Greater inequality (6–15 cm) requires more aggressive management. Contralateral limb shortening or ipsilateral lengthening procedures are usually necessary to restore a functional gait. Differences of greater than 15–20 cm are difficult to manage.

Other less common late effects may also need intervention. Partial epiphyseal-plate injury results in juxta-articular angular deformities of the long bones. These uncommon growth aberrations are difficult to treat and often require complete physeal arrest and osteotomies for correction. Their infrequent occurrence is now ascribed to more careful attention to irradiation technique, so that the entire physis is incorporated within the portal.

The occurrence of a slipped capitofemoral epiphysis is a medical emergency requiring immediate referral to an orthopedic surgeon. A slipped capitofemoral epiphyses necessitates an in situ pin fixation. If the other leg has also been irradiated, an increased possibility of a slipped capitofemoral epiphysis in that leg warrants consideration for a prophylactic pinning. Severe slips (greater than 60°) may require a proximal femoral osteotomy and osteoplasty (Barrett 1985). Total hip replacement may be needed, though all attempts should be made to manage the condition more conservatively in children.

A few extoses may require excision because of symptoms or malignant degeneration.

9.2.2 Mature Bone

Pathologic fractures in the irradiated field, more common if the irradiated bone was biopsied or involved with tumor, will rarely heal without internal fixation. Pathologic

fractures through irradiated bone are a challenging problem and often require long periods of treatment and multiple procedures to unite. The concomitant radiation changes in the surrounding soft tissue envelope of the bone further complicate the management of these fractures. These compromised tissues greatly increase the risk of postoperative infection. Rigid internal fixation is mandatory and bone grafts are utilized liberally. Vascularized bone grafts are the gold standard for obtaining union in patients who have failed to unite their fractures after other procedures (Lin et al. 1998). In the event of severe wound complication and nonunion, an amputation should be considered.

Necroses of bone, including those of the mandible, sometimes heal with conservative management. Hyperbaric oxygen has been used for bone necroses with success, as has pentoxifylline and vitamin E (Delanian et al. 2005).

9.2.3 Muscle: Chronic Fibrosis

RIF has been reported to respond to a combination of pentoxifylline and tocopherol (vitamin E). In a series of 43 patients with 50 distinct zones of significant RIF who were given 400-mg pentoxifylline and 500 IU tocopherol twice a day, clinical improvement occurred in 83 % of lesions at 12 months. The average time from the end of treatment until the start of therapy in this group was 8.5 years. Treatment was given for 6 months or until clinical improvement had ceased. The mean SOMA score changed from 13.2 at the start of treatment to 6.9 at 12 months (Delanian et al. 1999). Neither drug was effective alone; the combination was necessary.

Further studies by the same team have shown that even better results can be obtained with prolonged treatment. In two-thirds of patients, the maximal response was by 2 years; however, 3 or more years may be necessary to produce a maximal response in more severe RIF. If the treatment is too short, a rebound effect may occur (Delanian et al. 2005).

9.2.4 Joints

Loss of range of motion and joint stiffness can be due to radiation effects on the muscles operating the joint or may be intrinsic to the joint itself. If the muscles are severely affected, a contracture may result making it impossible to fully extend the limb. These are difficult to correct and take a great deal of effort by the patient, but may be worth trying. Directed physical therapy combined with pentoxifylline and tocopherol may improve loss of function in severe cases.

10 Future Research Directions

Newer radiation-delivery techniques, including high-dose-rate brachytherapy, intraoperative RT, and the spectrum of conformal external-beam.

RT planning and delivery techniques seek to confine the prescription dose to the region at risk and minimize the dose received by normal tissues. Computerized treatment planning technology and the use of 3-dimensional imaging permits the delineation of both target- and normal-tissue structures to the extent that the dosimetry for a defined normal-tissue structure, such as bone or soft tissue, may be known with a high degree of precision. This information can be used relatively to compare different treatment plans for a given patient. Prospectively assessed, this information may be used as a clinical variable to correlate treatment dosimetry to abnormalities in growth and development including their time to onset and severity. This will provide better dose and volume data to correlate with late effects, allowing more accurate prediction of complications.

In addition, better knowledge of the molecular causes of radiation damage should provide drug development that can prevent or ameliorate radiation toxicities. The finding that pentoxifylline and tocopherol can reverse severe radiation fibrosis is an important step. In addition, animal data indicate that pentoxifylline, given during RT, can decrease the degree of limb shortening (Pateder et al. 2002). There is rationale for trials of pentoxifylline as a preventative therapy in the clinic. Further research should provide or develop other drugs that can prevent or reverse radiation damage.

11 Literature Landmarks

The sensitivity of bone to radiation damage was noticed shortly after the discovery of radiation. In 1903, Perthers first reported stunting of wing growth in chicks after irradiation. A thorough review of clinical and laboratory studies provided the pathophysiology of growing and mature bone and muscle (Rubin and Casarett 1968). Soon there followed a similar observation by Recaimier and Tribondeau who also demonstrated the first histologic evidence of radiation effects on the epiphyseal plate (Rubin et al. 1959). These and similar animal studies triggered active biology research in this area, and for many decades investigators demonstrated alterations in growing cartilage and bone after even relatively small doses of irradiation. The clinical utilization of radiation soon was found to cause significant musculoskeletal side effects, particularly in children. In 1926, Ewing performed a histologic study of radiation bone injury and introduced the term *osteitis*, which manifests with a gradual reduction of periosteal and endosteal cells (Ewing 1926).

As the clinical use of therapeutic radiation expanded, growth abnormalities, deformities, and other late effects of RT were reported in patients treated for both childhood and adult tumors. The data on scoliosis risk were particularly striking in children treated for Wilms' tumor and neuroblastoma. The medical literature of the 1950 and 1960s was

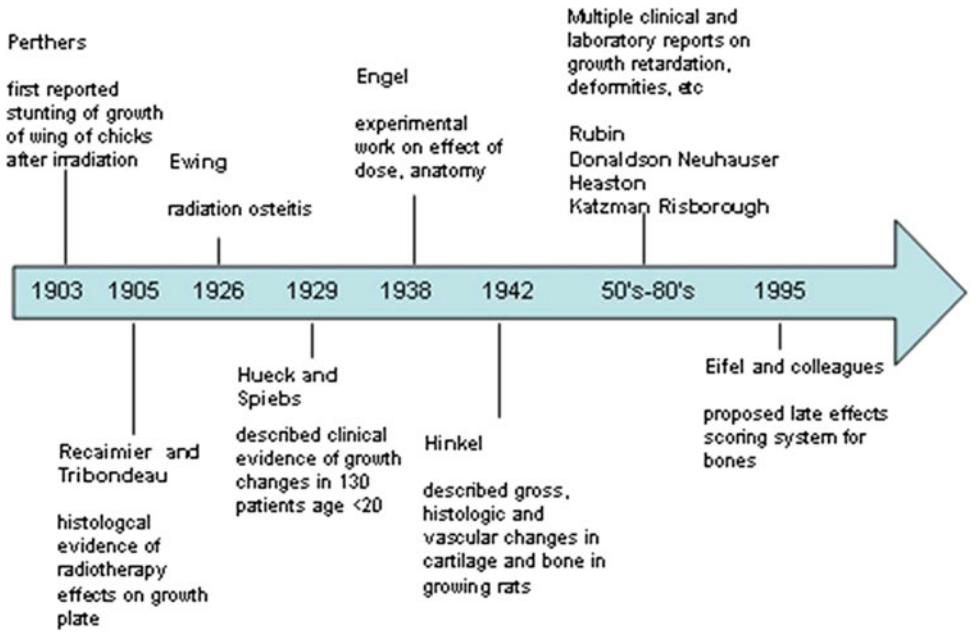


Fig. 9 Literature landmarks

flooded with case series on this topic. Early reports, however, were difficult to compare because of the lack of a consistent scoring system for any late effects, including those of the musculoskeletal system. Chronological data on publications on this topic are outlined in (Fig. 9). Accumulated data triggered great interest in defining contributions from not only RT fields and doses but also patient related, disease related, and other potential variables also affecting the severity of this problem. The question about radiation dose thresholds was continuously evaluated in both animal experiments and clinical research but still remains open.

As clinical knowledge of the effects of radiation on the musculoskeletal tissues became more prevalent toward the end of the last century, laboratory study of these effects expanded in an effort to discover the mechanisms of action. Only now is the molecular basis for these effects beginning to be understood, but considerable work needs to be done.

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Hematopoietic System

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Abstract

Radiation effects on the hematopoietic system affect not only blood forming cells but also stromal elements. Toxicity to marrow from radiation has many parallels with chemotherapy—induced toxicity, and additive or synergistic effects can occur. Acute toxicity from radiation to marrow can be manifest by decline in peripheral blood counts, and the degree of toxicity is affected by radiation dose, dose rate, and treatment volume. In humans, marrow ablation due to total body irradiation has been difficult to study, since this is used only in the setting of stem cell transplantation which ameliorates some but not all of the marrow toxicity. Chronic toxicity to marrow from radiation is dependent on fraction of the marrow organ irradiated and total amount delivered. Patterns of regeneration have been well studied in murine and rabbit models. Measures to overcome marrow toxicity from radiation include chemical radioprotectors, hematopoietic growth factors, and potential amelioration of marrow stromal damage through cytokine support.

Abbreviations

ARS	Acute radiation syndrome
BMT	bone marrow transplantation
BFU-E	Burst-forming units for erythrocytes
CFU	Colony-forming units
LD	Lethal dose
ME	Microenvironment
MnSOD	Manganese superoxide dismutase

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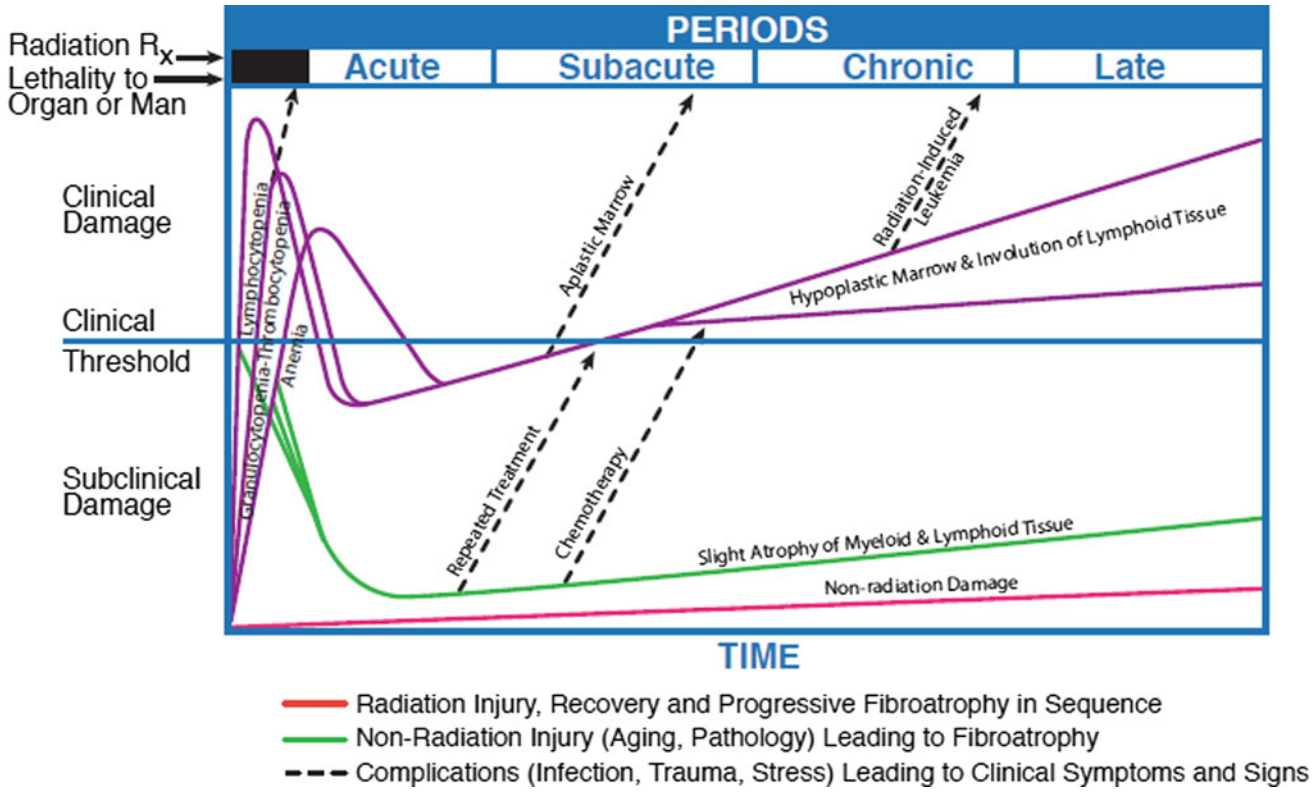


Fig. 1 Biocontinuum. Clinicopathalogic course: the blood and marrow (total-body-irradiation). The elements of the blood and bone marrow follow a response pattern of decreased number after irradiation owing to their cell kinetics after destruction of primitive radiosensitive precurser cells. The neutropenia seen in the first week is due to a cessation of production and rapid turnover of these cells. This is followed in two to three weeks by thrombocytopenia and into two to three months by anemia. Recovery is related to the degree of initial response and generally begins with a regeneration of the depleted stem cells. If large volumes of bone marrow have been irradiated, a hypoplastic marrow can persist and occasionally become aplastic. This latter event may be due to cancer infiltrating to the marrow and should be suspected if the depression in blood count does not occur at a predictable time and only if a limited volume of bone marrow has been irradiated. The upper heavy lines represent the course after exposure of large volumes of bone marrow; the lower heavy lines, after localized bone marrow irradiation (Rubin and Casarett 1968)

SCF	Stem cell factor
SDF	Stroma derived factor
TPO	Thrombopoietin
TBI	Total body irradiation
DOTMP	166Ho-1, 4, 7, 10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid

1 Introduction

Tumor cell killing by radiation and chemotherapy, individually and in tandem, is dose-dependent. Coincidental bone marrow injury, as reflected by a depression in peripheral blood counts, is frequently the dose-limiting toxicity because of risks for infection and bleeding (Fig. 1) (Rubin and Casarett 1968). Strategies to protect hematopoietic progenitor cells or bone marrow stroma from therapy-induced death, or to accelerate hematopoiesis following therapy, would ideally permit more intensive treatment with minimized associated risks. Furthermore, agents which enhance radiation or chemotherapy effect might also enhance therapeutic efficacy but at increased risk of marrow toxicity. To understand the impact of radiation and chemotherapy on the bone marrow organ, its organization and function must be considered. New insights into the complexity of this critical organ offer the potential to modulate and modify its response to radiation.

Studies of radiation effects on marrow were stimulated during the era of atomic bomb development as it was felt important to discover acute and chronic effects of radiation on blood forming elements since this was recognized as one of the crucial determinants of ultimate toxicity. Such studies contributed much to understanding mechanisms of hematopoeisis, the presence of clonal hematopoietic progenitors and stem cells, and provided much of the basic and pre-clinical work which made possible the field of human

stem cell transplantation (Hewitt 1973; Walker 1994; Moeller 1978). *Biocontinuum of adverse early and late effects are shown in Fig. 1.*

2 Anatomy and Histology

2.1 Anatomy

The geographical distribution of the bone marrow (BM) is relevant to understanding radiation effects on the bone marrow compartment (Fig. 2a, b, c). A schematic of bone marrow architecture (redrawn from M. Brooke's classic work, the blood supply of bone, London: Butterworths; 1971). The nutrient artery penetrates the cortex of bone in an angulated fashion and in the marrow bifurcates into ascending and descending medullary arteries from which radial arteries arise. The radial arteries enter the canalicular system of cortex through the endosteum and become cortical capillaries at which point blood from periosteal and endosteal capillaries can communicate. The cortical capillaries enter the marrow sinuses. The sinuses eventually collect and enter and central sinus from which blood leaves the marrow and enters the systemic venous circulation via emissary veins. Hematopoiesis occurs in the interstitial spaces.

2.1.1 Geographic Child Distribution

In childhood, bone marrow fills all cancellanous marrow spaces including long bones (Fig. 2b). The transition to adult begins at adolescence when there is accelerated skeletal growth and the involution occurs with recession in long bones except for proximal portions of humerus and femur. The adult marrow tends to be more central in the skull, vertebrae, pelvis, ribs, clavicle, and sternum. Although variations occur, the major functional sites are the pelvis and vertebrae that make up approximately 60 % of the total body marrow. The ribs, sternum, skull, scapulae, and proximal portions of the femur and humerus also contain functioning marrow (Atkinson 1962). In children, the humerus, femur, and other long bones are active, but marrow retraction from the peripheral (appendicular) toward central (axial) skeleton, and from diaphyseal to metaphyseal in individual long bones gradually occurs, so that by age 20 years the mature adult distribution pattern is present (Fig. 2b, c).

2.1.2 Marrow Distribution in Adults

The geographic distribution of the bone marrow is particularly relevant to understanding radiation effects (Fig. 2b, c). Although variations occur, the major functional sites are the pelvis and vertebrae. In the past, this was determined based upon semiquantitative histopathologic studies, but recently, FLT-PET imaging has been utilized to determine marrow distribution (Hayman et al. 2011). In addition to the pelvis and vertebrae, the ribs, sternum, skull, scapulae, and proximal portions of the femur and humerus contain virtually all of the functioning marrow (Hayman et al. 2011). In children, the humerus, femur and other long bones are active, but marrow retraction from the peripheral (appendicular) toward central (axial) skeleton, and from diaphyseal to metaphyseal in individual long bones occurs. By age 20 years, the mature adult distribution pattern is present (Custer and Ahlfedt 1932).

2.2 Histology

Hematopoietic stem cells replicate and differentiate along lymphoid or myeloid lineages regulated by a network of hematopoietic growth factors and cellular interactions (Clark and Kamen 1987; Sieff 1987) (Fig. 3). Families of colony stimulating factors (CSFs) have been identified that control the process of replication and differentiation. Understanding the specific mechanisms of the action and interaction of the different cytokines is only beginning. The hematopoietic system is also dependent on the microenvironment (ME) that consists of endothelial cells, adventitial cells, fibroblasts, macrophages, and fat cells. This ME maintains hematopoietic function in part through the secretion of CSFs and in maintaining cell–cell contact.

The ME is heterogenous both in its function and anatomic structure. Hematopoiesis takes place in the extravascular spaces between marrow sinuses, which are the channels through which blood flows in the bone marrow (Fig. 3a). These sinuses are the finer branches of a complex vascular network. The arterial blood supply of marrow comes predominantly from the nutrient artery that penetrates the cortex of bone, enters the marrow, and bifurcates into ascending and descending medullary arteries. These give rise to radial arteries that enter the canalicular system of cortex through the endosteum and become cortical capillaries at which point blood from periosteal and endosteal capillaries can communicate. The cortical capillaries enter the marrow sinuses, which eventually leaves the marrow and enters the systemic venous circulation via emissary veins. The resulting interstitial spaces, which are composed of the various stromal cells, make up the hematopoietic ME (Lichtman 1981).

2.2.1 Hemopoietic Tissue and Blood Cells

In the adult body, there are two kinds of hemopoietic tissues: red bone marrow and lymphatic tissue (Fig. 3b, c). The former produces erythrocytes, leukocytes, and platelets, and the latter is the source of lymphocytes. The red bone marrow is composed chiefly of sinusoids and three cell types: reticular cells, adipose cells, and hemopoietic cells (blood-forming cells). Along with reticular fibers

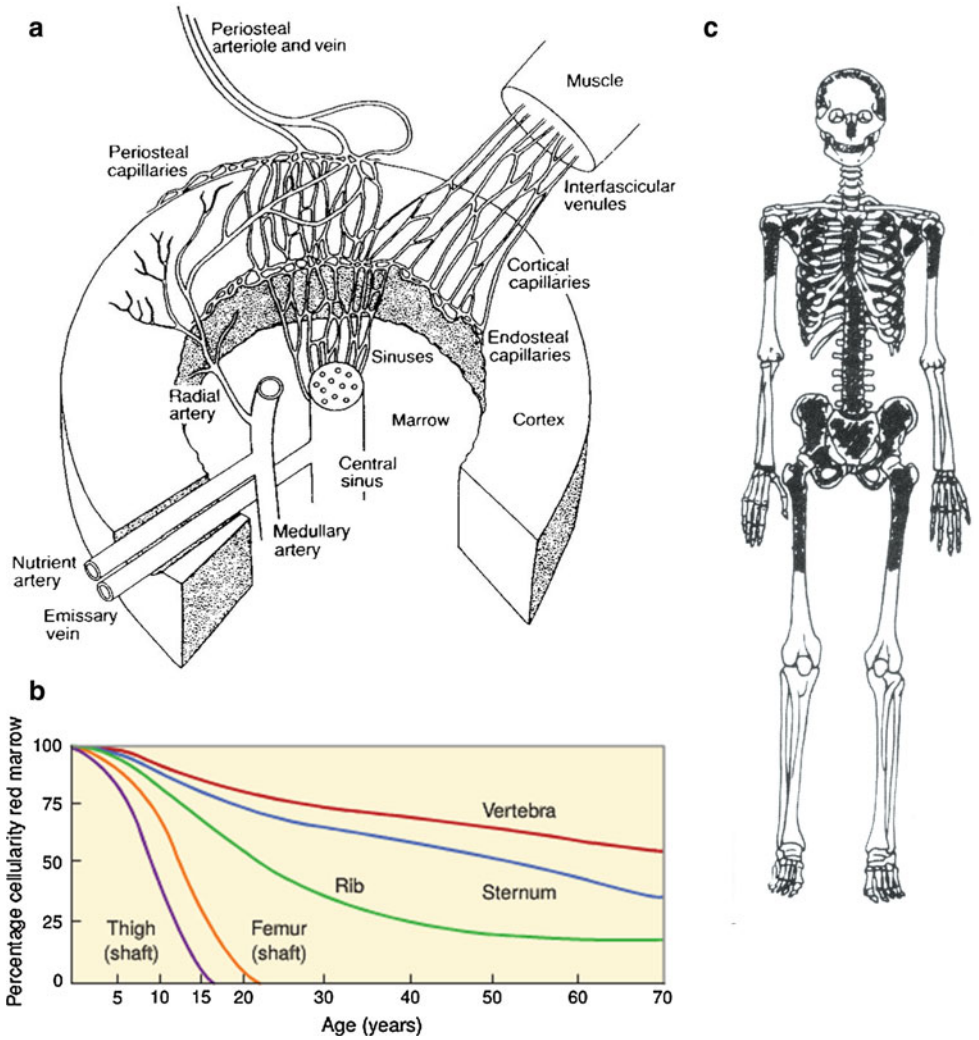


Fig. 2 **a** A schematic diagram of bone marrow architecture (redrawn from M. Brooke's classic work, the blood supply of bone, London: Butterworths; 1971). The nutrient artery penetrates the cortex of bone in an angulated fashion and in the marrow bifurcates into ascending and descending medullary arteries from which radial arteries arise. The radial arteries enter the canalicular system of cortex through the endosteum and become cortical capillaries at which point blood from periosteal and endosteal capillaries can communicate. The cortical capillaries enter the marrow sinuses. The sinuses eventually collect and enter and central sinus from which blood leaves the marrow and enters the systemic venous circulation via emissary veins. Hemopoiesis occurs in the interstitial spaces (Reprinted with permission from Lichtman 1981). **b** The relative amount of red and yellow bone marrow in different anatomic sites as a function of age (based on cortex) (Reprinted with permission from Kricun 1985). **c** bone marrow distribution in adult humans as determined by autopsy finding: active regions are shaded (Reprinted with permission from Hashimoto 1960)

(not shown in Fig. 3), the reticular cells, which have ovoid nuclei and several processes, form a framework of reticular tissue in which the hemopoietic cells are contained. Adipose cells are the largest cells in the bone marrow, occupying more and more of the bone marrow cavity with age. Hemopoietic cells differentiate into erythrocytes and leukocytes. They are in different developmental stages, and some of them are seen undergoing mitotic division (in mitosis). In a marrow section, stages of hemopoietic differentiation are difficult to see, but they can be recognized in the bone marrow smear (Zhang 1999).

3 Physiology and Biology

3.1 Physiology

3.1.1 Stages of Development

The formation of the hematopoietic cells of bone marrow are in different stages of development from both the erythrocytic series and the granulocytic series. The erythrocytic series contains the proerythroblast, basophilic erythroblast, polychromatophilic erythroblast, orthochromatophilic

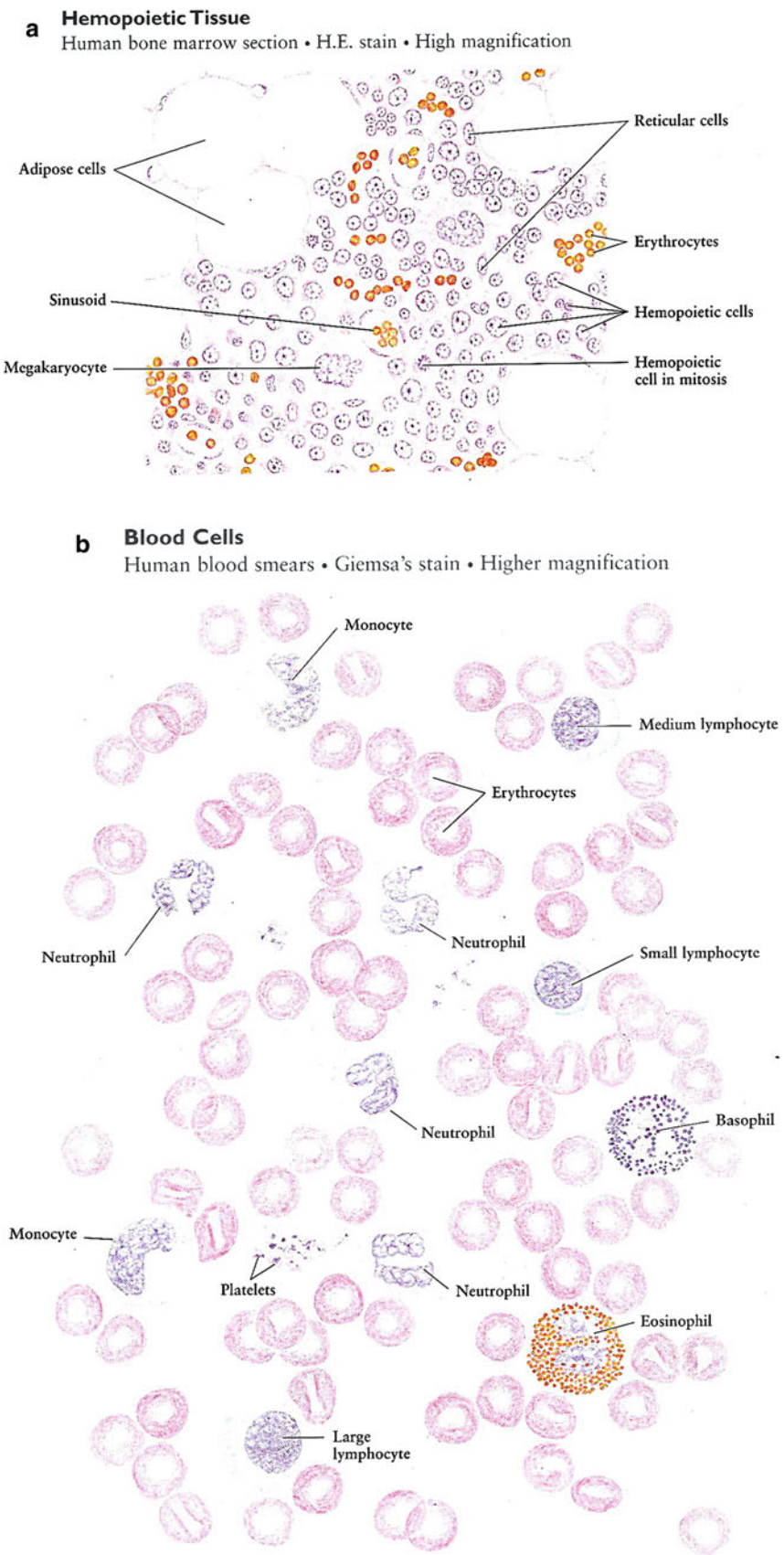
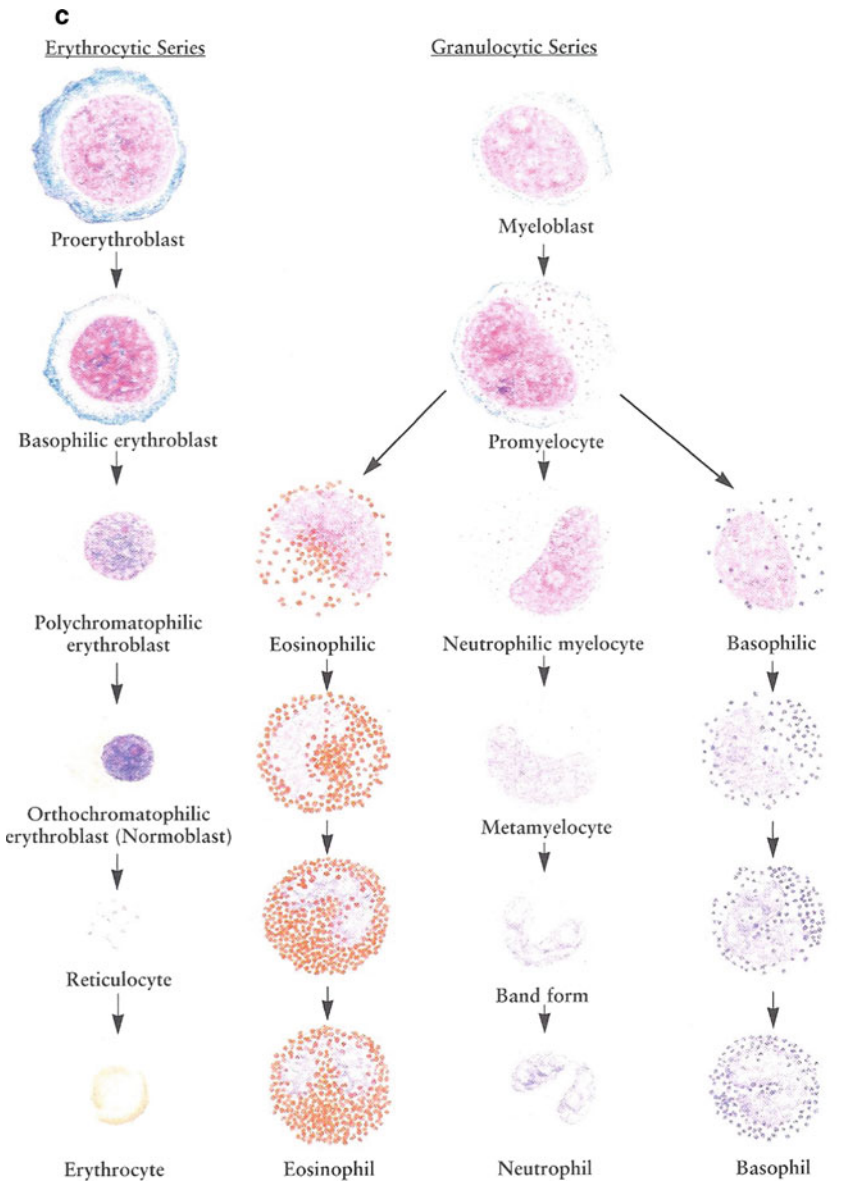


Fig. 3 **a** bone marrow. **b**: Blood smear. **c** Formation of blood cells (hemopoiesis) human bone marrow, high magnification (Reprinted with permission from Zhang 1999)

Fig. 3 (continued)



erythroblast, and reticulocyte; the granulocytic series contains the myelocytes and metamyelocytes. These cells are drawn from a human bone marrow smear stained by the Wright method. The characteristic features of these cell types are briefly described (Zhang 1999) (Fig. 3c).

3.1.2 Erythrocytic Series

- Proerythroblast is the earliest cell recognizable in the development of the erythrocyte (20 μm).
- Basophilic erythroblast shows a reduction in size (15–17 μm in diameter).
- Polychromatophilic erythroblast is formed by mitotic division of a basophilic erythroblast. It becomes smaller (12–15 μm in diameter) than the basophilic erythroblast, and the chromatin of the nucleus becomes more condensed.
- Orthochromatophilic erythroblast (normoblast) continues to decrease in size, measuring 8–10 μm in diameter.
- Reticulocyte, an immature erythrocyte, is an anuclear round cell with a diameter of 9 μm.

3.1.3 Granulocytic Series

- Myeloblast is the earliest cell recognizable in the granulocytic series.
- Promyelocyte, the largest cell in the granulocytic series, measures 19–24 μm in diameter.
- Myelocytes are smaller than promyelocytes, 16–20 μm in diameter.
- Metamyelocytes continue to decrease in size (about 8–12 μm in diameter).

3.2 Biology of Hematopoiesis (Family of Growth Factors)

The pluripotent stem cell replicates and differentiates along lymphoid or myeloid lineages through a complicated process regulated by a network of hematopoietic growth factors and cellular interactions (Clark and Kamen 1987; Sieff 1987; Abboud and Lichtman (2006). (Fig. 4 and Table 1). The cascade through myeloid differentiation leads to erythrocytes, platelets, granulocytes, and macrophages, and the lymphoid cascade to T and B cells (Fig. 4 and Table 1). Families of growth factors (or cytokines) that control these processes of replication and differentiation have been identified. The hematopoietic progenitor cells and their offspring are cradled on a stroma of endothelial cells, adventitial cells, fibroblasts, macrophages, and fat cells within the bone marrow. This ME is both supportive and directive in the developmental and replicative processes and is also affected by radiation. Not only do the stromal elements respond to and secrete growth factors, but the geometric niches formed by the stroma maintain cell-to-cell contact of progenitors and their offspring. Mesenchymal stem cells are able to constitute the marrow stromal elements (Bonnet 2002) including osteoblast, smooth muscle, chondrocyte, and adipocyte lineages (Wolf et al. 2003). Recently, interleukin-6 has been found to be important in regulation of stromal function. In murine models, the percentage of Lin-SCA-1+ hematopoietic progenitors undergoing DNA synthesis is diminished in IL-6 deficient bone marrow. This defect is also observed in long-term bone marrow cultures (Rodriguez et al. 2003). How growth factor production by stromal layers changes during periods of chemotherapy and radiation—induced toxicity is only beginning to be defined.

3.2.1 Composition of Microenvironment (Niches)

Recently, both vascular and osteoblastic niches have been described in the murine marrow microenvironment. Whether such distinct niches are operative in human marrow is uncertain as direct studies of microenvironmental function are more difficult in humans. Hematopoietic stem cells are found in close proximity to osteoblasts which are affected by parathyroid/parathyroid receptor interactions. When murine stroma is treated with parathyroid hormone, it secretes increased stem cell factor (SCF, c-kit ligand), stroma derived factor (SDF)-1 alpha/CXCL12, and IL-6. Long-term culture initiating cells and hematopoietic stem cells are also increased (Calvi et al. 2003). C-terminal PTH also increases vascular endothelial growth factor expression in osteoblastic cells (Esbrit et al. 2000), which could also impact hematopoiesis. These effects can be blocked with gamma-secretase inhibitors, suggesting that Notch and its ligands, Delta and Jagged, play a role in PTH effects (Weber et al. 2006). An interesting laboratory study that supports stromal contribution was the observation of past radiation of the lower extremity that iron uptake increased at 3 months, however, the bone marrow was ablated histologically. A radioautograph of the tibia revealed the iron was concentrated in the bone cortex in 3 months. Over the next 3 months the bone marrow regenerated as a sleeve juxta-opposed to the cortex before following the entire bone marrow cortex (Rubin et al. 1997).

Human marrow stroma contains pluripotent mesenchymal progenitor cells that give rise to many mesenchymal lineages, including chondroblasts, adipocytes, myoblasts, ligament, tendon, or osteoblasts. The differentiation of these cells toward a specific lineage is dependent on humoral and local factors activating specific transcription factors. The family of transforming growth factors, for example, may promote osteoblast differentiation and inhibit adipocyte conversion of rat marrow stromal cells in vivo (Ahdjoudj et al. 2004). The role that angiogenesis plays in marrow toxicity from chemotherapy and radiation is just beginning to be understood. Increased microvessel density in marrow of multiple myeloma, acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplasia, and myeloproliferative disorders is well-described. Targeting these vessels with anti-angiogenesis agents will influence the nutrient and oxygen supply of tumors and may also reduce the growth stimuli provided by the endothelial cells. How angiogenesis protects or sensitizes to chemotherapy and radiation toxicity and effectiveness remains an area of active investigation (DeRaeve et al. 2004).

4 Pathophysiology

4.1 Histopathologic Sequence

Bone marrow dysfunction in the setting of cancer therapy has several possible etiologies (Gale 1985) (Fig. 5a, b, c, d, e and Table 2).

1. Direct injury to hematopoietic stem cells or their depletion.
2. Structural or functional damage to the stroma or microcirculation.
3. Injury to other accessory cells which have regulatory (cytokine-secreting) functions.
4. Perturbation of bone marrow functions by the underlying disease (e.g., leukemia).
5. An inherent defect in bone marrow stem cells associated with the underlying disease.

These various injuries translate into a disturbance in the production and release of growth factors, and in the finely tuned cell-to-cell interactions important for marrow

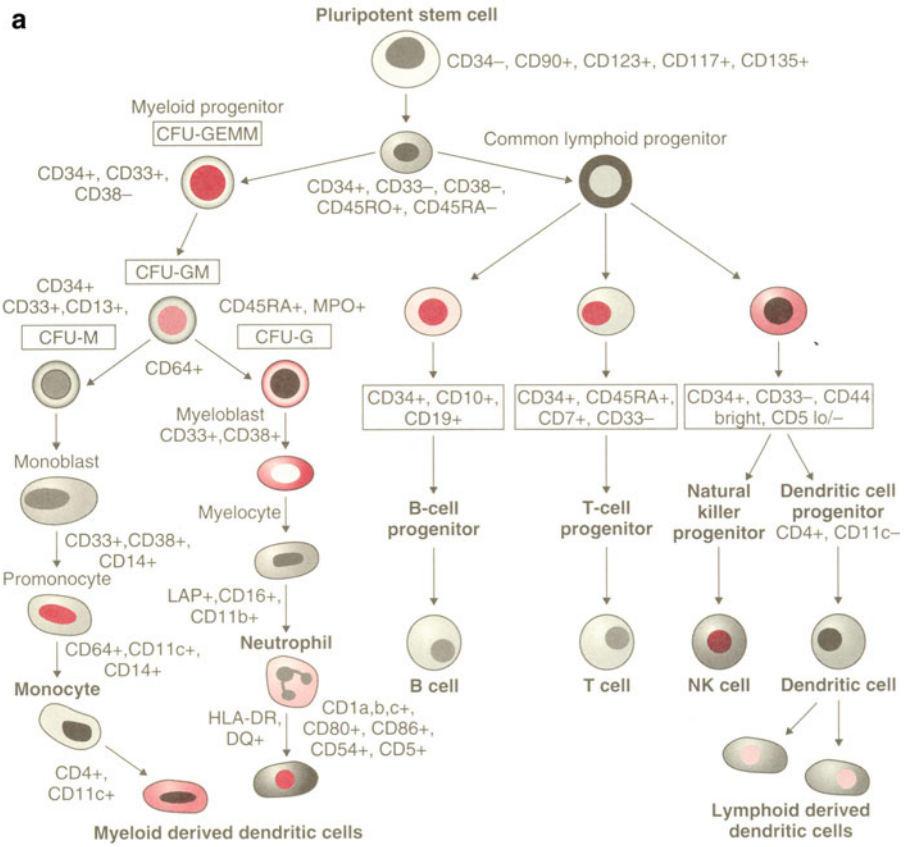


Fig. 4 Growth factors: schematic representation of hematopoiesis with surface antigen markers displayed. CD90, Thy-1; CD123, IL3Ralpha; CD117, c-kit; CD135, FLK2/FLT2; CD80, B7-1; CD86, B7-2; CD64, FcR1; CD16, FcRIII; CFU, colony-forming unit; GEMM, granulocyte/erythroid/macrophage/megakaryocyte; GM, granulocyte/macrophage; HLA, human leukocyte antigen; LAP, leukocyte alkaline phosphatase (Reprinted with permission from Devita 2008)

functioning. Thus, the regulation or process of hematopoiesis is disrupted. The precise mechanism of radiation damage to marrow is not yet clear; both apoptosis and necrosis can occur in different settings (Peng et al. 1999). Radiation results in increased macrophage activation with increased lysosomal and nitric oxide synthase enzyme activities. This results in increased respiratory burst activities and a neutrophil infiltration which results in clearance of radiation-induced apoptotic cells. These infiltrative and apoptotic cells may damage other cells by bystander effects, thus contributing to induced genomic instability. That mitochondrial generation of toxic radical oxygen species is important in radioresistance, and radiotoxicity has been demonstrated in nitric oxide deficient mice in which radioresistance and improved hematopoiesis in continuous marrow cultures was noted as compared to that in wild type mice (Epperly et al. 2007). Levels of certain cytokines may also influence response to radiation. For example, TGF-β1 transgenic mice are more sensitive to radiation than controls in terms of marrow suppression (Vodovotz et al. 2000). This has relevance in that TGF-β is elevated in some tumor states. After radiation to marrow, the alkaline phosphatase network increases in advance of hematopoietic recovery and then recedes once blood production is restored from a given marrow site (Almohamad et al. 2003).

Morphologic appearance of bone marrow after radiation is dependent on a variety of radiation dose, time, fractionation and volume, but generally follows this sequence: (Fig. 5a, b, c, d, e)

Figure 5a: Normal State: note ratio of hematopoietic cells to fat cell (adipose)

Figure 5b: Marked necrosis

Figure 5c: Marked hypocellularity

Figure 5d: Early regeneration

Figure 5e: Fatty replacement although occasional deposition of reticulin, fibrosis does not occur in bone marrow after radiation.

The only exception relates to irradiated metastasis which replaced marrow or pre-existing myeloproliferative disease, in both of which reticular collagen deposition can occur.

4.2 Histologic Alternations as a Function of Dose/Time

The histopathology during a fractionated course of radiation treatment with a standard schedule of 200 cGy daily fraction, 1000 cGy/wk to 5000 cGy is noted in Table 2.

Table 1 Hematopoietic growth factors approved for use by the US Food and Drug Administration with applications in cancer therapy

Hematopoietic growth factor	Generic name	Brand names	Molecular description	Hematopoietic effects	Applications in cancer
EPO	Epoetin alfa	Epogen, Procrit	rHu EPO	Red cell lineage	Chemotherapy-induced anemia in nonmyeloid malignancies
	Darbepoetin	Aranesp	rHu EPO with altered glycosylation	Red cell lineage	Chemotherapy-induced anemia in nonmyeloid malignancies
G-CSF	Filgrastim	Neupogen	rHu G-CSF	Neutrophil lineage	Reduce febrile neutropenia in patients receiving myelosuppressive chemotherapy; reduce duration of neutropenia after bone marrow transplantation, mobilize progenitor cells
	Pegfilgrastim	Neulasta	Pegylated rHu G-CSF	Neutrophil lineage	Reduce febrile neutropenia in patients receiving myelosuppressive chemotherapy
GM-CSF	Sargramostim	Leukine	rHu GM-CSF	Myeloid lineage	Reduce duration of neutropenia after bone marrow transplantation; mobilize progenitor cells
IL-11	Oprelvekin	Neumega	rHu IL-11	Megakaryocytes	Treatment of chemotherapy-associated thrombocytopenia

5 Clinical Syndromes (Endpoints)

Depression of each hematopoietic cell lineage translates into potential or observed difficulties for the patient (Table 3). The definitions of granulocytopenia, thrombocytopenia, and anemia are all somewhat arbitrary and appropriately operational in nature. LENT/SOMA1995 tables define grade of radiotoxicity (Table 3) (LENT SOMA 1995).

5.1 Detection

5.1.1 Complete Blood Counts: Local Field, Standard Fractionation

Although the alterations in Complete Blood Counts (CBCs) occur with most regionally localized cancers (brain tumors, head and neck cancers, lung and breast cancer, digestive tract, gland cancers, pelvic malignancies such as prostate and cervix), multiple factors including combined modality treatment, associated bleeding, and suppression of CBC elements occur (Fig. 6a). Figure 6a illustrates the classic figure of peripheral blood elements being depressed from time of total body irradiation (TBI) with variations depending on the dose and volume of bone marrow irradiated.

5.1.2 Severely Granulocytopenic

Severely granulocytopenic (or neutropenic) patients are generally considered to be those with an absolute granulocyte count (consisting of poly-morphonuclear cells and band forms) of 500/μL or less. These patients are at substantial risk for infection (David 2003). Counts between 500 and 1000/μL and declining due to antineoplastic therapy are considered by most oncologists to represent moderately severe neutropenia. Most patients clinically tolerate granulocyte counts between 1000 and 1500/μL.

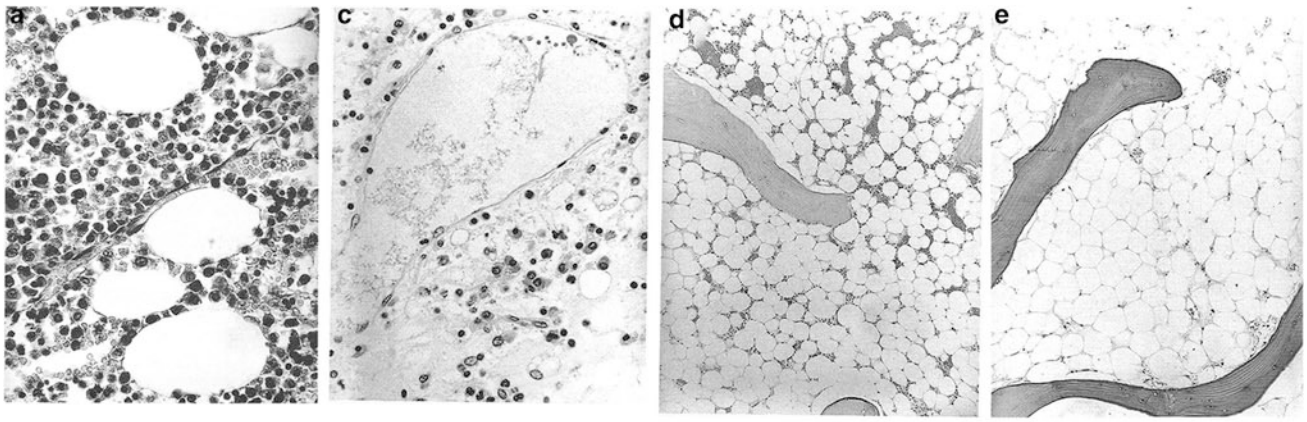
5.1.3 Thrombocytopenia

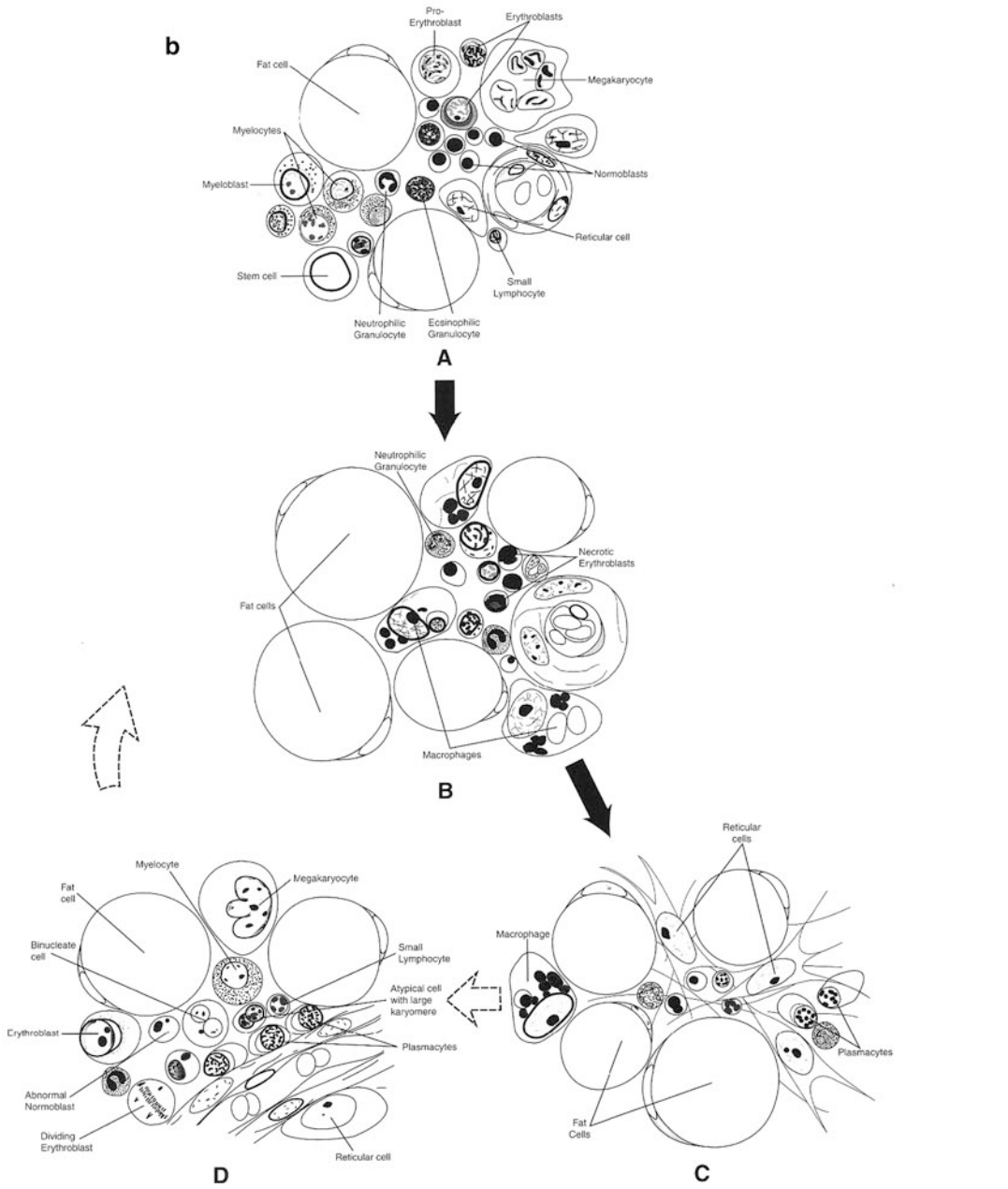
Thrombocytopenia has been strictly defined as a platelet count below 140000/μL, but the manifestations of bruising, petechiae, and mucosal bleeding rarely occur with counts of 100000/μL or above, and in fact are infrequent unless counts fall below 20000/μL (Beutler 1993). Intracranial hemorrhage is particularly rare, and most episodes occur at counts less than 10000/μL.

5.1.4 Anemia

Anemia prompting red blood cell transfusion is even more difficult to define because various clinical judgments are used. In practice, hematocrits as low as 23–25 % are tolerated by most patients. Those with cardiorespiratory difficulties may not tolerate hematocrits below 30 %.

As noted above, chronic marrow injury following cytotoxic therapy is poorly understood. The hematopoietic system appears to recover promptly after sub-ablative doses of chemotherapy and radiotherapy. However, heavily treated patients are known to have a reduced tolerance to additional therapy, showing lower nadirs of peripheral counts, particularly platelets. Decreased marrow functioning as reflected by marrow scanning after radiotherapy (Rubin et al. 1988; Rubin et al. 1973), or the CFU-GM pool after chemotherapy (Lohrmann and Schremi 1988) has been demonstrated up to 5 years following therapy. Hypoplastic and myelodysplastic syndromes have been observed at late intervals, but may represent a mutagenic or carcinogenic event.


a
c
d
e


b
Pro-Erythroblast
Erythroblasts
Fat cell
Megakaryocyte
Myelocytes
Myeloblast
Normoblasts
Reticular cell
Stem cell
Small Lymphocyte
Neutrophilic Granulocyte
Eosinophilic Granulocyte
A
Neutrophilic Granulocyte
Necrotic Erythroblasts
Fat cells
Macrophages
B
Myelocyte
Megakaryocyte
Fat cell
Binucleate cell
Small Lymphocyte
Atypical cell with large karyomere
Erythroblast
Plasmacytes
Abnormal Normoblast
Dividing Erythroblast
Reticular cell
D
Reticular cells
Macrophage
Plasmacytes
Fat Cells
C

◀ **Fig. 5** **a** Normal state: note ratio of hematopoietic cells to fat cell (adipose). **b** Hemopoietic system: Diagrammatic representation of key events of early injury of bone marrow after a single dose in the midlethal range. *A* Normal state; note the ratio of fat to hemopoietic elements. *B* Period of marked necrosis; the marrow is hypocellular, and many residual cells are nonviable. The macrophages have phagocytized remnants of necrotic cells. *C* Marked hypocellularity; the marrow is markedly hypocellular, with few if any identifiable hematopoietic elements. *D* Early regeneration; numerous mitoses are apparent, and most hematopoietic cells are immature (White 1975). Normal human bone marrow aged individual. *Note* the ratios of fat cells to hematopoietic precursors. High power, H&E, ×480. (Reprinted from Bonnet 2002 with permission form the American Journal of Neurogical pathology)**c** Vertebral bone marrow 24 days after initiation of local radiotherapy for mediastinal neoplasm. The total fractionated dose received up to the day of death was 26.9 Gy. Note the almost complete absence of normal hematopoietic elements. Residual cells consist primarily of plasma cells, macrophages, stromal cells, and neutrophils. Also note the large, dilated sinus occupying most of the upper field. H&E, ×480. **d** Hypoplastic bone marrow more than 12 months after local radiotherapy with fractionated dose >50 Gy. Note small foci of hematopoiesis. H&E, ×80. **e** Aplastic bone marrow more than 12 months after local radiotherapy with a fractionated dose >50 Gy. Bone marrow consists of adipose tissue with complete absence of hematopoietic activity. H&E ×120

Table 2 Histologic alterations at indicated times after initiation of fractionated local radiotherapy in humans

Fractionated exposures		
Total dose (R)	Time	Morphologic alterations
400	3 days	Moderate decrement in precursor cells
1000	8 days	Absence of precursor cells, dilated sinusoids, acute hemorrhage
2000	16 days	Marked decrement of all hematopoietic precursors, dilated sinusoids
5000+	35 days	Nearly complete absence of hematopoietic precursors, sinusoids less dilated
5000+	3–12 months	Continued nearly complete hypoplasia; abortive recovery followed by progressive hypoplasia may occur

Source with permission from Sykes et al. (1964)

5.2 Diagnosis

5.2.1 Bone marrow Assessments

The acute and chronic consequences of bone marrow injury by cytotoxic therapy can be considered in the context of these mechanisms. However, dissecting out the most relevant variables can be difficult due to limitations in the assessment of structure and function. *Peripheral blood counts* fail to demonstrate the true extent of marrow suppression or its likelihood of tolerating additional cytotoxic therapy because of the ability for the bone marrow to transiently compensate for injury. *Progenitor cell cultures* (Table 4) such as colony-forming units for granulocytes, macrophages (CFU-GM), burst-forming units for erythrocytes (BFU-E), colony-forming units for granulocytes, erythrocytes, macrophages, megakaryocytes (CFU-GEMM); *histopathology* (bone marrow aspirate and biopsy), *radioisotopic scanning* (^{111}In ^{52}Fe, ^{99m}Tc-sulfur colloid reflecting the myeloid, erythroid, and reticuloendothelial compartments respectively); and *stromal cell cultures* such as colony-forming units for fibroblasts (CFU-F), are all used to evaluate various quantitative or functional aspects of the bone marrow but are all limited in scope. *The long-term culture initiating cell assay and the NOD-SCID reconstituting cell assay can measure early multipotential progenitor cells* (Bonnet 2003). Most of these assays are not helpful in real time as most except for peripheral blood counts take weeks to conduct and analyze. Levels of Flt3 ligand in plasma have been postulated to serve as a bioindicator for radiation-induced aplasia (Bertho et al. 2001). There are some reports that nuclear magnetic resonance imaging may be useful to assess marrow damage from chemotherapy and radiation (Ollivier et al. 2006), and some of these changes may mimic metastases, so caution is advised in their interpretation in settings of malignancy since paratrabecular fibrosis and inflammatory cell infiltration after radiation can generate a T1 hypointense/T2 hyperintense signal on MRI (Kanberoglu et al. 2001). Studies of the use of positron emission tomography are also being evaluated as means to assess marrow function and health (Table 4) (Hayman et al. 2011).

Furthermore, the ability of all these assays to demonstrate irradiation effects is particularly marginal because of volume and dose considerations. Small segments or large compartments of previously active marrow may become aplastic, hypoplastic, or hyperplastic, and previously quiescent areas may become active (Rubin and Scarantino 1978). Finally, chronic marrow damage from cytotoxic therapy depends on stromal or stem cell defects resulting from the underlying malignancy (e.g., leukemia) or the specific cytotoxic agents used. Normal numbers of mature hematopoietic cells probably result from an increase in stem cell cycling with amplification, and the long-term capacity for normal marrow to function or to respond to stress is not immediately apparent (Testa et al. 1985). Nevertheless, our current understanding of bone marrow damage following cytotoxic therapy is based on the aforementioned evaluations.

Another consideration in ultimate marrow damage from radiation is that as stem cells replicate through life, their telomere length is shortened. It has been noted that elevated telomerase activity and minimal telomere loss occur in cord blood during long-term cultures, but adult CD34+ cells show SCID reconstitution capacity for only 3–4 weeks with

Table 3 Bone marrow LENT-SOMA (with permission from Rubin et al. 1995)

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Anemia symptoms Leukopenia symptoms Thrombocytopenia symptoms		Fatigue	Exhaustion Fever Easy bruisability	Spontaneous bleeding
Objective				
Anemia Leukopenia Thrombocytopenia	Abnormal aspirate/biopsy	Abnormal Hgb/Hd <10 / <30 Abnormal WBC <2000 Platelets >20–I00 K	Pallor Infection Platelets >5–20 K, petechia	Tachypnea Sepsis Platelets <5 K. hemorrhage
Management				
Anemia Leukopenia Thrombocytopenia			Occasional use of red blood products Antibiotics/ cytokines Platelets/red blood cells	Frequent use of red blood products bone marrow transplant
Analytic				
Assays	Assessment of bone marrow reserves with: Hematopoietic progenitor cell assays in common use (CFU-GM, BFU-E_1, CFU-GEMM, CFU-blast etc.) Stromal cell assays (CRU-F, support of long-term bone marrow cultures) Growth factor production Primitive stem cell assays (HPP-CFC, CFU-Dexter, LTC-1C, somatic mutation analysis/DNA analysis)			
Chimerism, clonality	In setting of bone marrow transplant (studies of mixed (donor/host) chimerism, studies of clonality (donor vs. host)) Future consideration: challenge with growth factors to assay stem cell reserve			

telomere shortening and low levels of telomerase (Weisel KC et al. 2004). Therefore, age at which stem cells are exposed to radiation or chemotherapy may determine extent of effect on long-term proliferation potential (Goytisolo et al. 2000). There is also interest in understanding how the timing of radiation and chemotherapy treatments relates to host circadian rhythmicity and how this might affect the toxic/therapeutic ratio (Haus 2002). Circadian variation exits in the proliferative activity of acute-reacting normal tissues like the gut and bone marrow, and a potential therapeutic gain can be realized by the chronomodulated administration of S-phase chemotherapeutic agents at a time when normal tissues are in a different cell cycle phase and may be spared (Rich et al. 2002).

Historically, it was thought that high doses of chemotherapy or radiation were required to create space for donor hematopoietic cells in allogeneic transplant situations. Recently, it has been shown that with non-myeloablative regimens, complete donor engraftment may occur. This would suggest that in cases where sufficient immune suppression allows ongoing presence of the graft, the emergence of stem cells may be based on cell cycle or other proliferative advantage as compared to a true hierarchical system (Giralt 2003).

It is not yet certain how acute versus low-dose chronic exposures differentially affect human marrow. Chromosomal painting studies in radiation workers exposed to plutonium had high frequencies or structural aberrancies with high exposures which correlated with marrow dose but not external dose. These aberrations could remain stable for decades after intake suggesting that chronic irradiation of hematopoietic precursors in marrow induced cytogenetically altered cells that persisted in blood (Livingston et al. 2006). There is also some evidence that a single exposure to

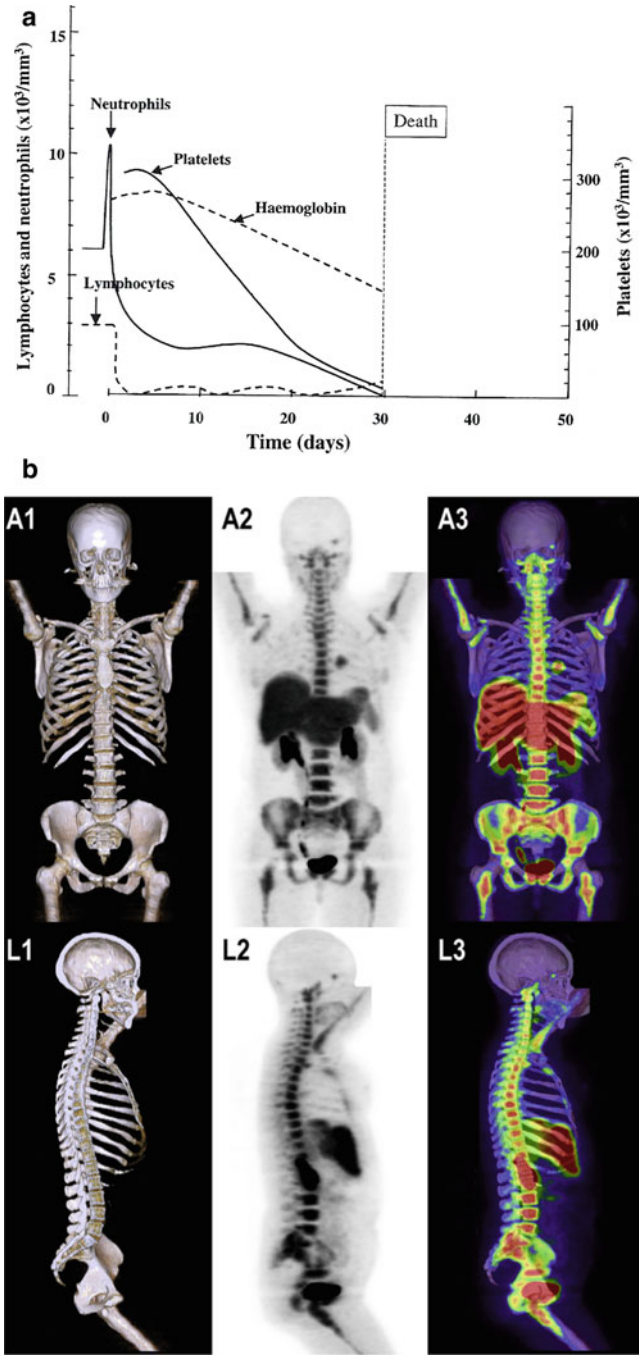


Fig. 6 **a** Expected hematologic response in a human following a single total body dose of 4.5 Gy (with permission from Andrews 1967). **b** Bone marrow distribution in adult humans as determined by 18F-flurodeoxythymidine (FDT), PET in adult cancer patients. (with permission from Hayman et al. 2011; Hashimoto 1960)

a low dose of radiation might induce long-term damage with more apoptotic cells in marrow compartments 6 months after exposure than in control mice and in mice irradiated with higher doses. Marrow from mice with exposure to low doses was also more sensitive to extra in vitro irradiation (Giovanetti et al. 2003).

Table 4 Stem cell assays (with permission from Rubin et al. 1995)

Primitive stem cell assays	
1	HPP-CFC or high proliferative potential colony-forming unit culture assay
2	CFU-Dexter culture assay
3	LTC-IC, long-term culture initiating cell assay
4	Somatic mutation analysis/DNA analysis (strand breaks, translocation)
5	Stem cells in SCID mice
6	Challenge with growth factors to assay stem cell reserve (in vivo)
Stromal cell assays	
7	Fibroblast colony-forming unit (CFU-F)
8	Support of long-term bone marrow cultures
9	Growth factor production

In humans, late effects of radiation on the hematopoietic system have been incompletely studied. Wong et al. reported long-term effects of radiation exposure on hemoglobin levels in Japanese atomic bomb survivors over a 40-year period for 1958–1998 who were estimated to have a 1 Gy marrow dose. These individuals had lower hemoglobin levels than controls at age 40 and age 80 (Wong et al. 2005). In children who were less than 6 years of age at the time of the Chernobyl accident and were followed from 1986 to 2000, a significant increase in leukemia risk was seen but all had <10 mGy to bone and most lived in the Ukraine away from the epicenter suggesting that prolonged exposure to very low radiation doses may increase leukemia risk as much as or even more than acute exposure (David 2003).

5.3 Imaging

5.3.1 Radioisotope Scans

Radioisotope Scans (RIS) provide a means of dynamically assessing bone anatomically as well as functionally; and with serial RIS the status of HBM can be reassessed over time longitudinally from initial suppression to eventual regeneration and compensatory expansion to ablation. Invivo/invitro allows labeling of different compartments i.e., myeloid (^{111}In) erythroid (Fe^{52}) and reticuloendothelial (^{99M}Tc) (Fig. 6b). Bone marrow distribution is often determined utilizing 18F-flurodeoxythymidine (FDT), PET scans.

5.3.2 MRI Versus CT

MRI is preferable to CT for visualized bone marrow and the reverse is true for imaging cortical and cancellous bone. MRI can assess replacement of fat for radiation or chemotoxic ablation of HBM which is normal in bone architecture. The MRI appearance of the acute response of bone marrow

to radiation injury is very similar to the changes seen after chemotherapy. Within a few days, tissue edema leads to a drop in signal intensity of T1-weighted images. The edema is then replaced by fatty transformation, which is seen as an increase in T1 signal intensity. Unlike the changes after radiation injury, however, bone marrow changes after chemotherapy are temporary. After 3–4 weeks, with reseeding of the hematopoietic red marrow, the MRI appearance of bone marrow returns to its normal low signal intensity on T1-weighted images (Husband and Reznek 1998). Unlike other normal tissue postradiation which undergoes late fibrosis, bone marrow is the only tissue to be replaced by fat, adipose cells.

6 Radiation Tolerance and Radiation Toxicity to Marrow

The bone marrow is extremely radiosensitive to the degree that some injury is produced by any fractional dose. Peripheral blood cell counts acutely and progressively decrease in number due to the destruction of both mature and progenitor cells.

6.1 Dose-Time Fractionation

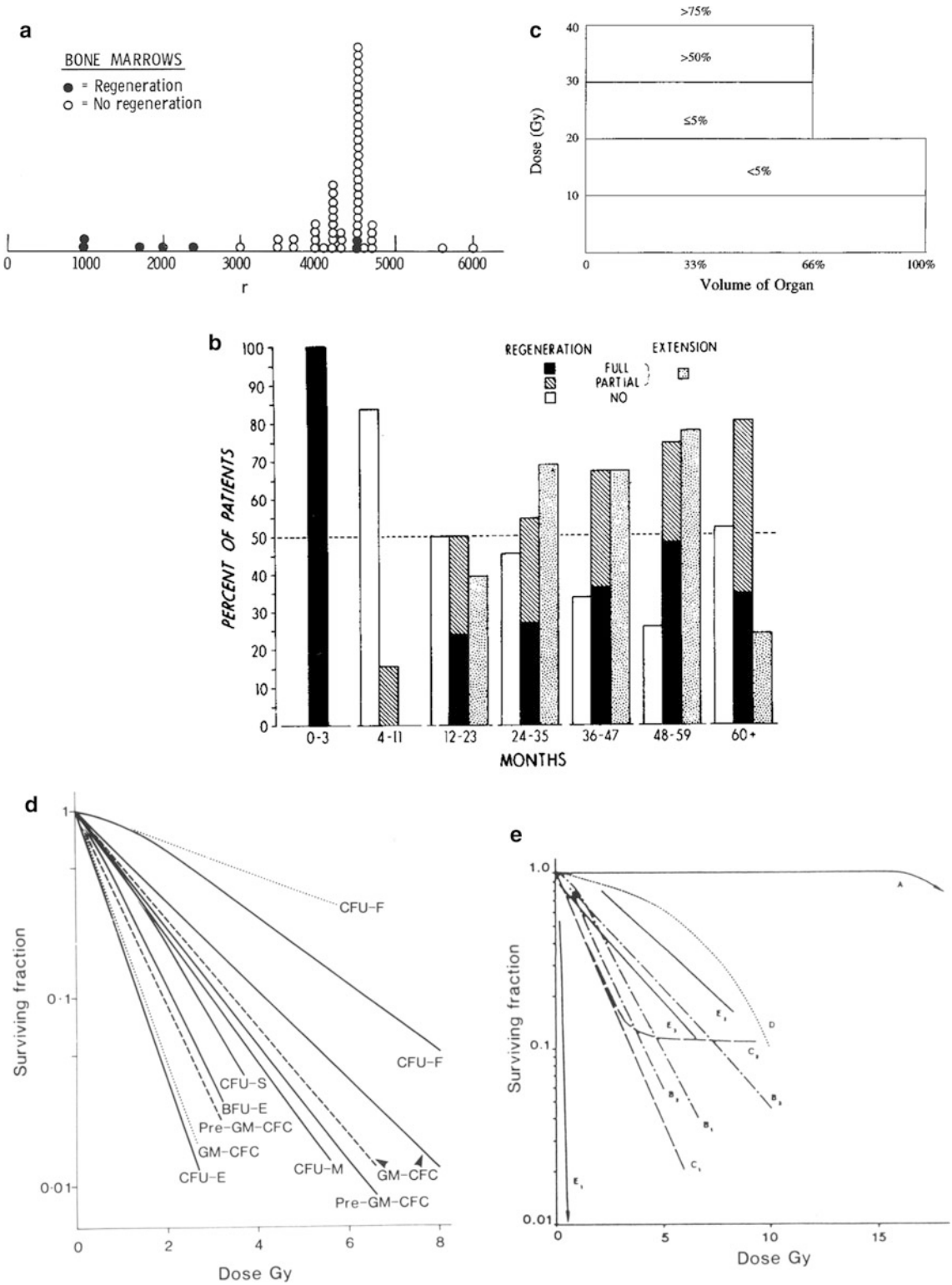
The pathophysiology of HBM response to fractionated radiation has been addressed in the pathophysiology Sect. 4, and serves as a basis to understand the radiation factors that determine the sequence of clinical events which again reflects the kinetics of bone marrow cell production, maturation, egress, and longevity, as well as the bone marrow reserve (Fig. 7a and Table 5). *Lymphopenia* occurs almost immediately after even modest radiation doses because these cells are exquisitely sensitive and die in interphase. After 3000–4000 cGy to large bone marrow volumes, neutropenia occurs in the first week, followed by thrombocytopenia in 2–3 weeks and anemia in 2–3 months (Table 5). Early recognition of this sensitivity prompted investigations to characterize the morphologic and functional consequences of marrow irradiation. Knopse et al. performed animal studies with single irradiation doses and demonstrated a rapid loss of cellularity with sinusoidal dilatation (1–4 days), immediately followed by an increasing deposition of fat and collagen (by 14 days). By 3 months, fibrosis and fatty replacement obliterated the marrow cavity. Hematopoietic and sinusoidal regeneration occurred between 6 and 12 months only at the lower doses (Knopse et al. 1966). Rubin demonstrated that, within 2 weeks following irradiation of rabbit marrow, there is a dose-related depletion of bone marrow cells (Rubin 1973). Studies in humans performed by Sykes et al. actually preceded much of the animal experimentation, and revealed consistent data (Sykes et al. 1964). A sequence of histologic alterations occurred due to the accumulation of radiation doses administered in successive fractions:

Sykes data were obtained and presented using the original irradiation unit of R or roentgen, and not in centigray (cGy) as indicated (Fig. 7a).

1. At 3 days (400 cGy), there was a moderate decrease in nucleated cells, especially red cell and granulocyte precursors.
2. At 8 days (1000 cGy), there was dilatation of sinusoids with hemorrhage, and an absence of young hematopoietic precursors.
3. At 16 days (2000 cGy), the cellularity (nucleated) had decreased to 20 %.
4. At 35 days (5000 cGy-end of therapy), hypoplasia is extreme and fat has accumulated, but sinusoids are less dilated.
5. At 3 months, 50 % of patients show a reappearance of the young hematopoietic cells but cellularity is still reduced.
6. At 5–12 months, recovery continues in some patients, but others show a second irreversible picture of marrow depression with limited cellularity and/or fibrosis.

6.2 Dose-Volume Histogram

The radiation dose, dose rate, and treatment volume all affect the acute response of the bone marrow to therapy (Fig. 7b, c, d, e). Although the complex compensatory mechanisms of the marrow are primarily relevant to understanding chronic radiation effects (discussed in the next section), some come into play acutely. When small fields comprising only 10–15 % of the bone marrow are irradiated, the unexposed bone marrow responds by increasing its population of progenitor cells (Rubin et al. 1984; Scarantino et al. 1984; Croizat et al. 1976; Bierkens et al. 1989; Gualtieri et al. 1984; Song and Quesenberry 1984; Naparstek et al. 1985; Alberico et al. 1987; Gualtieri 1987; Greenberger et al. 1984; Naparstek et al. 1986a; Naparstek et al. 1986b; Naparstek et al. 1986c; Knopse 1988; Parmentier et al. 1988). Often the bone marrow organ fails to regenerate the small irradiated portion of marrow because the compensatory process is able to meet the demands for hematopoiesis. Thus, acute effects are not seen. Conversely, exposures to larger but less than total body fields are associated with peripheral blood count depressions in the sequence previously noted. Figure 7b shows the pattern of bone marrow regeneration and extension in a patient irradiated for Hodgkin Lymphoma with total nodal fields. Figure 7c shows a dose-volume histogram depiction


a
BONE MARROWS
● = Regeneration
○ = No regeneration
0
1000
2000
3000
4000
5000
6000
r
c
>75%
>50%
≤5%
<5%
Dose (Gy)
40
30
20
10
0
33%
66%
100%
Volume of Organ
b
REGENERATION
EXTENSION
FULL
PARTIAL
NO
PERCENT OF PATIENTS
100
90
80
70
60
50
40
30
20
10
0
0-3
4-11
12-23
24-35
36-47
48-59
60+
MONTHS
d
Surviving fraction
1
0·1
0·01
CFU-F
CFU-F
CFU-S
BFU-E
Pre-GM-CFC
GM-CFC
CFU-E
CFU-M
GM-CFC
Pre-GM-CFC
0
2
4
6
8
Dose Gy
e
Surviving fraction
1.0
0.1
0.01
A
D
0
5
10
15
Dose Gy

◀ **Fig. 7** **a** Dose-time fractionation: effects on likelihood of bone marrow regeneration. Variable factors in response and recovery; bone marrow. Effects of varying doses of radiation upon sternel-marrow regeneration. (From Sykes et al. 1964). **b** Pattern of bone marrow regeneration and extension in Hodgkin's disease patients (after total nodal irradiation) as determined by ^{99m}Tc-S colloid. Reprinted with permission from Epperly et al. (2003). **c** Dose-volume histogram for in-field bone marrow hypoplasia, illustrating the relationship between volume and tolerance and doses. A different dose-volume histogram would be required for other end points, for example, peripheral cell counts suppression. **d** Survival of hemato-poietic and stromal progenitor cells after doses of low LET radiation (usually gamma rays): (——) mouse; (- - -) human; (…) dog. *CFU-F* colony-forming units for fibroblasts; *GM-CFC* colony-forming units for granulocytes-macrophages; *CFU-S* spleen colony-forming units; *BFU-E* burst-forming units for erythrocytes; *CFU-M* colony-forming units for macrophages; *CFU-E* colony-forming units for erythrocytes from (Hendry 1985). **e** Radiosensitivity of the marrow stroma using different assays. *A* loss of sinusoids at 1 year; Loria et al. 2000: CFU-F after in vivo irradiation (420 cGy/min.); *B2* CFU-F after in vitro irradiation, *B3* CFU-F after in vivo low-dose rate (1.4 cGy/min.) irradiation, *C1* and *C2*: CFU-S in kidney implants using 400 and 160 cGy/min, respectively; *D* CFU-S and GM-CFC and CFU-F content in subcutaneous femur implants; *El* nonadherent CFU-S in type I long-term bone marrow cultures after 7 weeks; *E2* and *E3* nonadherent and adherent CFU-S in type II long-term bone marrow cultures after 5 weeks. From Bierkens et al. (1989), Pergamon Press Ltd

Table 5 Radiation Tolerance

Histologic alterations at indicated times after initiation of fractionated local radiotherapy in humans		
Fractionated Exposures		
Total dose (R)	Time	Morphologic alterations
400	3 days	Moderate decrement in precursor cells
1000	8 days	Absence of precursor cells, dilated sinusoids, acute hemorrhage
2000	16 days	Marked decrement of all hematopoietic precursors, dilated sinusoids
5000+	35 days	Nearly complete absence of hematopoietic precursors, sinusoids less dilated
5000+	3–12 months	Continued nearly complete hypoplasia; abortive recovery followed by progressive hypoplasia may occur

Source After Sykes et al.1964

of the percentage bone marrow hypoplasia as a function of the dose and volume that were irradiated.

Greater understanding of these phenomena is provided by studies of the effects of irradiation on the release of growth factors from the marrow stroma (Fig. 7d, e). In mice, the CFU-Ss decrease in the shielded areas of bone marrow soon after irradiation, probably due to stem cell differentiation and cell migration to other regions of the body. Within a few more hours, the unirradiated stem cells are triggered into proliferation. Humoral (growth) factors probably mediate these events (Scarantino et al. 1984; Croizat et al. 1976). Most frequently, the measurable growth factor concentration is positively correlated with radiation dose and negatively correlated with the relative number of mature hematopoietic cells. Other explanations for the appearance of these factors include radiation-induced elimination of an inhibitory cell population of hematopoietic cells that would otherwise internalize such factors. Conflicting data on the identification of such growth factors induced by irradiation probably relate to the different cell targets and assay systems tested. The autocrine, paracrine, and endocrine effects of the release of growth factors remain under investigation.

6.2.1 Compensatory Hematopoietic Bone Marrow Response to Volume Loss Due to Radiation Treatment (Chronic Toxicity From Radiation Therapy)

If the appropriate assay is used, residual effects of all but the lowest doses of radiation therapy can be detected; their clinical importance, however, varies according to the fascinating capacity of the bone marrow to sense and compensate for such injury (Fig. 7d, e and Table 6). An appreciation of the extensive communication network that apparently exists in this organ is necessary to understand the patterns of bone marrow function following radiation therapy:

1. *Regeneration* within the irradiated field
2. *Hyperactivity* in non-irradiated regions
3. *Extension of function* into previously quiescent regions
4. *Extramedullary hematopoiesis*.

The contrasting radiosensitivities of the bone marrow stroma and hematopoietic stem cells, and the elaboration of growth factors following irradiation, underlie the mechanisms for compensation of damage. Early investigations in mice by Fried et al. demonstrated that the stromal cells supporting hematopoietic regeneration were more radioresistant than the CFU-S; single whole-body doses of 500 cGy or less did not consistently affect the ME but destroyed more than 99 % of CFU-S (Fried et al. 1976). The stroma both proliferates and supports hematopoiesis, and these capacities are diverse in their radiosensitivity. Low single doses of less than 600 cGy can prevent the establishment of a stromal layer in long-term culture systems (Laver et al. 1986) and prevent stromal cell proliferation (Zuckerman et al. 1985). Conversely, greater than 10000 cGy to an established stroma are tolerated in terms of the ability to produce growth factors (Zuckerman et al. 1985; Gualtieri and McGraw 1985), or support hematopoietic progenitor cell proliferation and adherence (Zuckerman et al. 1985). The influence of dose fractionation and

Table 6 Bone marrow regeneration (BMR) patterns and compensatory mechanisms

	Regeneration				Doses (cGy)	
Techniques (irradiation)	Exposed	Unexposed	Extension	Non-exposed marrow activity	Daily	Total
	Bone Marrow	Bone Marrow				
Small field	N	Local-regional BMR	N	□	200	>4000
Large field	N		N	□	200	>3000
Subtotal body	Suppressed BMR which then recovers	Generalized BMR	□□	□	200	4000
Total body	Active	Generalized BMR	N		5–10	> 100

N None; □ Increased activity; □□ Greatly increased activity

rate is also relevant because of the contrasting ability of the stromal and hematopoietic precursors to repair damage. In vitro studies by Laver provide D_o values of 130 and 115 cGy for CFU-F and CFU-GM respectively; however, the CFU-F survival curve exhibits a shoulder ($n = 1.3$), whereas the CFU-GM curve does not ($n = 1.0$) (Laver et al. 1986).* Similar D_O values for CFU-S and other progenitors have been demonstrated by Hendry (Fig. 7d) (Hendry 1985). Various survival curves have been demonstrated for the stroma, apparently dependent on the assay used (Fig. 7e) (Bierkens et al. 1989). Greenberger et al. have shown the relevance of low (5 cGy/min) and high (120 cGy/min) dose rates to several parameters of marrow stromal cell support function for engrafted hematopoietic stem cells (Greenberger et al. 1988). Conversely, the radiosensitivity of multipotential stem cells is independent of dose rate (Hendry). The understanding of these data must await further investigate because of the demonstrated differences between the ability for marrow stroma to regenerate and repair damage when assayed in vitro versus in vivo (Chertkov et al. 1983; Knopse and Husseini 1986).

A cascade of direct and indirect responses of both irradiated and unirradiated bone marrow regions underlies the patterns of marrow activity observed after therapy. On the most basic level, the individual radiosensitivities of the ME and hematopoietic stem cells determine the potential for any locally irradiated region to maintain function. On a higher level, the interactive capabilities of treated and untreated bone marrow volumes determine the potential for the organism to sustain radiation injury. Table 6 is an attempt to categorize what must be a continuum of events in this regard.

1. When a small field with less than 10–15 % of the bone marrow organ is irradiated beyond (fractionated) total doses of 3000 cGy or single doses of 2000 cGy, permanent ablation or hypoplasia occurs. The capacity of the unexposed bone marrow to compensate by accelerating its rate of hematopoiesis is sufficient, obviating the need for in-field regeneration.
2. When large fields of 25–50 % of the bone marrow are irradiated, permanent ablation or hypoplasia occurs at similar dose levels as for small fields. However, the unirradiated marrow becomes hyperactive in order to meet the demands for hematopoiesis. This is best demonstrated by the failure of bone marrow to regenerate in-field after 3000–4000 cGy mantle irradiation for Hodgkin's disease (Parmentier et al. 1983; Morardet et al. 1973; Sacks et al. 1978).
3. When subtotal body volumes including 50–70 % of the bone marrow organ are irradiated, a mosaic of events occurs to compensate for the ensuing large volume of bone marrow suppression. Hematopoietic activity increases in the unexposed marrow segments, followed by extension of functioning marrow into previously quiescent areas, such as the femora and humeri (Rubin and Scarantino 1978). Parmentier et al. have shown hyperactivity in the nonirradiated bone marrow 8–13 years after exposure (Parmentier et al. 1983). Paradoxically, infield marrow regeneration also occurs between doses of 3500 and 4000 cGy (Sacks et al. 1978). This suggests both a capacity for the stroma to sustain high fractionated radiation doses, and for disparate bone marrow regions to respond to each other.

6.2.2 Temporal Patterns of Hemopoietic bone marrow Regeneration

The temporal pattern of bone marrow regeneration is variable in patient studies, and for previously noted reasons, lags behind the recovery in peripheral blood counts (Fig. 7b). Rubin studied patients treated for Hodgkin's disease with 4000–4500 cGy total nodal irradiation (encompassing 60–70 % of the bone marrow) and noted depression of the WBC to 2500/μL or less in 63 % of patients, and of the platelets to 50000/μL or less in 41 %. Although count recovery occurred in 1–2 months after completion of therapy in 90 % of patients, bone marrow regeneration and recovery required a much longer time. Using ^{99m} Tc-S colloid (phagocytosed by reticuloendothelial cells) as a tracer for active marrow, the sequence of alterations was as follows: full suppression of uptake in the cervicothoracic spine after mantle irradiation; then lumbar and sacroiliac suppression following completion of

paraaortic and pelvic irradiation. At 6–12 months there was no evidence of in-field bone marrow regeneration. At 1–2 years there was a gradual return of in-field bone marrow activity with 54 % of the patients showing partial or complete regeneration. At 2–3 years 66 % of the irradiated sites showed regenerative activity, equally divided between partial and complete. At 4–5 years the rate had increased to 75 %, the level at which it appeared to remain. Extension of bone marrow activity into previously quiescent regions of the femora was not seen until after 1 year. Extension was apparent in 37 % of patients by 2 years, 68 % by 3 years, and 77 % by 5 years (Rubin and Scarantino 1978; Rubin et al. 1973). Subsequently, this marrow activity appeared to decrease gradually, suggesting that the drive mechanism had abated. Presumably, endocrine effects of growth factors are involved in this scenario.

The scanning studies of Knopse et al. using ^{52} Fe to trace recovery of erythropoietic marrow in irradiated lymphoma patients provide consistent findings. Regeneration was evident 2 years after 4000–5000 cGy in 7 of 8 patients, though 6 of 8 also showed persistent suppression in at least one irradiated field. Forty percent of patients showed extension of bone marrow into the peripheral skeleton by 12 months, whereas less extension was seen at more than 24 months (Knopse et al. 1976). Although other reports attest to patient variability in the time course and degree of bone marrow regeneration and extension following irradiation, the above general patterns of regeneration hold true.

Data from animal models are consistent with the slow regenerative pattern seen in patients. Following TBI or partial body irradiation in mice, the stem cell (CFU-S) pool is reduced at 6–18 months, whether bone marrow samples are taken from within or at distances from the irradiated field (Croizat et al. 1979). Rubin irradiated rabbits with 2000–3000 cGy in 200 cGy fractions and observed cortical regeneration beginning at 3 months, but not until 6 months following 4000–5000 cGy. Bone marrow regeneration was first seen in the cortex and along endosteum with the central marrow cavity being repopulated in a centrifugal fashion, and not randomly throughout the marrow cavity as seen after BMT (Rubin 1973). Data from Maloney et al. suggest that the stromal stem cell domains within the irradiated marrow cavity are reduced at these time intervals, probably reflecting damage to the ME (Maloney et al. 1983). Knopse et al. have performed experiments using cellulose ester membranes coated with stromal cells from bone marrow or bone and implanted intraperitoneally in mice (Knopse et al. 1989). These studies show that stromal cells produce substances that can induce differentiation of early mesenchymal, prestromal cells into stromal cells that are capable of providing a ME supportive of hematopoiesis. This is consistent with the data in rabbits from Rubin and emphasizes the importance of growth factors in bone marrow regeneration.

In summary, although hematopoietic stem cells are exquisitely radiosensitive, damage to the bone marrow stroma primarily accounts for chronic radiation injury. Although such injury can be detected in vitro after less than 500 cGy, the capacity for repair in vivo appears to be great, particularly after fractionated irradiation. Marrow recovery can occur over extended periods, but this depends on the volume irradiated. Irreversible injury after doses greater than 5000 cGy is a consequence of irreparable damage to the microvasculature manifested by irrevocable bone marrow fibrosis.

7 Chemotherapy Tolerance

7.1 Acute Toxicity From Chemotherapy

Antineoplastic drugs are selected for their toxicity to malignant cells, and concomitant bone marrow suppression is an expected side effect of most of these agents. The degree of toxicity varies according to drug type and dose (Table 7). The rate at which this marrow suppression occurs also varies. An immediate decrease in granulocytes within 48 h can be seen after hydroxyurea. However, the depression in peripheral blood counts caused by most chemotherapeutic agents, including the alkylators and anthracyclines, is not apparent for 1–3 weeks due to their effect on relatively immature cells. This time course is best explained by the kinetics of cell maturation and egress from the marrow, the life span of the mature peripheral blood cells (6 h for granulocytes, 10–12 days for platelets, and 120 days for erythrocytes) and the bone marrow reserve. Granulocyte counts decline prior to the platelets and anemia can take several weeks to develop. A few drugs, such as the nitrosoureas and mitomycin C, cause a count depression, which is not observed for 3–5 weeks. The observed thrombocytopenia is often more severe and precedes leukopenia. This rate of change also varies according to several other parameters, including the drug dose, schedule and route of administration, and concomitant or previous treatment with other drugs or irradiation (Gale 1988). (Tables 7 and 8).

Although the mechanisms by which suppression occurs are those previously discussed under "Mechanisms of damage," the precise explanation for this action by each particular drug is poorly defined and not necessarily identical to its antineoplastic action. It should be noted that much of the information available to us is derived from studies in mice. Using this model, the spleen colony-forming unit (CFU-S) is considered a stem cell, whereas the CFU-GM is a progenitor cell more committed to differentiation (granulocytes and macrophages). Alkylating agents affect both, but sublethal doses allow preservation of sufficient CFU-S in mice or LTI-IC in humans for recovery.

Additional examples include the relative sparing of the CFU-S by 5-FU and cyclophosphamide, which thus preferentially affect more mature cells, particularly neutrophils (Schremi et al. 1985; Hodgson and Bradley 1979). Conversely, the nitrosoureas appear to damage a precursor whose maturation period is 3–4 weeks, and busulfan damages stem cells only when administered in high doses (Testa et al. 1988), although long-term low-dose use can cause marrow aplasia in some instances (Table 8).

Other explanations including effects on regulatory cells (and thus growth factor secretion) or cell-to-cell interactions are also possible (Testa et al. 1988). For example, data suggest that chemotherapy may affect the erythropoietin response to anemia, causing a deregulation in the normal control of red blood cell production (Miller et al. 1990; Miller and Weiner 1988). The acute effects of drugs on hematopoietic cells may also involve mechanisms referable to cell cycling characteristics. Some agents, such as many *antimetabolites* (e.g., *cytarabine* (Ara-C), 5-FU, 5-azacytadine), are cycle phase-specific for hematopoietic progenitors, and have plateaus in their dose survival curves that differ for each agent; fractional survival after single doses ranges from 5 to 80 %. The length of drug exposure also influences survival characteristics. Other drugs, including some *alkylating* agents, *antibiotics*, and topoisomerase inhibitors, kill cells in all phases of the cell cycle including noncycling cells, and have exponential survival curves (Marsh 1976, 1985). Hydroxyurea directly inhibits DNA synthesis in the bone marrow (Kennedy and Yarbro 1966). The importance of understanding these issues relates to the potential for reversibility of toxicity because drugs that have direct effects on blood cells but spare the ME and the earliest stem cell pool are associated with marrow recovery.

Chemotherapy toxicity is managed by delaying and reducing chemotherapy doses or with hematopoietic growth factors and antibiotics. Reducing chemotherapy doses may compromise treatment outcomes. Alternatively, G-CSF and the longer-acting pegylated granulocyte CSF, pegfilgrastim, when administered after chemotherapy, are helpful in reducing the incidence and severity of neutropenia and its sequelae (Crawford 2003). Commercial preparations of erythropoietin may be used to lessen the severity of anemia after repeated cycles of chemotherapy, but there are now concerns about poorer outcomes in patients receiving erythropoietin with active malignancy who have been treated with chemotherapy or radiation (Hartlye et al. 2003; Dharmarajan and Widjaja 2008). Growth factors also make possible the use of dose-dense chemotherapy, standard dose chemotherapy administered in shortened cycles. This may improve outcomes in early stage breast cancer and non-Hodgin's lymphoma. Factors which have been identified as placing patients at increased risk of neutropenic complications include marrow involvement with tumor, liver dysfunction, older age, other medical problems, decreased performance status, the type of chemotherapy, the number of prior chemotherapy regimens, and concurrent radiotherapy (Dale et al. 2003).

Table 7 Acute chemotherapy toxicity

Anti-neoplastic drug category/agent with their relative degree and duration of myelosuppression			
Drug or drug class	Degree of suppression[a]	Myelosuppression	
		Nadir (days)	Time to marrow recovery (days)
Anthracycline	III	6–13	21–24
Vinca alkaloids	I—II	4–9	7–21
Mustard alkylator			
Nitrogen mustard	III	7–14	28
Antifolates	III	7–14	14–21
Antipyrimidines	III	7–14	22–24
Antipurines	II	7–14	14–21
Podophyllotoxins	II	5–14	22–28
Alkylators	II	10–21	18–40
Nitrosoureas	III	26–60	35–85
Miscellaneous[b]			
Busulfan	III	11–30	24–54
Cisplatin	I	14	21
Dacarbazine	III	21–28	28–35
Hydroxyurea	'II	7	14–21
Mithramycin	I	5–10	10–18
Mitomycin	11	28–42	42–56
Procarbazine	II	25–36	35–50
Razoxane (ICRF)	II	11–16	12–25

[a] I—mild, II—moderate, III—severe (based on common dose schedules), [b] Agents differing from their class of compounds, Reprinted with permission from Hoagland 1982

7.2 Chronic Toxicity From Chemotherapy

Chronic marrow damage following cytotoxic therapy may be subclinical and thus not apparent until the marrow is stressed by additional therapy, or exposed to otherwise tolerable external factors (Table 9). Through an increase in cycling and amplification of precursor cells, normal peripheral counts persist, thereby "hiding" such damage until depletion of stem cells occurs. However, injury to the hematopoietic progenitors can only partially explain the occurrence of chronic marrow injury. It is the interplay between these cells and the ME, with its supportive and regulatory functions, that must be considered to understand potential long-term sequelae.

Table 8 Classification of the effects of specific cytotoxic agents on the bone marrow unpublished data from Heilman, Botnick, and Mauch

Group	Cytotoxic agent	CFU-S/ADC kill	CFU-S recovery	Self-renewal
I	Ara-C Vinblastine	ADC > CFU-S	Rapid	Normal or increased
2	Cyclophos Doxorubicin L-PAM 5-fluorouracil Actinomycin-D	ADC = CFU-S	Intermediate	Normal or increased
3	BCNU Cisplatin MeCCNU Chlorambucil	CFU-S > ADC	Slow	Decreased (late recovery)
4	Busulfan	CFU-S > ADC	Slow	Decreased

Cytotoxic agents were administered as a single i.p. dose. The doses resulting in a 37 % survival of ADC (in vivo agar diffusion chamber colony assay; similar to CFU-GM, or d8 CFU-S were determined from survival curves to compare the sensitivities of the two populations. CFU-S recovery and marrow self-renewal were measured at 15, 30, and 60 days after administration of a drug dose calculated to give d8CFTJ-S survivals of 10–30 %. If the self-renewal had not returned to normal by 60 days, later time points were also measured

Damage to the stem cell compartment can be conceptualized as resulting from a permanent reduction in stem cell numbers or their intrinsic proliferative potential (Lohrmann and Schremi 1988). A long lasting depletion of cells is a characteristic effect of some chemotherapeutic agents, such as busulfan and the nitrosoureas, but not of others such as the antimetabolites and many alkylating agents. A loss of the proliferative potential of individual stem cells may be conceived of as premature senescence or aging, which impairs the stem cell compartment from endlessly repopulating the marrow. Evidence of this defect was provided by Botnick using serial transplantation experiments in a murine model; certain chemotherapeutic agents decreased the repopulating capability of the stem cells (Botnik et al. 1979). This effect appears to be substantial following the use of BCNU and busulfan, but not after the use of antimetabolites. This is consistent with the preferential effect of the former drugs on the pluripotent subpopulation of stem cells that are less actively cycling, and of the latter drugs on the more mature (committed) actively proliferating subpopulation. In vivo correlates in the murine model are demonstrable, such as the development of late marrow hypoplasia after busulfan and the nitrosoureas (Morley et al. 1978). Damage to the stem cell compartment can also manifest as myelodysplasia or secondary leukemia (Smith et al. 2004). Some agents such as alklyators result in deletion of whole chromosomes and parts of chromosomes and have latencies of 5–7 years before leukemia or myelodysplasia occur. Others such as the topoisomerases result in balanced chromosomal translocations and have a shorter latency.

After high-dose chemotherapy or radiotherapy with stem cell rescue, a prolonged and severe deficiency of marrow progenitors can be documented for several years, especially of erythroid and megakaryocytic progenitors, even though the peripheral blood cells and marrow have reached relatively normal levels of cellularity in few weeks. This appears to involve both quantitative and qualitative changes involving both stem cell and stromal cell compartments and impaired capacity for stem cell self-renewal and commitment toward the erythroid and megakaryocytic lineages. This may also be dependent on the underlying disease, the pre-graft chemotherapy regimens, and the graft processing itself (Domenech et al. 1997). Also, various agents such as lenalidomide and fludarabine as well as other stem cell toxic agents may affect the ability to mobilize stem cells for transplantation purposes.

Damage to the marrow ME, including its vasculature, is a critical component of chronic bone marrow injury. Conceptually, this target may be easily disrupted due to the necessity for several cell populations to appropriately interact in order to maintain the integrity of both the supportive and regulatory functions (Testa et al. 1988). The complexity and importance of such cellular interactions make the study of the ME difficult. Assays of individual cell populations, such as the CFU-F (fibroblastic-reticular precursors), are inadequate reflections of ME integrity. Other assays, such as long-term bone marrow culture systems, or ectopic hematopoiesis in implanted femora, provide additional insight. Using these systems, select drugs that can be shown to cause injury, such as cyclophosphamide to the CFU-F (Molineux et al. 1986), or busulfan to subcutaneously implanted femora (Fried et al. 1973).

Studies to date on populations of patients treated for various cancers confirm the existence of long-term injury after cytotoxic therapy (Testa et al. 1998). For some diseases, such as acute lymphoblastic leukemia, information exists on the presence of stem cell and ME injury. In this setting, peripheral blood counts and CFU-F numbers are normal, but CFU-GMs are reduced in number although

Table 9 Agents causing long-term damage to the hematopoietic system

Malignancy	Drugs (dose, schedule)	Parameter	Type of damage	Permanence of damage
Gastric	Mitomycin C	Blood count	Thrombocytopenia	Long lasting, reversible
	Nitrosoureas	Blood count	Neutropenia, thrombocytopenia	Long lasting
	BCNU	GM-CFU in peripheral blood	Almost complete disappearance	Long lasting
		GM-CFU in bone marrow	Reduction, severe	Long lasting after regeneration of peripheral blood granulocytes
Brain	MeCCNU (120 mg/m^2 q 3 wks)	Blood count	Severe myelosuppression	Long lasting
Breast	L-phenylalanine mustard	Bone Marrow granulocyte reserve	Hypocellular marrow with reduced PMN reserve	8–21 mos after cessation of chemotherapy
	Doxorubicin (50 mg/m^2) + cyclophosphamide (500 mg/m^2) × 6	Peripheral blood granulocytes	Decrease	6–8 mos after chemotherapy
		GM-CFU in bone marrow	Delayed regeneration and reduced numbers	55 days after chemotherapy
		GM-CFU in peripheral blood		For at least 5 yrs after chemotherapy
	Cyclophosphamide + methotrexate + 5-FU	GM-CFU in peripheral blood	Reduced	More than 1 yr
Small cell lung	Doxorubicin + cyclophosphamide + vincristine q 3 wks	GM-CFU in bone marrow	Delayed regeneration	No long-term follow-up

BCNU carmustine; *q* every; *MeGCNU* lomustine; *5-FU* 5-fluorouracil; *GM-CFU* granulocyte–macrophage colony-forming unit; *PMN* polymorphonuclear leukocytes

From Mauch P, Constine L, Greenberger J, et al. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. Int J Radiat OncoJ Biol Phys 1995; 31:1319-1339, with permission from Elsevier Science: modified from Lohrmann and Schreml (1988)

accelerated in their cycling, and the capacity of the marrow stroma to support hematopoiesis in long-term bone marrow cultures is low (Testa et al. 1998).

7.3 Combined Chemoradiation

Therapeutic strategies for combining these modalities are based on the goal of tumor eradication, but must also take into account dose-limiting toxicities, notably marrow suppression. The observed interactions are founded on the previously discussed mechanisms for acute and chronic toxicity, but nevertheless are not entirely understood. The complexity of the interactions is nicely illustrated by the studies of Kovacs et al. on the alteration in hematopoietic reserve that follows radiotherapy and different chemotherapeutic agents (Kovacs et al. 1988). CFU-S and CFU-GM recovery kinetics were assessed in mice in the setting of drug treatment followed by 450 cGy TBI. Treatment with Adriamycin, which affects the more primitive hematopoietic precursor cells, caused an increased radiosensitivity of the bone marrow both immediately and progressively over prolonged (and perhaps permanent) intervals. The radio enhancing effects of cyclophosphamide and 5-FU, which are more selectively harmful to relatively mature, hematopoietic cells, are seen shortly after treatment. Cyclophosphamide, in addition, produced a prolonged stromal effect, resulting in a second, though transient, interval of increased radioenhancement.

Taken together, the data showed that the selectivity of drugs for different hematopoietic cell subpopulations determined the temporal consequences of radiation tolerance of the marrow after chemotherapy. The drugs that diminish radiation tolerance at prolonged intervals do so in a dose-dependent manner and affect the more primitive stem cells. Thus, the initial drug-induced lesion in the stem cell compartment, resulting in long-term sensitization to radiation damage, involves a major restriction (in either cell number or intrinsic proliferative potential) of the capacity for recovery from subsequent radiation insult. Hellman and Hannon also studied the effects of Adriamycin on the

radiation response of murine hematopoietic stem cells (Hellman and Hannon 1976). Although small Adriamycin doses did not alter the single dose radiation survival curve, larger doses resulted in a modification of the curve with disappearance of the shoulder, indicating repair inhibition. However, when fractionated radiation doses followed Adriamycin, repair was not inhibited. It was hypothesized that Adriamycin prevented the cells from entering a radiosensitive phase of the cell cycle and thus permitted the cell to benefit from sublethal damage repair. Further experiments are necessary to clarify these points.

From the standpoint of hematologic toxicity, the optimal sequencing of radiotherapy and chemotherapy would maximize the likelihood of delivering both in full doses. The cytotoxic agent that is most often associated with injury to hematopoietic stem cells or stroma would conceptually be better tolerated at the end rather than the beginning of therapy. From the previous discussions, it would appear that, depending on the chemotherapeutic agents employed, the ideal sequencing would most often be chemotherapy followed by irradiation. This is a consequence of the relatively increased radiosensitivity of less committed hematopoietic cells and stroma to irradiation. Conversely, when chemotherapeutic agents, which also preferentially damage stem cells, are used, sequencing may be less critical.

Additional considerations in this regard relate to the kinetics of cell turnover following cytotoxic therapy. Most commonly, chemotherapy is associated with a 2-to-3-week period of myelosuppression followed by a stimulation of early and more committed cells, so that the bone marrow is "turned on." Irradiation of limited volumes after chemotherapy should be well tolerated since unirradiated areas are compensating with increased cell replication. However, it might also be expected that local field irradiation followed by chemotherapy would be well tolerated. Conversely, when large field irradiation precedes chemotherapy, tolerance might be expected to be poor. This could result not only from the ablation or suppression of bone marrow segments, but the increased sensitivity of the unexposed marrow which has become hyperactive. With a greater proportion of progenitor cells cycling in the unirradiated segments as a compensatory mechanism, increased chemosensitivity is likely.

Experimental data available on this subject are sparse. Rubin and Scarantino studied rabbits treated with 1 g/m^2 cyclophosphamide preceded or followed by 1000 cGy hemibody irradiation (Rubin and Scarantino 1978). Bone marrow regeneration occurred at a slower rate than in animals treated with either modality alone, and no significant difference in CFU-GM numbers was seen at one month following the combination in either sequence.

Clinical data are also sparse. Hreschchyshyn studied patients with ovarian cancer given melphalan before or after irradiation; preirradiation chemotherapy was marginally less toxic (Hreschchyshyn 1976). In patients treated for Hodgkin's disease, MOPP chemotherapy is better tolerated preceding rather than following total nodal irradiation, although regimens that alternate cycles of chemotherapy and irradiation appear optimal in this regard (Hoppe et al. 1979). Studies of patients treated with combined irradiation and chemotherapy for bowel or small cell lung cancer simply attest to the increase in myelosuppression compared to chemotherapy alone (Sugarbaker et al. 1986; Abrams et al. 1985; Lee et al. 1986).

The chronic toxicities that follow the combined modes would be expected to be at least additive in terms of reduction or premature senescence of the hematopoietic stem cell compartment or injury to the stroma. Data from bone marrow transplant patients treated with TBI and chemotherapy indicate progressive stem cell depletion over time, presumably resulting from an increased demand on stem cells for differentiation that takes precedence over self-renewal (Knopse 1988).

8 Special Topics

8.1 Total Body Irradiation

The acute response of the marrow organ to single total body exposures provides additional insight and relevance in the setting of bone marrow transplantation (BMT). Following total body doses of 150–750 cGy, a rapid depletion of vital stem cells occurs within one week (Tubiana et al. 1979). Death usually results from granulocytopenia and thrombocytopenia. Doses of 300–500 cGy result in a lethal dose (LD) of 50/100 (50 % of patients dying within 100 days). Doses of 750–1050 cGy are associated with more frequent death rates and shorter intervals to death (reactor safety study (Reactor safety study 1975)). However, these doses are well tolerated if healthy compatible marrow is infused. The microvasculature survives these doses and allows implantation and proliferation of transferred stem cells (Kim et al. 1980). Fractionated TBI doses are rarely used except in the setting of BMT when combined with chemotherapy, which precludes identification of the rate of marrow ablation due to TBI. Other clinical applications have included non-Hodgkin's lymphoma, in which 10–15 cGy were given two or three times weekly to total doses as high as 300–450 cGy with acceptable toxicity (Carbell et al. 1979). In multiple myeloma and chronic lymphocytic leukemia, similar schedules to total doses of 150 cGy caused severe thrombocytopenia, presumably due to marrow defects associated with these diseases (Rubin et al. 1981; Bergsagel 1971). This assumption is supported by the data of Rubin et al. using a rabbit model in which

small daily doses of 5–25 cGy given repeatedly to very high total doses are well tolerated, greatly exceeding the single dose of LD 50/30 (dose resulting in death of 50 % of animals within 30 days) (Rubin et al. 1984).

8.2 Toxicity From Radioimmunotherapy

The recent advent of the use of radioimmunoconjugates has led to the realization that many of these compounds when used to treat hematologic malignancies have marrow toxicity as their dose-limiting toxicity. Beta emitters have been utilized most commonly in these constructs, and most protocols restrict their use to cases where marrow involvement with the malignancy in question is ≤20–25 %. Some of the radioimmunoconjugates being tested are bone seeking; for example the use of 166Ho-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetramethylene-phosphonic acid (DOTMP) which is utilized in high-dose myeloablative multiple myeloma treatment (Giralt et al. 2003).

Methods to predict toxicity and desired dosimetry with radioimmunotherapy have been imperfect. Whole-body dosimetry is routinely utilized in radioimmunotherapy with tositumomab and iodine-131 tositumomab and has been used as a reliable method to determine the patient—specific maximally tolerated therapeutic dose to maximize efficacy (Wahl 2003). Thrombocytopenia was more marked in patients who had had a prior BMT. By determination of the patient-specific total body residence time by the administration of a trace labeled dose of the radionuclide, the therapeutic dose can be precisely adjusted to maximize the therapeutic effects and minimize toxicity. The calculated red marrow absorbed dose in patients receiving radioimmunotherapy has not been highly predictive of the dose-limiting hematologic toxicity observed (Siegel et al. 2003). This may occur because blood-based red marrow dose methodologies would have to assume no specific uptake in red marrow or bone due to presence of free radionuclide, disease, or retention of activity due to metabolism by the reticuloendothelial system (Stabin et al. 2002). The attempt to take bone marrow absorbed doses and overall treatment time into consideration with a linear-quadratic model did not produce a stronger association than that observed between granulocyte and platelet counts. This was thought to be due to the variable bone marrow reserve at the start of therapy and the delivery of heterogeneous absorbed doses of radiation to the bone marrow (Wahl et al. 1998). Juweid et al. estimated red marrow uptake by sacral scintigraphy in RIA patients with diffuse uptake and found that the red marrow dose may be predictive of myelotoxicity and should be used in patients with diffuse red uptake on their scans (Juweid et al. 1995). In the case of 90Y-ibritumomab tiuxetan, hematologic toxicity did not correlate with estimates of red marrow radiation absorbed dose, total-body radiation absorbed dose, blood effective half-life, or blood AUC. Fixed weight-adjusted dosing schedules, dosimetry, and pharmacokinetic results were not predictive of toxicity (Wiseman et al. 2000, 2003). Factors other than dose were thought to play a role. One group found that circulating levels of FLT3-L (FMS-related tyrosine kinase 3 ligand), proved to be a better indicator of progenitor recovery of hematologic progenitors and red marrow radiosensitivity than dose itself. A FLT-3L adjusted red marrow radiation dose was found to provide improved correlation with hematologic toxicity (Du et al. 2003).

131(I)-anti-CD33 and CD45 have been utilized before stem cell transplantation as has Rhenium-188-labeled CD66 (Reski et al. 2001; Bunjes 2002; Burke et al. 2003a, b). (131)I-anti-CD45 antibody can safely deliver substantial supplemental doses of radiation to the marrow (approximately 24 Gy) and spleen (approximately 50 Gy) as compared to conventional TBI (Matthews et al. 1999). This occurs without undue extramedullary acute organ toxicity.

8.3 Pediatric

The hematopoietic progenitor cells and their offspring are cradled on a stroma of endothelial cells, adventitial cells, fibroblasts, macrophages, and fat cells. Mechanisms of marrow-induced failure include direct killing of hematopoietic progenitor cells, accessory cells (e.g., lymphocytes and monocytes), damage to the stroma and microcirculation, and disturbance of hematopoietic growth and regulatory factors (Hendry 1985).

The bone marrow is extremely sensitive to irradiation, to the degree that some injury is produced by any fractional dosage. Irradiated bone marrow becomes hypocellular. There is destruction of fine vasculature followed by fatty marrow replacement of the normal hematopoietic marrow (Storb et al. 1990). If the radiation dosage is sufficiently high, destruction of the sinusoidal circulation precludes migration of hematopoietic cells from distant nonirradiated sites. After 40 Gy fractionated irradiation, 85 % of irradiated sites show a return of activity in 2 years; in 55 % of those areas, recovery becomes complete. Conversely, single doses of 20 Gy to localized regions can produce permanent aplasia. Radiation-induced changes in bone marrow may be detected by increased signal intensity on MRI because of the decreased T1 relaxation time of the increased fatty marrow content. MRI findings support those of nuclear medicine scanning and bone marrow aspiration studies, namely that dosages of up to 40 Gy, to limited areas, do not preclude repopulation of the irradiated marrow in the years after treatment (Yankelevitz et al. 1992). Dosages greater

than 50 Gy seem to produce irreversible depletion of myeloid tissue (Casamassima et al. 1989).

The regenerative capacity of the bone marrow depends on the volume irradiated (Sacks et al. 1978). After irradiation to less than 25 % of the bone marrow, the unexposed portion is stimulated and successful in compensating for hematopoietic demands, and the treated portion may never regenerate. When volumes in excess of 50 % are irradiated, the unexposed bone marrow is not adequate to meet the body's demands. Consequently, the paradoxical phenomenon of in-field regeneration is seen 2–5 years later, and extension of bone marrow activity into previously quiescent long bones is seen within 1–2 years.

Differences between children and adults in the response of the bone marrow to irradiation relate primarily to the differing extent of active bone marrow at different ages (Cristy 1981). In the immediate postnatal period, conversion from active red to fatty yellow marrow begins and is first evident in the extremities. This conversion progresses from peripheral (appendicular) toward the central (axial) skeleton and from diaphyseal to metaphyseal in individual long bones (Fig. 2b).

The acute and chronic effects of chemotherapeutic agents on the hematopoietic compartment in children will not be detailed in this section. However, radiation oncologists must be familiar with the acute myelosuppressive effects of various drugs, and they are summarized in Table 7.

8.4 Secondary Leukemias

The incidence of leukemia is increased after radiation exposure, whether it is whole body or localized irradiation. In comparison to other radiation-induced malignancies, the latent period can be short but the increased risk persists for decades. Evidence from atomic bomb survivors suggests the threshold can be as low as 1 Gy. Low LET irradiation has been shown to increase the risks of acute leukemias, both myelogenous and lymphocytic, as well as chronic myelogenous type. There is no convincing data to link T cell leukemia and chronic myelogenous leukemia induction to radiation. The relative risk of 1 rad exposure is greatest for acute lymphocyte leukemia, least for acute myelogenous leukemia.

9 Prevention and Management

9.1 Prevention

Strategies to minimize the hematologic sequelae of irradiation and chemotherapy, alone or in combination, will be built on our understanding of the mechanisms for normal marrow functioning and toxicity (Tables 10 and 11).

9.1.1 Hematopoietic Growth Factors

Hematopoietic growth factors have been found to protect hematopoietic precursors from chemoradiotoxicity (Zhao et al. 2005). These include IL-11, which also has gut—protective properties (Orazi et al. 1996; Leonard et al. 1994) and BB-10010, an active variant of human macrophage inflammatory protein-1 alpha (Hunter et al. 1995) which protects hematopoietic progenitors from cytotoxic effects. Keratinocyte growth factor may also have protective effects not only on mucosa but also on marrow (Okunieff et al. 2001; Panoskaltiss-Mortari et al. 2000). Thrombopoietin protects mice from mortality and myelosuppression following high-dose irradiation (Kaushansky et al. 1995; Mouthon et al. 2002a). Timing of administration was important, with administration 2 h before radiation giving the best marrow protection. Also, thrombopoietin has prothrombotic effects, and ticlopidine has been found to ameliorate thrombotic tendencies post-irradiation (Mouthon et al. 2002b). What role recently developed thrombopoietin receptor mimetics might play in improving radiotoxicity is yet to be explored (Kuter 2008; Kobos and Bussel 2008).

9.1.2 Expanding the Hematopoietic System

Expanding the hematopoietic system before or after therapy through the use of growth factors (e.g., IL-1, IL-3, GM-CSF) is an important approach (Constine et al. 1991; Wagemaker et al. 1998; MacVittie and Farese 2001; Farese et al. 1996). The stem cell reserve could be increased, or more cells could be recruited into the maturing cell compartments (Appelbaum 1989; Metcalf 1990). In mice, long-term donor cell engraftment can be strongly augmented by treatment of recipient mice prior to low-dose TBI with hematopoietic growth factors that act on primitive cells. Hematopoietic growth factors prior to low-dose TBI in recipients of autologous transplantation can establish high levels of long-term donor cell engraftment. SCF plus IL-11 or SCF plus FL have been examined in this regard. G-CSF treatment showed no beneficial effect of cytokine treatment on stem cell numbers. Long-term donor cell engraftment could be strongly augmented by treatment of recipient mice prior to low-dose TBI with hematopoietic growth factors that act on primitive cells (Noach et al. 2002). The timing of growth factor administration during radiation or cytotoxic agent administration is critical, however, as there is some evidence that GM-CSF or G-CSF can enhance stem cell damage in this situation by stimulating cell cycling and eventual differentiation (Gardner et al. 2001; Van Os et al. 1998, 2000).

The rationale for use of hematopoietic growth factor treatment after TBI is the presence of residual hematopoietic stem cells in some marrow locations due to constitutive heterogeneity of dose distribution involving notably the attenuation related to body thickness and the presence of

Table 10 Summary of American Society of Clinical Oncology 2006 guidelines for administration of granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor (Based on Smith et al. 2006)

Indication	Recommendation
Primary prophylactic CSF administration (administration of a CSF beginning with the first cycle of a treatment regimen)	The chemotherapy regimen has an expected 20 % or more incidence of FN
	A decrease in dose intensity would compromise long-term outcomes (survival/cure)
	The patient is at increased risk for serious complications or death from FN (e.g., advanced age, prior treatment, low performance status, infection)
Secondary prophylactic CSF administration (administration of a CSF in all subsequent cycles after an episode of FN)	Use if a decrease in dose intensity would compromise long-term outcomes (survival/cure)
Treatment of established FN	Use with antibiotics in patients predicted to have a poor outcome
Treatment of established neutropenia in afebrile patients	Not recommended
Use of CSF to increase dose intensity	Not recommended
Use of CSF to enable delivery of dose-dense chemotherapy regimens	Use with dose-dense ACT for lymph node-positive breast cancer; results inconclusive with other regiments
Adjuncts to stem cell transplantation	Use of CSF is warranted for PBSC mobilization and following PBSC or bone marrow transplantation
Delayed engraftment-graft failure	Use of CSF is warranted
Acute myeloid leukemia	Use after induction in patients older than 55 years if determined to be cost-effective based on shortened hospitalization secondary to shortened during neutropenia. Routine use in younger patients, postconsolidation, in relapsed disease, or for priming of leukemic cells is not recommended
Acute lymphoblastic leukemia	Use with chemotherapy after initiation of induction or postemission chemotherapy in an effort to reduce the duration of neutropenia
Myelodysplastic syndromes	Routine use not recommended
Concurrent administration of CSFs with chemotherapy and radiation therapy	Avoid

FN, febrile neutropenia, *ACT*, adriamycin, cyclophosphamide, taxol

Table 11 Recommended dosing and timing of colony-stimulating factors

Agent	Recommended dosing schedule
Filgrastim	For neutropenia associated with myelosuppressive chemotherapy: 5 mcg/kg/d subcutaneous administration is preferred over intravenous until absolute neutrophil count is 2–3 $\times$ 10^9/mcL or up to 14 d
	For peripheral blood stem cell collection: 10 mcg/kg/d to begin at least 4 d before the first leukapheresis and continue until the last leukapheresis
	For bone marrow transplantation: 5 mcg/kg/d, subcutaneous route preferred.
Pegylated filgrastim	6 mg subcutaneously once per chemotherapy cycle. Do not administer within 24 h of administration of chemotherapy or within 14 d before administration of chemotherapy
Sargramostim	Following chemotherapy in AML: 250 mcg/m^2/d intravenously during 4 h starting approximately 4 d after the completion of induction chemotherapy, if bone marrow biopsy at day 10 shows less than 5 % blasts. Continue until the absolute neutrophil count is above 1500/mcL or a maximum of 42 d. If severe adverse reaction occurs, reduce the dose by 50 % or stop therapy
	For peripheral blood stem cell collection: 250 mcg/m^2/d intravenously during 24 h or subcutaneously once daily. The optimal schedule for duration of administration has not been established
rHu IL-11	For prevention of thrombocytopenia: 50 mcg/kg/d subcutaneously for 10–21 days or until postnadir platelet count exceeds 50000/mcL. Administration should start 6–24 h after chemotherapy and end 48 h before the subsequent cycle

AML, acute myeloid leukemia, *rHu*, recombinant human, *IL*, interleukin

radiation-resistant stem cells (Daniak 2002). This has been noted in both animals and humans. Drouet et al. found that a single administration of stem cell factor, FLT-3 ligand, megakaryocyte growth and development factor, and

interleukin-3 in combination soon after irradiation prevented nonhuman primates from myelosuppression. These cytokines are thought to protect against apoptosis and then to increase proliferation and differentiation (Drouet et al. 2004).

9.1.3 Radioprotectors

Chemical agents that protect bone marrow from cytotoxic therapy, such as WR-2721, have not shown impressive efficacy to date but continue to be explored (Constine et al. 1986). Biologic agents such as interleukin-1 are also under investigation in this regard (Constine et al. 1986; Neta et al. 1986). Overexpression of the human manganese superoxide dismutase (MnSOD) transgene in 32D cells results in stabilization of mitochondria and reduction in radiation-induced damage. Thus, MnSOD stabilization of the mitochondrial membrane is relevant to reduction of apoptosis by several classes of oxidative stress inducers (Epperly et al. 2003). Glutathione may protect against X-ray induction of micronuclei in erythroblasts (Mazur 2000). Amifostine protects normal tissue from the cytotoxic damage induced by radiation and chemotherapy (Petrilli et al. 2002; Antonadou et al. 2003). Because there are lower levels of alkaline phosphatase in tumor vessels, amifostine is marketed as a selective protector of normal versus malignant tissues, but there are few ways to directly measure such differential effects (Lindegaard and Grau 2000). Protection against gamma-irradiation with 5-androstenediol has been noted (Whitnall et al. 2002), and oral oxymetholone reduces mortality induced by gamma irradiation (Hosseinimehr et al. 2006). Both androstenetriol and androstenediol protect and restore immune function of both B-and T-cells after radiation (Loria et al. 2000).

Plant flavonoids which have antioxidant properties in vitro and have free radical scavenging potential may be important in radioprotection (Shimoi et al. 1996). An herb, Brahma rasayana, increases WBC when is given to animals for 15 days around radiation and has been shown to increase IL-2 and IFN-gamma serum levels (Rekha et al. 2000). Ginger rhizome has effects on survival, glutathione levels, and lipid peroxidation in mice after total body radiation (Jagetia et al. 2003). The drug curcumin, a component of tumeric, has been evaluated for both radioprotective and radiosensitizing activities. The dual mode of action is dose-dependent. It might reduce oxidative stress and inflammation at low doses whereas the radiosensitivity might be due to upregulation of genes responsible for cell death (Jagetia 2007). Vitamin E is also a scavenger of oxygen-derived free radicals postulated to have a radioprotective effect (Satyamitra et al. 2003). 5-aminosalicyclic acid has been reported to protect mice against radiation-induced micronuclei formation and mitotic arrest (Sudheer et al. 2003).

9.2 Management

9.2.1 Correcting Stromal Cell or Microenvironmental Damage

Correcting stromal cell or microenvironmental damage is likely to be the most difficult problem after radiation damage. Stromal damage has been found to reduce retention of homed cells in marrow of lethally irradiated mice which may implicate retention of donor cells in transplant situations (Madhusudhan et al. 2004; Thierry et al. 2002). Approaches that include the use of stromal growth factors or methods to effectively replace or replenish the stroma are possible avenues (Dexter 1988). Mesenchymal stem cells are marrow-derived multipotential cells which can differentiate into osteoblastic, chondrogenic, adipogenic, and other lineages of limited potential. Radiation can damage the osteogeneic activity of marrow by suppressing osteoblasts with osteoporosis occurring later (Li et al. 2007). 12 Gy gave the greatest effect, and bisphosphonates such as alendronate are postulated to have benefit postradiation to improve bone density (Li). In bone marrow transplant recipients, fibroblast colony forming units (CFU-F) frequencies were reduced by 60–90 % for up to 12 years after transplantation, and this was associated with decreased bone density and reduced levels of LTC-ICs (Galotto et al. 1999).

There is also evidence that MSCs may aid in repair after marrow radiation injury. MSCs home to marrow and tissues damaged by irradiation in NOD-SCID mice without loss of any of their differentiation capacities (Mouiseddine et al. 2007). Local irradiation has also been found to induce homing of human MSCs at exposed sites but also to promote their widespread engraftment in multiple organs consistent with an abscopal effect (Francois et al. 2005). It has been postulated that MSCs may be able to repair damaged normal tissue following accidental irradiation and perhaps in patients receiving therapeutic radiation (Tables 10 and 11).

9.2.2 Hemopoietic bone marrow Transplant

HBM transplant will be discussed in more detail in the next chapter.

10 Future Research Directions

Recently, much attention has been focused on toxicity from accidental radiation exposure and potential chances to ameliorate this (Weisdorf et al. 2006). Total body ionizing irradiation between 2 and 10 Gy causes the hematopoietic component of the acute radiation syndrome (ARS) in humans. Survival in this setting requires hematologic

recovery and limited trauma to nonhematopoietic organs (Weisdorf et al. 2006). For relatively low doses (2–4 Gy), endogenous recovery of autologous hematopoiesis is expected, with early cytokine therapy providing possible benefit. Victims receiving higher doses (6–10 Gy) may require allogeneic or autologous stem cell support. Given the availability of nonablative stem cell transplantation, the availability of cord blood units for transplantation purposes, and improved supportive care, it has been proposed that these measures could be applied on a large scale if contingency plans were in place and their rapid activation were possible (Herodin et al. 2007; Herodin and Drouet 2005).

Several hematopoietic cytokines have been investigated for their potential to provide protection from the lethal consequence of marrow aplasia after TBI. Some of these cytokines can increase the dose of irradiation tolerated by animals, but none allow endogenous recovery after doses administered in clinical blood or marrow transplantation or above those which would be involved in accidental exposures. Granulocyte colony stimulating factor has been reported to improve recovery and survival in canine and nonhuman primate models after TBI (Farese et al. 1996; Northdurft et al. 1997). Combinations of cytokines have also been reported to improve survival in murine models, including stem cell factor (SCF; c-kit ligand), FLT-3 ligand, thrombopoietin, interleukin-3, and keratinocyte growth factor which also aids in amelioration of endothelial toxicity (Weisdorf et al. 2006). When administered early, growth factors may be beneficial, but after 48 h, they often have no benefit over antibiotics or other supportive care (Herodin and Drouet 2002). Thrombopoietin (TPO) given to C57Bl6/J mice 2 h after irradiation with 9 Gy protected 62 % of mice as compared to no survival in the control group (Herodin and Drouet 2002). Interleukin-11 has been found to accelerate platelet count recovery and to result in higher platelet nadirs in mice exposed to 3 Gy TBI (Hao et al. 2004). Interleukins 2, 7, and 15 have been proposed for utilization postradiation to improve immune recovery (Farese et al. 2001), but data regarding this is quite limited. Whether these types of murine studies would have applicability in settings of nondeterministic radiation exposure in humans is uncertain.

Radiation exposure from an accident or a detonation will likely be inhomogeneous, unlike the case of TBI administration in the setting of stem cell transplantation. Partial shielding from walls or furniture may leave reservoirs of viable hematopoietic cells. In these cases, some radioresistant accessory or stem cells may promote hematologic reconstitution (Drouet et al. 2005; Bertho et al. 2005). In a previously studied canine model, when marrow was extracted immediately after radiation exposure to 4 Gy, and subsequently reimplanted, successful engraftment occurred, thought due to cytokines from stroma stimulating restoration of hematopoiesis (Rozhdestvensky and Sernichenko 2004). Whether stem cells postradiation would need to be collected from marrow or from cells mobilized to blood remains uncertain (Drouet et al. 2005). Chute et al. have shown that when lethally irradiated nonhuman primates (1050 cGY) had marrow harvested after irradiation and co-cultured with porcine microvascular endothelial cells, such cells were radioprotective in 12 out of 16 mice (Chute et al. 2002, 2004). While cell–cell contact was important for this effect, vascular endothelial cells produce soluble factors which can aid postradiation recovery of hematopoietic stem cells (Muramoto et al. 2006).

There is continued interest in circadian patterns of marrow injury and response capability and also in the effects of long-term radiation exposures such as those from nonionic electromagnetic fields (Demsia et al. 2004) or from daily low-dose gamma irradiation (Mothersill and Seymour 2003; Lorimore et al. 2001). There is much yet to be discovered about signal transduction responses to radiation of marrow (Henry et al. 2001) and regarding how inflammatory responses influence marrow responses to radiation (Seed et al. 2002). Much remains to be learned about manipulating marrow response to therapy and injury to improve therapeutic outcomes and to minimize both short- and long-term toxicities which can ensue after irradiation of marrow-containing areas. With the availability of new imaging techniques which may aid in assessing injury and response patterns, the next decade should be an eventful time in enhancement of understanding of radiation effects on marrow.

11 Review of Literature and Landmarks

1904 Heineke: Conducted the initial studies of radiation effect on the hematopoietic process in bone marrow.

1913 Shouse, Warren and Whipple: Demonstrated aplasia of bone marrow as a cause of death after total-body irradiation.

1926 Tsuzuki: Found that low doses of radiation lead to depression of bone marrow, lymphocytes, and immature mononuclear cells in rabbits.

1935 Dahl: Recorded the disappearance rate of elements in bone marrow after a dose of 100 R in 3 h to long bones in rats.

1940 Bauer: Maintained that erythroblasts react more rapidly to irradiation than myeloid elements of bone marrow.

1952 Hempelmann, Lisco and Hoffman: Described blood and bone marrow changes in the acute radiation syndrome in man after lethal accidental exposure.

1960 Sykes, Chu and Wilkerson: Described a reversal phenomenon in locally irradiated bone marrow in which recovery took place within 2 months and then reverted to the hypoplastic state in next 8 months

1965 Bond, Fliedner and Archambeau: Gave a thorough presentation of the data on total-body irradiation of the blood and bone marrow based on concepts of cellular kinetics.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

2003 Trotti and Rubin: Modified and developed the Common Toxicity Criteria CTC V3.0 which applied similar scales to grade adverse effects of all major modalities—surgery and chemotherapy in addition to irradiation.

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Late Effects of Hematopoietic Cell Transplantation Including Total Body Irradiation

James G. Douglas and Debra L. Friedman

Contents

Abstract

It is estimated that over 50,000 autologous or allogeneic hematopoietic cell transplants (HCT) are performed worldwide every year and that number continues to grow. Total body irradiation (TBI) began as and remains an integral part of the transplantation conditioning process in addition to high-dose chemotherapy (HD-CTX). In addition to its role as a tumor cytotoxic agent, the eradication of host hematopoietic and immunological cells is equally important particularly for allogeneic transplants. As the number of HCT increases worldwide and the survival continues to improve, the late deleterious consequences of HCT will increasingly become paramount. The late effects of HCT and in particular, TBI are manifest in practically every organ system and may have significant impact on the quality of life of surviving patients years after transplantation. Patients must be followed meticulously and appropriate interventions executed to minimize the impact of late treatment effects. This chapter examines the acute and long-term consequences of TBI in combination with various preparative regimens by specific organ sites.

1 Introduction

It is estimated that over 50,000 autologous or allogeneic hematopoietic cell transplants (HCT) are performed worldwide every year and that number continues to grow. Since the pioneering studies by ED Thomas and his colleagues in the early 1970s from Seattle describing the use of total body irradiation (TBI) as part of a conditioning regimen for bone marrow transplantation (Thomas et al. 1977, 1975a, b), the

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indications for HCT have continued to expand and treatment procedures have vastly changed. TBI began as and remains an integral part of the transplantation conditioning process in addition to high-dose chemotherapy (HD-CTX). In addition to its role as a tumor cytoxic agent, the eradication of host hematopoietic and immunological cells is equally important particularly for allogeneic transplants. The object then is to cause sufficient tumor cell kill, immunosuppression, and hematopoietic cell suppression while at the same time maintaining an acceptable late toxicity profile. The original TBI schedule reported by Thomas and colleagues was a single 10 Gy fraction delivered prior to HCT and was based on animal studies suggesting that a dose of at least 9.5 Gy in a single fraction was required to produce a consistent, reproducible, and sustained engraftment (Thomas et al. 1977, 1975a, b; Deeg et al. 1988). Toxicity was prohibitive, particularly pulmonary toxicity and thereafter various strategies involving TBI and HD-CTX in the conditioning regimens were employed to abrogate untoward normal tissue complications through the ensuing years. As less toxic preparative regimens as well as improvements in diagnosis and treatment of HCT-related acute complications (infections, graft vs. host disease (GVHD), etc.) have come about survival has markedly improved. As a result delayed complications, which may present years after HCT, have become more of a concern in long-term survivors. Late sequelae may occur as a result of the disease for which the patient was transplanted or a direct result of the HCT process. The latter include: HD-CTX alone or accompanied by TBI; the toxic effects of antibiotics and antifungal agents used to treat infections; the toxicity associated with GVHD and its treatment both acutely and chronically; TBI total dose, dose rate, and fractionation schedule; age of the patient; and other currently unknown factors. Particularly, difficult to disentangle from HCT-related late effects but equally important, are the consequences of previous treatment of the primary disease, especially malignant disorders. In that HCT is such a complicated, multifactorial procedure, the determination of the contribution of each component to late complications is convoluted at best.

In the following sections, we will discuss late sequelae associated with TBI containing transplant regimens organized by organ system and compare long-term consequences from HCT in adults and children.

2 Pulmonary

Pulmonary complications occur in approximately 40–60 % of patients undergoing HCT and are a significant source of morbidity and mortality and in fact the lungs were the dose limiting organ system in the early HCT studies (Thomas et al. 1975a, b, 1982). Thomas et al. (1977) reported a 54 % incidence of interstitial pneumonitis in the initial 100 patients with acute leukemia treated with HCT and was the primary cause of death in 34 %(Thomas et al. 1997). The factors thought to be contributors to this toxicity are numerous and often difficult to ascertain secondary to the multitude of variables involved in the HCT process. The most likely contributing variable to pulmonary toxicity are defects in immunological functions secondary to the underlying disease and its treatment, the conditioning regimen, previous exposure to thoracic irradiation, and the development of GVHD (Khurshid and Anderson 2002; Leiper 2002a; Yen et al. 2004). Despite changes in a variety of parameters in the conditioning regimen, treatment of GVHD, and diagnosis and treatment of infectious complications, pulmonary toxicity continues to cause substantial morbidity and mortality.

Specific pulmonary toxicities tend to occur within well-defined periods determined by the evolution of immunosuppression recovery following HCT (Fig. 1). The phases are: (1) neutropenic phase (first 30 days); (2) early phase (30–100 days post-HCT); and (3) late phase (>100 days post-HCT). In addition, the complications are categorized as having infectious or noninfectious etiologies (Yen et al. 2004; Gosselin and Adams 2002; Soubani et al. 1996). Table 1 displays the pulmonary complications reported, the phase post-HCT in which they usually occur, their incidence, and findings on chest imaging studies. As demonstrated in Fig. 1, infectious complications are seen most frequently during the neutropenic and early phases, while noninfectious toxicities are more frequently encountered in the early to late phases (Yen et al. 2004; Gosselin and Adams 2002; Soubani et al. 1996). The most commonly encountered noninfectious toxicity in the early phase is idiopathic pneumonia syndrome (IPS) which is characterized and defined by the presence of widespread alveolar injury in the absence of documented lower respiratory infection or heart failure (Clark et al. 1993; Afessa and Peters 2008) and may be a direct consequence of radiation- and chemotherapy-induced pulmonary injury or a consequence of GVHD (Khurshid and Anderson 2002; Gosselin and Adams 2002; Clark et al. 1993; Afessa and Peters 2008; Alam and Chan 1996). The incidence of IPS post-transplant is approximately 10–12 %. IPS, however, may also be present in the late phase of recovery and has a slightly increased incidence in allogeneic transplant recipients than allo- or autologous-transplant recipients (Gosselin and Adams 2002). Other late occurring pulmonary complications include bronchiolitis obliterans (BO) which appears to be associated with chronic GVHD (cGVHD) and/or viral infections and restrictive lung disease (RLD) (Khurshid and Anderson 2002; Yen et al. 2004; Gosselin and Adams 2002; Soubani et al. 1996; Afessa and Peters 2008). Patients with

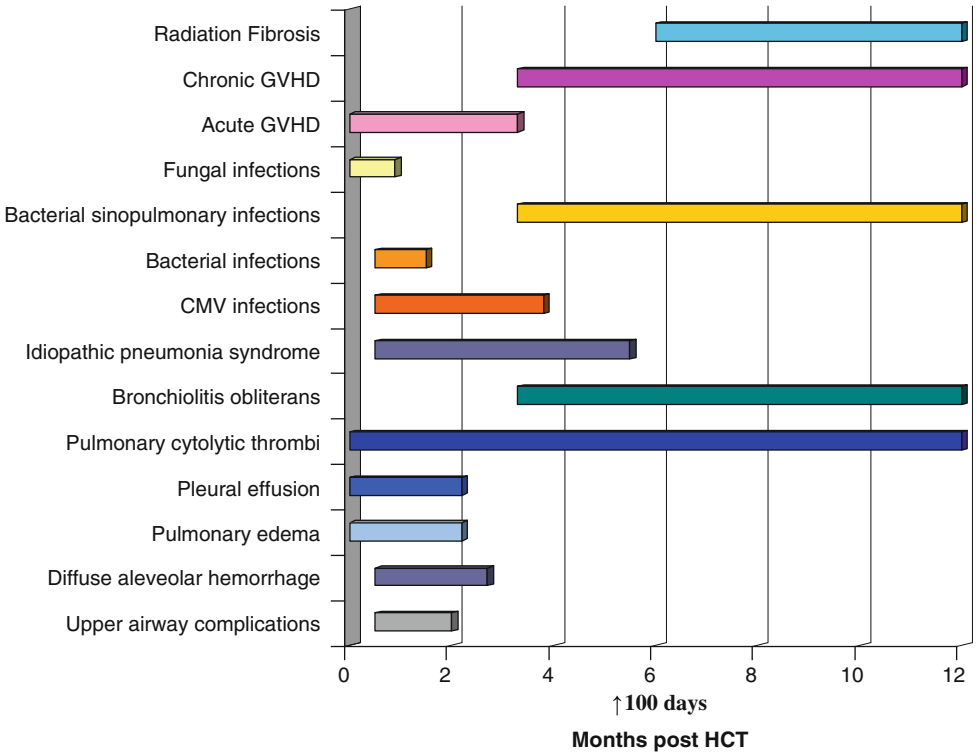

Fig. 1 The chronology of pulmonary injury after HCT (high-dose chemotherapy)

Table 1 Pulmonary complications in bone marrow transplantation

Complications	Days after BMT	Incidence (%)	Pulmonary infiltrates
Pulmonary edema	1–30	Unknown	Diffuse
DAH	1–30	5	Diffuse
Bacterial pneumonia	1–30	20–50	Focal
Aspergillus	1–30	20	Focal
HSV	1–30	5–7	Diffuse
CMV	31–100	10–40	Diffuse
IPS	31–100	10–17	Diffuse
PCP	31–100	<1	Diffuse
COP	≥31	1–2	Diffuse
Chronic GVHD	>100	20–45	No infiltrates
BO	>100	6–10	No infiltrates
DPTS	>100	Unknown	Diffuse
RLD	>100	<20	No infiltrates
PAP	>100	<5	Diffuse
Vasculopathy	>100	<5	No infiltrates

From Yen et al. (2004) (used with permission)
DPTS delayed pulmonary toxicity syndrome, *HSV* herpes simplex virus, *PAP* pulmonary alveolar proteinosis, *PCP Pneumocystis carinii* pneumonia, *RLD* restrictive lung disease

RLD most often also have reduced diffusion lung capacity measured by DLco and those findings as well as the time frame are consistent with a component of radiation-induced lung injury or fibrosis (Khurshid and Anderson 2002; Movsas et al. 1997). Other factors are also likely to be involved in this process that increase the incidence and severity of RLD and include concomitant or prior use of certain cytotoxic agents, cGVHD, and recurrent pulmonary infections (Soubani et al. 1996).

As mentioned previously, pulmonary complications are caused by a host of interrelated factors including cytotoxic agents. Numerous chemotherapy agents have direct pulmonary toxicity and inflict damage upon the lungs in the absence of any other contributing factors and are listed in Table 2. In addition, these agents frequently work synergistically with radiotherapy which causes even further pulmonary toxicity when used in combination with TBI. The pathological features of both drug- and radiation-induced pulmonary injury are alveolar septal thickening with interstitial fibrosis, the presence of atypical type 2 pulmonary cells, and endothelial damage (Gosselin and Adams 2002; Alam and Chan 1996). Drug-induced injury is manifest in a varied pattern including capillary leak pulmonary edema, a hypersensitivity reaction, diffuse alveolar damage, and a nonspecific interstitial pulmonary pneumonitis (Gosselin and Adams 2002; Wilczynski Stephen et al. 1998). Symptoms secondary to drug-induced injury are most likely to become apparent within the first 100 days from transplant. Bleomycin in particular, is a known pulmonary toxin which causes pulmonary fibrosis and its use either prior to or as part of the conditioning leads to a high rate of long-term lung damage (Hartsell et al. 1995).

Table 2 Parameters associated with pulmonary toxicity

Variable	Reduced incidence	Increased incidence
TBI Total dose (higher)		X
Fractionation effect	X	X
STBI		
FTBI		
TBI dose rate	X	
Chemotherapy		X
ACT-D		X
Dox		X
Bleo		X
BU		X
CY		X
BCNU		X
Interferons		X
MTX		X
ARA-C		X

STBI single fraction TBI, *FTBI* fractionated TBI, *ACT-D* actinomycin D, *Dox* doxorubicin, *Bleo* bleomycin, *BU* busulfan, *CY* cyclophosphamide, *BCNU* carmustine, *MTX* methotrexate, *ARA-C* cytosine arabinoside

There are several irradiation-related factors which have been shown to influence the incidence of late pulmonary toxicities in most clinical reports although controversies still exist as to their magnitude. These factors include total dose, fractionation schedule, dose rate, and use of lung shielding. One of the earliest clinical studies examining the relationship of total dose of irradiation and the incidence of pneumonitis was reported by Van Dyk and colleagues at the Princess Margaret Hospital. The incidence of IP was collected in 245 patients who had received various single whole lung doses for metastatic solid tumors. At doses below approximately 7.5 Gy, the incidence of pneumonitis was minimal. Above 7.5 Gy to approximately 11 Gy, the incidence rapidly increased to almost 100 % in a sigmoid fashion (Van Dyk et al. 1981). This corresponded well to studies subsequent to the Seattle report documenting that the incidence of IP for patients treated with a single fraction TBI preparative regimen ranged from approximately 20 to 50 % (Thomas et al. 1977; Hartsell et al. 1995; Van Dyk et al. 1981; Barrett et al. 1987; Cordonnier et al. 1986; Granena et al. 1993; Kader et al. 1994; Morgan et al. 1995; Weiner et al. 1986; Fryer et al. 1978). As animal models began to suggest that there was no deleterious effect of fractionation on marrow reconstitution (Deeg et al. 1988; Collis and Down 1984; Storb et al. 1999; Kolb et al. 1990), fractionated TBI began to be utilized in the clinical setting. There is now ample data that confirms the reduction in pulmonary and other late toxicities through the use of fractionated TBI (Leiper 2002a; Beddar et al. 1995; Forsl et al. 2006; Sampath et al. 2005; Savani et al. 2005; Shank et al. 1982, 1990; Hoffmeister et al. 2006; Gopal et al. 2001) to <15 % in most centers. Recent mathematical modeling derived from clinical data from human trials is consistent with this data. The model predicts that the incidence of radiation pneumonitis is <10 % at total lung doses of ≤15 Gy fractionated at 2 Gy per fraction in the absence of any other pulmonary insults (Semenenko and Li 2008). The dose rate at which TBI is administered also has an impact on the development of pulmonary toxicity with high dose (HD) rates leading to an increased incidence of pulmonary complications than lower dose rates (<approximately 15 cGy/min) in both animal models as well as clinical trials (Deeg et al. 1988; Yen et al. 2004; Gosselin and Adams 2002; Soubani et al. 1996; Afessa and Peters 2008; Alam and Chan 1996; Kader et al. 1994; Storb et al. 1999; Kolb et al. 1990). In an effort to further abrogate the toxicity of TBI, many centers employ lung shielding to reduce the total irradiation dose to the lungs (Sampath et al. 2005; Forslöw et al. 2006; Rutter and Chien 2007). The Seattle group showed that pulmonary function tests were better with the use of lung shielding (lung dose < approximately 9 Gy) versus no lung blocking at 100 days but not at 1 year (Rutter and Chien 2007). Sampath and colleagues demonstrated an incidence of interstitial pneumonitis of 11 % in unshielded patients treated to 12 Gy in 6 daily fractions versus 2.3 % when the lung dose was limited to approximately 6 Gy (Sampath et al. 2005). The rate of marrow engraftment was not different in lung blocked patients compared to patients whose lungs were not shielded in either of these studies (Sampath et al. 2005; Rutter and Chien 2007).

The incidence of pulmonary dysfunction after HCT appears to be similar in children to that in adults and the etiologies alike (Hoffmeister et al. 2006; Beinert et al. 1996; Cerveri et al. 2001; Nysom et al. 1996; Frisk et al. 2003). In the largest longitudinal study, Hoffmeister and colleagues demonstrated pulmonary function declines in 55 % of pediatric patients followed for a median time of 10 years (Hoffmeister et al. 2006). However, only 26 % of those with decreased pulmonary function tests were symptomatic. Risk factors associated with pulmonary toxicity included single fraction TBI, time from transplant, cGVHD, and prior exposure to CY or anthracyclines among the most important (Hoffmeister et al. 2006).

2.1 Summary

Pulmonary toxicity from HCT has been substantially reduced from the early transplant experience due to numerous factors including the use of fractionated TBI,

dose rate, total dose, lung blocking, improved diagnosis and treatment of pulmonary infections, and improved treatment of GVHD, as the most important. Conditioning with BU-CY may cause the same pulmonary toxicity risk as TBI containing regimens. Patients who develop GVHD have a higher rate of lung dysfunction as are patients who have previously had chest irradiation. Finally, the rate of pulmonary toxicity is similar in both children and adults.

3 Optic Structures

Ocular complications after BMT are common and can be classified as to the region of the eye which is affected: the anterior segment (lens, lacrimal gland); and the posterior segment (retina, optic disc). Damage to the anterior segment most often manifests as late complications occurring months to years after treatment while complications to the posterior segment are more likely to arise within 6 months to the first year after transplant (Coskuncan et al. 1994) and include microvascular retinopathy, optic disc edema, and hemorrhagic and infectious complications. The most commonly observed late complications of the anterior segment of the eye are posterior subcapsular cataracts and keratoconjunctivitis (Leiper 2002b).

Cataract formation in the crystalline lens of the eye has long been recognized as a complication of ionizing radiation (Chalupecky 1897). The lens has a high intrinsic radiosensitivity with a calculated α/β of approximately 1.2 Gy which suggests a HD rate and fractionation effect (Ozsahin et al. 1993; Schenken LL Hagemann 1975; van Kempen-Harteveld et al. 2000, 2002a). The latency period from irradiation to cataract formation ranges from 6 months to 35 years with an average latency period of 4 years for doses in the range of 6.5–11.5 Gy (Hall 1994). The latency period decreases with increasing radiation dose, with single fraction TBI, and increasing dose rate of TBI (Belkacemi et al. 1998a; Deeg et al. 1984).

The early experience with single fraction TBI (10 Gy) demonstrated an 80 % actuarial risk of cataract formation at 5 years (Deeg et al. 1984) (Fig. 2). The hazard rate of cataract development for patients treated with this regimen increased for the first 3 years and began to decline thereafter (Deeg et al. 1984). The probability of requiring surgical repair because of significant visual impairment was approximately 50 % at 6 years as determined by Kaplan–Meier analysis (Deeg et al. 1984). These findings have been confirmed in numerous subsequent publications (Ozsahin et al. 1993; van Kempen-Harteveld et al. 2002a, b; Belkacemi et al. 1998b; Bray et al. 1991; Tichelli et al. 1993).

As mentioned previously, the lens has a low α/β ratio which in radiation biological terms suggests that low dose rate schedules and fractionated schedules would reduce the

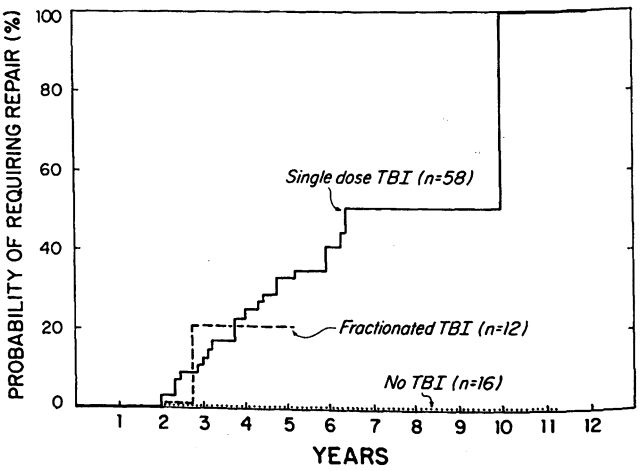

Fig. 2 Time course for RT-associated cateract formation requiring repair (with permission from Deeg et al.). Kaplan-Meier product limit estimates of the probability of requiring surgical repair of cataracts after marrow transplantation among patients given single-dose fractionated, or no TBI

cataractogenesis effect. Deeg and colleagues (1988) compared the incidence of cataracts in three groups of patients: single fraction TBI (10 Gy); fractionated (majority 12 Gy, 2 Gy bid × 3 days); and non-TBI preparative regimens (Deeg et al. 1988). As mentioned previously, the single fraction group had a 5-year actuarial rate of 80 versus 19 % for both the fractionated and the non-TBI prepared cohorts ($p < 0.00005$). These results have been confirmed by other investigators (Ozsahin et al. 1993; van Kempen-Harteveld et al. 2000, 2002a, b; Belkacemi et al. 1998b). However, with longer follow-up, the Seattle group found that even in patients receiving fractionated TBI, the probability of developing cataracts at 11 years was 34–50 % depending on the dose of TBI the patient received (Benyunes et al. 1995) which still is an improvement but not as favorable as initially reported. Fractionation appears to have its primary affect on the latency period to lens opacification (Leiper 2002b).

Other factors have been found to contribute to cataractogenesis in transplant patients in addition to irradiation. The use of steroids (prednisone) for the prevention or treatment of GVHD has been shown to increase cataract formation as has cranial irradiation (CI) preceding TBI (Deeg et al. 1984; Dunn JP et al. 1993; Frisk et al. 2000). On the other hand, the use of heparin post-transplant for the treatment of sinusoidal obstructive disease (SOS) appears to provide some measure of protection (Leiper 2002b; van Kempen-Harteveld et al. 2000, 2002a, b; Belkacemi et al. 1998a; Bray et al. 1991).

Pediatric transplant patients do not appear to be more susceptible to cataractogenesis than adult patients (Leiper 2002b) Most studies have not found age to be correlated with lens opacification (Deeg et al. 1984; Tichelli et al.

1993; Belkacémi et al. 1996) although Fife and colleagues suggested that patients ≤25 years of age had a lower corrective surgical rate than adults (Fife et al. 1994). As with adults single fractionated TBI is more cataractogenic than fractionated TBI (Deeg et al. 1984; Frisk et al. 2000). Frisk et al. (2000) suggested that two patterns for the progression were observed in children post-HCT. They reported either a rapid progression with loss of visual acuity within 2–4 years or little progression over time. Factors influencing rapid progression could not be determined due to the small numbers of patients.

Keratoconjunctivitis sicca (KCS) or dry-eye syndrome is a commonly encountered complication of BMT and it has similarities to Sjögrens syndrome in its clinical and pathological manifestatiöns (Tichelli et al. 1996). Diminished tear production resulting in superficial epithelial thinning and keratinization of the cornea and conjunctiva may progress to corneal ulceration, scarring, or in the most cases perforation. It has been reported to occur in up to 21–45 % of patients at 15 years (Tichelli et al. 1996; Calissendorff et al. 1989) although the incidence in children is not as well established and ranges from 6 to 47 % (Leiper 2002b; Calissendorff et al. 1989; Fahnehjelm et al. 2008). There is an association between KCS and the development of GVHD although KCS may develop in patients in whom no GVHD occurs (Leiper 2002b; Calissendorff et al. 1989; Fahnehjelm et al. 2008). KCS may also be related to the conditioning anti-neoplastic drugs, TBI, and/or the treatment for GVHD.

3.1 Summary

Cataract formation is common after TBI containing preparative regimens. Fractionation regimens appear to have a lower incidence of cataractogenesis although the major effect may be to prolong the latency period to cataract formation. Children do not appear to be more susceptible than adults to this complication. The use of steroids to treat GVHD increases the likelihood of cataract formation.

4 Renal Complications

Renal complications following irradiation are well documented in animal studies as well as human clinical trials. After single fraction whole-kidney irradiation, a dose associated with a 5 % renal complication rate (renal failure) at 5 years (TD 5/5) has been estimated to be 23 Gy to a single kidney, while the dose for a 50 % complication rate at 5 years (TD 50/5) has been estimated to be 28 Gy. If both kidneys are irradiated the TD 5/5 drops to 20 Gy (Emami et al. 1991; Kal and van Kempen-Harteveld 2006). The renal tolerance dose for TBI has been much more difficult to ascertain because of the myriad of factors involved in the transplant process including differing chemotherapy regimens, confounding infections or anti-infective therapies and the interaction of GVHD as a few of the variables involved. The tolerance dose does appear to be lower after TBI and is estimated to be approximately 14 Gy in adults and <12 Gy in children (Kal and van Kempen-Harteveld 2006).

Acute renal insufficiency or failure (ARF) is common in the post-transplant setting with an onset within 3 months of transplantation. The clinical presentation is that of severe anemia, hematuria, proteinuria, elevation of creatinine and blood urea nitrogen, hypertension, and evidence of microangiopathic intravascular hemolysis (Cohen et al. 1995; Tarbell et al. 1988). The pathophysiologically demonstrated injury is to the glomeruli which show severe changes, the hallmark of which is mesangiolysis (Leiper 2002b). The incidence of ARF in adults is estimated to be 26–53 % (Zager 1994; Zager et al. 1989; Gruss et al. 1995; Hingorani et al. 2005), while the incidence in children is estimated to be 5–50 % (Leiper 2002b; Kist-van Holthe et al. 1998; Van Why et al. 1991; Detaille et al. 2007). The cause of acute renal failure has many contributing nephrotoxic factors including sepsis, shock, SOS, allogeneic transplantation, conditioning chemotherapy agents (teniposide, fludarabine), and other nephrotoxic drugs including the use of cyclosporine for GVHD, aminoglycosides, amphotericin, foscarnet, busulfan, and vancomycin (Leiper 2002b; Kist-van Holthe et al. 1998; Cheng et al. 2008; Cohen 2001) among others. TBI is generally not implicated in the development of ARF (Hingorani et al. 2005).

Chronic renal dysfunction/failure (CRF), on the other hand, which commonly occurs 3–12 months after transplantation is a recognized but frequently underreported complication with only scattered case reports through the mid to late 1980s (Spruce et al. 1982; Steele and Lirenman 1979). Since that time, CRF has become a more recognized complication of BMT/HSCT in both adults and children. The clinicopathological findings and timing is suggestive of a radiation nephritis attributed to damage to the vascular epithelium (Leiper 2002b) with typical histopathological findings of mesangiolysis, tubulointerstitial scarring, and in late stages thrombotic microangiography (Cohen and Robbins 2003). Cohen and colleagues reported that approximately 5–20 % of adult patients developed late renal dysfunction after undergoing BMT(Cohen et al. 1995, 2007; Cohen 2001). Hingorani and colleagues (2007) from Seattle reported an incidence of chronic renal disease in 23 % in 1635 adult patients treated from 1991 to 2002. The determination of causative factors remains inconsistent from study to study. TBI has been invoked to be an important nephrotoxin (Kal and van Kempen-Harteveld 2006; Cohen et al. 1995, 2007; Cheng et al. 2008; Cohen and Robbins 2003; Lawton et al. 1991; Miralbell et al. 1996; Otani et al.

2005) Cheng et al. (2008) examined the impact of various drug therapies and radiation dose on the development of CRF by performing metanalysis on 12 published series. Their analysis suggested that total radiation dose, radiation dose rate (>10 cGy/min), and the use of fludarabine increased the likelihood of developing CRF in a mixed population of patients (adults and children). However, when the pediatric patients were analyzed separately, no TBI parameters were correlative but the use of cyclosporine or teniposide was associated with CRF (Cheng et al. 2008). In contrast Hingorani did not find any association between the development of CRF and conditioning with TBI (Hingorani et al. 2007) in a very large cohort of patients from a single institution. The development of ARF has been shown to be an important predictor of CRF in a number of studies (Kist-van Holthe et al. 1998; Detaille et al. 2007; Hingorani et al. 2007) but not in others (Van Why et al. 1991). The presence and/or the treatment of GVHD have also been implicated in the development of CRF particularly with the use of cyclosporine (Zager 1994; Cohen 2001; Cohen et al. 2007, 1993; Lawton et al. 1991).

The incidence of CRF in the pediatric transplant population has been variously reported to occur in 5–45 % of children undergoing transplantation (Tarbell et al. 1988; Kist-van Holthe et al. 1998, 2005) and may be higher than the incidence in adults. The factors discussed above associated with CRF in adults have been variously implicated in the pediatric population as well (Tarbell et al. 1988; Kist-van Holthe et al. 1998, 2005; Patzer et al. 2003). Cheng et al. (2008), however, suggest in their metanalysis that children are not more susceptible to the nephrotoxic affects of TBI, but rather the different conditioning chemotherapy regimens used in children are responsible for the apparent susceptibility and other series would support that finding (Van Why et al. 1991; Patzer et al. 2003; Chou et al. 1996).

4.1 Summary

Chronic renal insufficiency occurs in approximately 20 % of patients post-HCT and has many etiologies post-HCT including the use of nephrotoxic drugs, acute renal insufficiency during the transplant and shortly thereafter often due to hemodynamic changes, and TBI among the most notable. TBI appears to be a major risk factor for the development of CRF and seems to have a similar effect in adults and children.

5 Cardiac

Late cardiotoxicity may present in a variety of ways depending on the type and combinations of cardiotoxic drugs which are utilized in preparative regimens for HCT or prior exposure to agents before HCT (Leiper 2002a). These signs and symptoms include clinically significant congestive heart failure (CHF), arrhythmias, fatal cardiomyopathy, pericardial and valvular disease, electrocardiogram changes, or asymptomatic reduction in left ventricular ejection fraction as determined by echocardiography. Clinical Oncology Trials are not designed in most cases to closely monitor cardiac function over long follow-up periods so it is likely that clinically asymptomatic patients are underdiagnosed. The incidence of clinically significant symptoms has varied from 1 to 66 % as ascertained from the literature (Fujimaki et al. 2001; Lehmann et al. 2000; Morandi et al. 2005; Sakata-Yanagimoto et al. 2004; Pai and Nahata 2000) in adults.

The potential cardiotoxicity of numerous chemotherapeutic agents used either as single agents or in combination for the treatment of oncological diseases has been well established (Morandi et al. 2005; Pai and Nahata 2000). Table 3 lists the most commonly encountered agents in the transplant setting with estimated incidences and mortality rates associated with the use of those drugs which were generated from a literature review of publications over a 30-year period (Morandi et al. 2005; Pai and Nahata 2000). The most consistent associations with cardiac dysfunction reported are with anthracyclines and cyclophosphamide (Morandi et al. 2005), although other drugs have also been implicated as listed in Table 3. Other cardiotoxic drugs which are not used in HCT but may be used for treatment of malignancies prior to the transplant procedure include: alkylating agents, ifosfamide, Cisplatin, mitomycin, carmustine, and chlormethine; antimetabolites: fluorouracil; antimicrotubule agents: paclitaxel, vinca alkaloids, etoposide, and teniposide; and other miscellaneous drugs: amascarine, cladribine, asparaginase, pentostatin, and tretinoin (Pai and Nahata 2000; Carver et al. 2007). More recently, cardiac toxicity has been associated with several new tyrosine kinase inhibitors (sunitinib and sorafenib) with mild to life-threatening events in almost 20 % of patients (Carver et al. 2007; Schmidinger et al. 2008) and asymptomatic cardiac findings in an additional 16 %. Prior use of these agents with resultant cardiotoxicity may lead to worsening of cardiac function after HD chemotherapy used in HCT preparative regimens (Morandi et al. 2005).

Cyclophosphamide (CY) containing HD chemotherapy regimens (HD chemotherapy) used for HCT conditioning are the most commonly associated regimens with cardiotoxicity (Morandi et al. 2005) (Table 3). In studies from the 1970s and 1980s, the incidence was reported to be up to 43 %. It has been found, however, that cardiotoxicity is dose- and schedule-dependent and with modern multifractionated administration, this incidence has been substantially reduced (Morandi et al. 2005; Braverman et al. 1991). The injury appears to be initially to the endothelial cells

Table 3 Clinical cardiac toxicity of single-agent high dose chemotherapeutic agents and their combinations

Single-agent/combination	Risk factors		Type/incidence	Increased mortality
	Cardiac dysfunction[a]	Doxo ≥400 mg/m^{2}[b]		
Cyclophosphamide	No	No	CHF, acute restrictive cardiomyopathy, pericardial effusion (1.7–28 %)	Yes (2–14 %)
Cyclophosphamide and mitoxantrone	No	Yes	CHF (25–66 %)	Yes (4–33 %)
Cyclophosphamide and cytarabine	No	Yes	CHF, acute restrictive cardiomyopathy, pericardial effusion (1.7–33 %)	Yes (9–26 %)
Cytarabine	No	Yes	Arrhythmias, pericarditis	No
Melphalan	No	No	Arrhythmias/(5 %)	No
Melphalan and TBI	No	No	Constrictive pericarditis	No
Melphalan and fludarabine	No	No	CHF (2–14 %)	Yes (1–3 %)
Fludarabine		Yes	CHF (8 %)	No
Thiotepa and melphalan	No	Yes	CHF (4.1 %)	No
Thiotepa and carboplatin or TBI	Yes	Yes	CHF (5.3 %)	No
Ifosfamide	No	Yes	CHF, arrhythmias (15.2 %)	Yes (2 %)
Carmustine	No	No	Myocardial ischemia	No

Adapted from Morandi et al. (2005) (used with permission)
TBI total body irradiation, *CHF* congestive heart failure
[a] Presence of cardiac dysfunction at prehigh-dose chemotherapy cardiac evaluation
[b] History of cumulative doxorubicin dose exposure ≥400 mg/m2 in any patients experiencing cardiac toxicity

with subsequent extravasation of toxic CY metabolites which leads to myocyte injury, interstitial hemorrhage, and edema (Morandi et al. 2005). The injury occurs during or soon after (within 3 weeks) administration of the drug although the deleterious effects may manifest weeks to months afterward (Morandi et al. 2005; Baello et al. 1986).

The cardiotoxicity of anthracyclines is well established in adults as well as in children (Morandi et al. 2005; Pai and Nahata 2000; Carver et al. 2007; Alvarez et al. 2007; Yahalom and Portlock 2008; Uderzo et al. 2007; van Dalen et al. 2006; Lipshultz 2007; Lipshultz et al. 2005). Although this agent is not commonly used in HCT preparative regimens, its ubiquitous use for the treatment of numerous cancer types exposes many patients to the harmful effects prior to HCT. Approximately 60 % of children treated for malignancies receive anthracyclines (van Dalen et al. 2006). Risk factors associated with anthracycline toxicity include younger age at treatment, longer follow-up, female sex, cumulative doses, and higher dose rates (Fujimaki et al. 2001; Morandi et al. 2005; Carver et al. 2007; Alvarez et al. 2007; van Dalen et al. 2006; Lipshultz 2007; Simbre et al. 2005). The injury is to the myocytes and is progressive in nature. The left ventricular (LV) dysfunction develops through two separate pathways. The first is characterized by depressed LV function due to decreased LV contractility. The second pathway is characterized by an elevated afterload (stress on the heart wall) (Alvarez et al. 2007; Lipshultz 2007). Patients are then at risk for developing CHF and associated mortality from pump failure (Alvarez et al. 2007; Lipshultz 2007).

The role of TBI as a causative factor of late cardiac toxicity is less certain. The cardiotoxicity of irradiation to the heart has long been recognized (Carver et al. 2007; Yahalom and Portlock 2008; Adams et al. 2003a, b). Much of the data collected is from long-term survivors of treated childhood Hodgkin's disease. Mediastinal irradiation can cause damage to the pericardium, myocardium, endocardium, vascular system, conduction system, and cause autonomic dysfunction (Carver et al. 2007; Adams et al. 2003a). Factors which increase the risk of cardiac sequelae after mediastinal irradiation include the volume of the cardiac silhouette irradiated, total dose >30 Gy, and a dose fraction >2 Gy per day (Carver et al. 2007; Adams et al. 2003a). The effect of irradiation on the cardiac structures is felt to be "deterministic" that is there is a threshold below which no damaging effect is noted (Hendry et al. 2008; Schultz-Hector and Trott 2007) and that threshold from clinical studies appeared to be in the 30 Gy range. More recently, some investigators have suggested that there is no accurate threshold dose for cardiovascular risk and that a radiobiologically equivalent mean dose to the heart of 1–2 Gy may be the threshold dose above which late cardiovascular toxicity may occur (Hendry et al. 2008; Schultz-Hector and Trott 2007). If this threshold is correct,

TBI doses currently used would be expected to have some cardiac toxicity but it is unclear from published data whether there is or is not cardiotoxicity from TBI (Fujimaki et al. 2001; Lehmann et al. 2000; Sakata-Yanagimoto et al. 2004; Baello et al. 1986; Carlson et al. 1994). However, previous radiotherapy to the mediastinum or left chest wall increases the likelihood of cardiotoxicity especially if the patient has also been exposed to anthracyclines prior to HD—chemotherapy used for conditioning (Morandi et al. 2005; Sakata-Yanagimoto et al. 2004; Adams et al. 2003a, b; Cazin et al. 1986) or have preexisting cardiac dysfunction (Fujimaki et al. 2001).

The incidence of cardiotoxicity in children after HCT is difficult to ascertain as the data is sparse and results often conflicting (Leiper 2002a). Late cardiac toxicity manifests similarly in children and adults with the signs and symptoms mentioned above. The incidence of symptomatic cardiac abnormalities appears to be <15 % in most studies (Leiper 2002a; Uderzo et al. 2007; Eames et al. 1997; Leung et al. 2000a; Nicolini et al. 2000). The reported incidence of abnormalities found in asymptomatic patients is far higher and approximates 40 % (Leiper 2002a; Eames et al. 1997; Pihkala et al. 1994), while the incidence of abnormalities on treadmill exercise testing may be as high as 75 % (Eames et al. 1997). Children who have received previous mediastinal irradiation and/or anthracyclines are at an increased risk of developing cardiotoxicities just as their adult cohorts (Leiper 2002a; Eames et al. 1997; Pihkala et al. 1994; Shankar et al. 2008; Armenian et al. 2008). The effects of cardiotoxic agents used during HCT preparation seem similar in adults and children. The role of TBI in inducing cardiotoxicity remains as obfuscated in children as in adults with conflicting reports (Leiper 2002a; Eames et al. 1997; Nicolini et al. 2000; Pihkala et al. 1994).

5.1 Summary

Late cardiac toxicity does occur in both children and adults after HCT and is likely underreported because some abnormalities may only be discovered by cardiac stress testing. Exposure to cardiotoxic drugs either prior to HCT or during HCT is an important factor related to late cardiac effects as is prior mediastinal irradiation. TBI may be responsible for some added cardiotoxicity but is unlikely a major cause.

6 Gastrointestinal

Toxicity of the gastrointestinal organ system is common after HCT affecting primarily the liver although acute intestinal injury is a very early consequence of the preparative regimens. Liver injury is particularly common after HCT and has several etiologies including hepatic veno-occlusive disease (VOD) or more recently named sinusoidal obstruction syndrome (SOS), GVHD, viral and fungal infections, tumor invasion, and cholestatic disorders (Barker et al. 2005; Cheuk et al. 2007; Junghanss et al. 2002; Strasser et al. 1999). Although largely an early complication of transplantation, liver damage is a significant toxicity and so will be discussed. VOD/SOS does not appear to be related to cirrhosis in long-term survivors of HCT (Strasser et al. 1999).

One of the most serious complications of HD chemotherapy and HCT is VOD/SOS of the liver. As a transplant-related conditioning regimen toxicity, VOD/SOS is one of the most common causes of early morbidity and mortality after transplantation in both adults and children (Leiper 2002a; Barker et al. 2005; Cheuk et al. 2007; Cesaro et al. 2005; Kumar et al. 2003; Litzow et al. 2002; Wadleigh et al. 2003; Bresters et al. 2007; Carreras 2000; Palladino et al. 2008). The onset of VOD/SOS most commonly occurs within the first 20–35 days after transplantation although some cases are seen later and are associated with preparative regimens containing multiple akylating agents (Wadleigh et al. 2003; Carreras 2000). The clinical manifestations of VOD/SOS include: weight gain not attributable to fluid overload but due to renal sodium retention; development of edema (60 %) and ascites (25 %); hepatomegaly; and liver tenderness (Litzow et al. 2002; Wadleigh et al. 2003; Carreras 2000; Coppell et al. 2003; Ganem et al. 1988; Ho et al. 2007). Hyperbilirubinemia occurs in most patients and elevation of other liver function tests (transaminases, alkaline phosphatase) may occur (Carreras 2000; Coppell et al. 2003). The incidence of VOD/SOS ranges from 10 to 60 % in reported series with most suggesting an approximately 20 % rate (Kumar et al. 2003; Carreras 2000; Palladino et al. 2008; Coppell et al. 2003; Ganem et al. 1988; Ho et al. 2007). The classification of VOD/SOS into three groupings mild, moderate, and severe, is based on the ultimate outcome of the clinical syndrome rather than any clinical or laboratory findings at the time of diagnosis. In both the mild and moderate disease, most patients fully recover with or without treatment (Coppell et al. 2003). The mortality rate for severe VOD/SOS is extraordinarily high and approaches 100 % in some series (Ho et al. 2007), but appears to be 20–50 % in most studies (Kumar et al. 2003; Litzow et al. 2002; Wadleigh et al. 2003; Carreras 2000; Coppell et al. 2003; Ganem et al. 1988; Lazarus and McCrae 2008).

The earliest pathophysiological injury which leads to the development of VOD/SOS is injury to the hepatic venules and sinusoidal endothelium in the centrilobular zone (Zone 3) of the liver acinus (Kumar et al. 2003; Wadleigh et al. 2003; Coppell et al. 2003; Ho et al. 2007). Histological

early features include subendothelial edema, erythrocyte extravasation, fibrin deposition, and expression of factor VIII (von Willebrand factor) within the venule walls leading to concentric narrowing of these vessels (Kumar et al. 2003; Wadleigh et al. 2003; Coppell et al. 2003; Ho et al. 2007). As the process continues with release of other markers of inflammation, the hepatic sinusoids become dilated and hepatocyte necrosis occurs which eventually leads to intense collagen deposition in the sinusoids and venules and fibrosis of the lumens. Occlusion of the vessels causes hepatic outflow obstruction which leads to a post-sinusoidal intrahepatic portal hypertension (Carreras 2000). Additional ischemia leads to further hepatocellular necrosis with hepatorenal pathophysiology a clinical feature of this process. Most patients succumb to multiorgan failure as a byproduct of hepatic injury (Kumar et al. 2003; Wadleigh et al. 2003; Coppell et al. 2003; Ho et al. 2007) in the severe form of this complication. The treatment of VOD/SOS is largely supportive with maintenance of fluid and electrolyte balance among the most important measures. The use of defibrotide, a novel drug which has local antithrombotic, anti-ischemic, and anti-inflammatory activities in the past decade has shown promise in reversing the process is a substantial portion of patients as well as reducing the mortality without apparent long-term toxicities (Ho et al. 2007; Lazarus and McCrae 2008; Benimetskaya et al. 2008).

Risk factors that may be associated with the development of VOD/SOS have been evaluated by numerous investigators (Cesaro et al. 2005; Kumar et al. 2003; Litzow et al. 2002; Wadleigh et al. 2003; Carreras 2000; Coppell et al. 2003; Ganem et al. 1988; Ho et al. 2007; McDonald et al. 1993; Carreras et al. 1998) and often seem to have contradictory results largely reflecting differences in study design as well as HCT treatment dissimilarities. Table 4 lists the risk factors associated with VOD/SOS from several studies (Carreras 2000). The single most important factor from these and other studies appears to be the presence of hepatic injury prior to HCT (Coppell et al. 2003; McDonald et al. 1993; Carreras et al. 1998). The injury may be caused by a variety of factors including: active hepatitis, previous abdominal irradiation, and excessive alcohol intake. Other risk factors which are related to the transplant or the treatment of complications (infections, GVHD, etc.) include high-intensity conditioning regimens frequently seen in unrelated donor HCT; known hepatotoxic drugs such as cyclophosphamide, busulfan, dacarbazine, gemtuzumab, methotrexate, vancomycin, acyclovir, sirolimus, ketoconazole, cyclosporine, and amphotericin B; single dose TBI and total dose >12 Gy. In addition, there may be genetic factors such as mutations of genes encoding enzymes in the critical liver enzyme glutathione which are involved in the catabolism of many of the drugs mentioned above and when depleted leads to hepatic injury (Coppell et al. 2003). The presence of more than one risk factor increases the likelihood of developing VOD/SOS (Cesaro et al. 2005).

The incidence of VOD/SOS in children is approximately the same as in adults at 20 % (Barker et al. 2005; Cheuk et al. 2007; Cesaro et al. 2005; Reiss et al. 2002) and the mortality is also similar. The risk factors are also similar to those found in adults (Cheuk et al. 2007). The data reported by Cesaro et al. (2005) also suggests that younger age within the pediatric population is related to a higher incidence of VOD/SOS. The treatment of this complication is also the same as in adults, although the experience with defibrotide in the pediatric population is not as mature as in adults.

6.1 Summary

VOD/SOS remains a significant complication of HCT with a high mortality rate in both children and adults. Hepatic injury from drugs, irradiation, infections, and genetic factors prior to and related to HCT and its complications are associated with the development of this entity. Irradiation, either previously to the liver or single fraction TBI, or doses over 12 Gy likely add to the risk of hepatic toxicity.

7 Endocrine/Growth and Development

Endocrine complications are among the most prevalent late effects after HCT particularly in children and may have significant impact on quality of life (Brennan and Shalet 2002; Cohen et al. 2008; Ghavamzadeh et al. 2003; Kauppila et al. 1998a, b; Littley et al. 1991; Rutter and Rose 2007; Sanders 2004, 2007; Sanders et al. 2009; Tauchmanovà et al. 2002). The toxicities of various agents used in HCT (cytotoxins, irradiation, etc.) may occur at the central level (hypothalamus-pituitary axis) or at the target organ site (gonads, thyroid, parathyroid, and adrenal glands). The extent of endocrinological abnormalities depends on numerous factors of which the following appear to be most important: age; types and dose schedules of cytotoxic agents used; the inclusion of TBI and the dose regimen utilized; and previous irradiation. The deleterious effects can be particularly striking in children with growth and developmental inhibition, with younger aged children having more pronounced impairments (Chemaitilly and Sklar 2007).

7.1 Thyroid

Thyroid dysfunction is one most common endocrinopathies following HCT in both children and adults (Brennan and

Table 4 Risk factors for veno-occlusive disease of the liver after hemopoietic cell transplantation

Risk factor	Lower risk	Higher risk
Type of transplantation	Syngeneic/autologous	Allogeneic
Type of donor	HLA identical sibling: other related	HLA identical sibling: unrelated
Grade of compatibility	Match: minor-mismatch	Match: major mismatch
Type of progenitors	Peripheral blood	Bone marrow
	T cell depleted	Non T cell depleted
Diagnosis	Nonmalignancy (remission)	Malignancy (relapse)
Conditioning regimen	Fractionated	Single dose
TBI	Less than 12 Gy	More than 12 Gy
Total dose	Low dose rate	High dose rate
Busulfan	Cy alone: Cy-TBI	Cy alone: BVC
Administration	Non-containing: dose-adjusted	Non-containing: non-dose-adjusted
Timing	Others combinations	Busulfan first
	Cy to TBI 36 h	Cy to TBI 12 h
Age	Younger	Older
Sex	Male	Female
Karnofsky index	100 ± 90	Lower than 90
Transaminase level before conditioning	Normal	High
HCT number	First	Second
Previous liver radiation	No	Yes
Liver status	Normal	Fibrosis, cirrhosis, tumour
Concomitant drugs	No administration of progestogens, ketoconazole, cyclosporine, methotrexate, amphotericin B, vancomycin, acyclovir	

From Carreras et al. (1998) (used with permission)
Cy cyclophosphamide, *TBI* total body irradiation, *Gy* gray, *BVC* (BCNU, etoposide, cyclophosphamide), *HCT* hemopoietic cell transplantation

Shalet 2002; Cohen et al. 2008; Littley et al. 1991; Sanders 2004, 2007; Sanders et al. 2009, 1989; Chemaitilly and Sklar 2007; Al-Fiar et al. 1997; Katsanis et al. 1990). The most common biochemical finding is that of a mildly elevated basal thyroid stimulating hormone (TSH) level with normal serum thyroxine levels or an exaggerated response to TSH-releasing hormone (Brennan and Shalet 2002; Sanders 2004; Katsanis et al. 1990; Legault and Bonny 1999) indicating that the injury is to the target organ rather than the hypothalamic-pituitary axis. This compensated hypothyroidism may be transient or progress to overt (uncompensated) hypothyroidism over the ensuing decades. The incidence of compensated hypothyroidism ranges from approximately 10 to 50 % in most adult and pediatric series with uncompensated hypothyroidism occurring in approximately 0–15 % (Cohen et al. 2008; Kauppila et al. 1998a; Sanders 2004, 2008; Ishiguro et al. 2004; Berger et al. 2005) although Al-Friar and colleagues reported a lower incidence in adults (8.9 %) (Al-Fiar et al. 1997). The variability in incidence may be related to length of follow-up with Sanders et al. showing the risk for developing thyroid abnormalities extends at least up to 28 years in children (Sanders 2008) (Fig. 3). One consequence of hypothyroidism in children is its role among other factors in growth inhibition (Sanders 2008; Chemaitilly et al. 2007).

TBI as has been implicated as the major factor in post-HCT thyroid dysfunction in most reported series. Fractionated TBI has been reported in most studies to cause less thyroid suppression than single fraction TBI with an incidence of thyroid abnormalities of approximately 15 versus 40 % (Brennan and Shalet 2002; Sanders et al. 2009; Sanders 2008; Berger et al. 2005; Thomas et al. 1993; Ranke et al. 2005). Other radiotherapy factors which have been associated with an increased incidence of thyroid dysfunction include age <10 (Sanders et al. 2009; Ishiguro et al. 2004) and previous local irradiation involving the neck (Sanders et al. 2009). A higher incidence was also reported when Bu was used in conjunction with TBI compared with CY + TBI (Sanders et al. 2009) (Fig. 3). Interestingly, thyroid dysfunction may occur after chemical conditioning only regimens that contain BU/CY with an incidence of approximately 15 % (Sanders 2004; Sanders et al. 2009; Tauchmanovà et al. 2002; Al-Fiar et al. 1997; Berger et al. 2005; Bakker et al. 2004). Conditioning with HD-Cy alone has a very low incidence of thyroid dysfunction (Sanders et al. 2009, 1989).

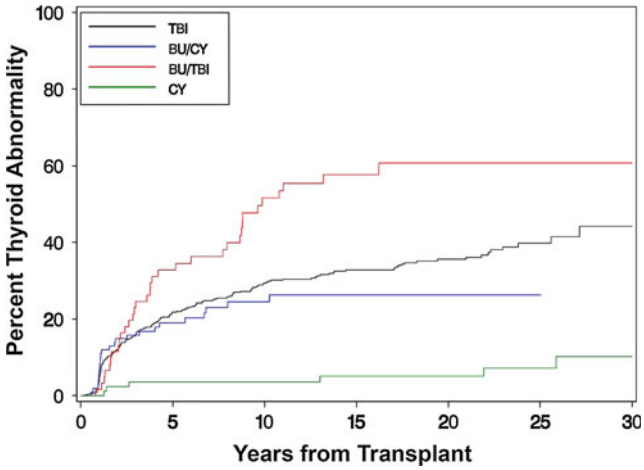

Fig. 3 Development of thyroid dysfunction by preparative regimen for patients undergoing transplant (with permission from Sanders 2008). Cumulative incidence of developing thyroid dysfunction after hematopoietic cell transplantation divided by type of preparative regimen received: TBI, busulfan, busulfan TBI, or cyclophosphamide only

7.2 Growth and Development in Children

Abnormalities of growth and development in children and young adults are among the most common and vexing late complications after HCT (Brennan and Shalet 2002; Sanders 2007, 2008; Chemaitilly and Sklar 2007; Sanders et al. 2005a). The causes of linear growth impairment are numerous and are both endocrine and nonendocrine in nature. Patient characteristics (age), treatment variables (preparative regimen, prior irradiation), and post-HCT complications such as GVHD, and nutritional status are the primary determinants of growth impairment in this population (Brennan and Shalet 2002; Chemaitilly and Sklar 2007; Sanders 2008; Bakker et al. 2006; Couto-Silva et al. 2006).

The age at the time of HCT is a significant factor in predicting final adult height. Children who are transplanted before the age of 6–8 years have the greatest risk of growth inhibition and significantly reduced adult height due both to GH deficiency and the direct effect of irradiation on the epiphyseal growth plates (Sanders 2008; Ranke et al. 2005; Bakker et al. 2006; Couto-Silva et al. 2006).

Growth hormone (GH) deficiency has been a long recognized complication of HCT in children with a reported incidence of 20–85 %. Variables which contribute to such inconsistent rates include differences in the age at HCT, preparative regimen, dose and fractionation scheme of TBI, previous CI, time to testing after HCT, and method of GH testing (Sanders 2008). GH stimulates growth of the epiphyseal cartilage and ensuing bone growth directly through the actions of insulin growth factor 1. When insufficient GH is present, growth velocity and bone maturation are impaired. Irradiation to the hypothalamic-pituitary axis has been shown to be a primary cause of GH deficiency and is related to total dose, fractionated scheme utilized, and time elapsed to treatment (Rutter and Rose 2007; Chemaitilly and Sklar 2007; Sanders 2008). Children receiving CI for acute lymphoblastic leukemia (ALL) at doses of 18 Gy have a significant incidence of GH deficiency (Rutter and Rose 2007). A threshold dose of 18 Gy has been suggested (Ranke et al. 2005), but GH declines have been reported after TBI fractionated doses of 12 Gy (Sanders 2008; Ogilvy-Stuart et al. 1992; Brauner et al. 1997). Fractionated TBI appears to interfere with GH secretion less than single fractionated TBI in most studies (Thomas et al. 1993; Sanders et al. 2005a; Bakker et al. 2006; Brauner et al. 1997; Cohen et al. 1999). Children who have received CI prior to HCT are more likely to have GH deficiency and lessened adult height compared to those not having CI (Cohen et al. 2008; Chemaitilly and Sklar 2007; Sanders 2008; Bakker et al. 2006; Cohen et al. 1999). HD-CT only preparative regimens have for the most part been shown to cause much less growth inhibition compared to TBI containing regimens (Chemaitilly and Sklar 2007; Sanders 2008; Cohen et al. 1999) with Bu containing regimens possibly having an affect although not likely mediated through GH deficiency mechanisms. The data pertaining to GH deficiency in adults after HCT is sparse, but there appears to be a negligible incidence of GH deficiency with little clinical relevance (Kauppila et al. 1998a; Chemaitilly and Sklar 2007).

In addition to the affect on GH secretion, TBI may cause direct damage to the epiphyseal growth plates of bone and cartilage with ensuing skeletal dysplasia (Brennan and Shalet 2002; Ranke et al. 2005). Disproportionate growth has been noted in several studies (Chemaitilly et al. 2007; Bakker et al. 2006), with spinal growth being more impaired than growth of the legs after TBI which is consistent with skeletal injury rather than GH deficiency. The influence on growth centers is age dependent with fractionated doses as low as 10 Gy causing growth inhibition (Hogeboom et al. 2001; Paulino et al. 2000). The growth of craniofacial bones may also be affected, particularly in very young children (Sanders 2004; Dahllöf et al. 1989) with a reduction in lower face height (Dahllöf et al. 1989). Prior irradiation to the spine such as for Hodgkin's disease or neuroblastoma amplifies the growth inhibition.

Other endocrinopathies which potentially can influence growth and development in children are hypothyroidism, deficiencies in Gonadotropin releasing hormone which stimulates the release of LH (luteinizing hormone) and FSH (follicle stimulating hormone), adrenal corticotrophin hormone, and prolactin. Deficiencies in these hormones are uncommon after TBI containing regimens unless prior CI was used and even in those patients the incidence of deficits is low (Rutter and Rose 2007; Ranke et al. 2005). Figure 4

from Rutter shows the doses of irradiation to the hypothalamus-pituitary axis which are felt to cause hormone deficiencies in children.

7.3 Gonadal and Reproductive Function

In contradistinction to late growth-related abnormalities associated with HCT, gonadal dysfunction is frequent in both children and adults. The prevalence is high and is upward of 90 % in men, women, and children (Brennan and Shalet 2002; Tauchmanovà et al. 2002; Mertens et al. 1998). Gonadal toxicity may result in failure to initiate or progress through puberty, infertility, sexual dysfunction, and require hormone replacement and is influenced by age, conditioning regimen, sex, and previous therapy (Kauppila et al. 1998a; Littley et al. 1991; Sanders 2004, 2007; Chemaitilly and Sklar 2007; Sanders et al. 1989; Mertens et al. 1998). A loss of gonadal function has a major negative impact on quality of life of HCT survivors (Claessens et al. 2006). The affects of HCT on gonadal and reproductive functioning will be examined in the following paragraphs.

7.4 Puberty

The transition from childhood to adulthood during puberty is a period of complex physiological transformations with substantial changes in gonadal and GH activity, development of secondary sex characteristic, and heightened growth velocity. The timing and sequence of these changes are variable between individuals but there is a delay in pubertal development by about 2 years in boys compared to girls. The initiation and progression through puberty requires an intact hypothalamic–gonadal axis and disruption in that system, which was addressed previously, may lead to growth delays, delayed or absent pubertal development, and infertility. The FSH/LH surge which initiates puberty stimulates the gonads to produce germ cells and secrete sex hormones which produce the physiological changes. Injuries to the target organs (testes, ovaries) may also result in a delayed or absent pubertal growth and development, and in fact gonadal injury is the principal cause of pubertal delay or arrest and infertility in both children and adults and is characterized by hypersecretion of FSH and LH (Brennan and Shalet 2002; Cohen et al. 2008; Kauppila et al. 1998a; Sanders 2004, 2008; Chemaitilly and Sklar 2007; Mertens et al. 1998).

7.5 Testes

The major causes of testicular dysfunction in children and young adults after HCT consists of the use of TBI and HD

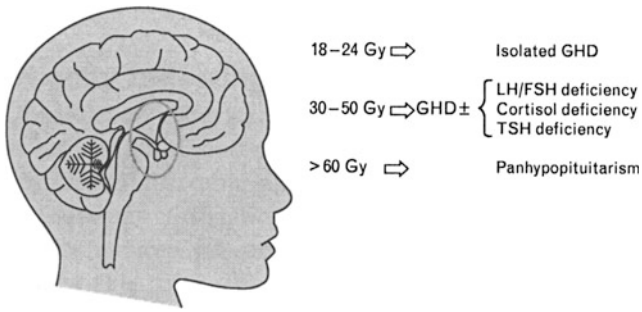

Fig. 4 Illustration of the doses of RT to the hypothalamus–pituitary axis felt to cause hormone deficiencies in children (with permission from Rutter and Rose 2007). *GHD* Growth hormone deficiency, *LH* luteinizing hormone, *FSH* follicle stimulating hormone, *TSH* thyroid stimulating hormone. Association between the dose of fractionated cranial irradiation, including the hypothalamic-pituitary axis within the field, and anterior pituitary hormone deficits

alkylating agents in the preparative regimens (Sanders 2004; Chemaitilly and Sklar 2007). The germ cell epithelium in the testis which is the target organ for FSH action is particularly sensitive to the affects of irradiation and HD-alkylating agents as compared to the Leydig cells (testosterone production). Transient azoospermia may occur after exposure to doses as low as 15 cGy. Complete recovery occurs after 50–60 days after 15 cGy; 9–18 months after doses <1 Gy; may occur 30 months for 2–3 Gy; and may occur 5 or more years for doses of 4–6 Gy (Greven and Paunesku 2006) although permanent sterility may result after doses as low as 2 Gy (Kauppila et al. 1998b; Shalet 1993). Cumulative doses above 6 Gy are likely to lead to permanent germ cell dysfunction and sterility in practically all males, and thus most male patients treated with TBI will be infertile (Littley et al. 1991; Sanders 2004, 2008; Chemaitilly and Sklar 2007; Mertens et al. 1998; Greven and Paunesku 2006; Sanders et al. 1986; Sanders et al. 1983). Pubertal status (prepubertal, pubertal, and postpubertal) at the time of TBI does not appear to affect the incidence of sterility. Leydig cells, in contrast, are much more resistant to the affects of irradiation with cumulative doses of >20 Gy necessary to interfere with testosterone secretion. Previous testicular irradiation as prescribed for testicular involvement (doses 24 Gy) may lead to Leydig cell insufficiency and require androgen replacement therapy (Sklar et al. 1990; Brauner et al. 1988). Fractionated TBI does not decrease the incidence of infertility but may actually be more deleterious than single fraction (Mertens et al. 1998; Greven and Paunesku 2006; Ash 1980). HD-alkylating drugs used in preparative regimens have the potential of causing infertility by damaging germ cells. Azoospermia in prepubertal boys occurs when they are exposed to cumulative doses >350–400 mg/kg of CY, but uncommonly observed with doses of ≤200 mg/kg (Sanders 2004; Chemaitilly and Sklar 2007; Sanders et al. 1983) in the absence

of irradiation. Leydig function is preserved at cumulative doses of ≤200 mg/kg in this population (Sanders 2004). The combination of Cy–Bu is also toxic to the testes. Sanders showed that 68 % of prepubertal boys receiving 16 mg/kg of Bu combined with 120–200 mg/kg of CY had delayed puberty and infertility (Sanders 2004). Grigg et al. (2000) reported a higher rate of testicular germ cell function (84 %) when the dose of Cy was 120 mg/mg in the Bu–Cy combination, and Leydig cell dysfunction only occurred in 12 % although patients who developed cGVHD had decreased sperm counts (Grigg et al. 2000; Wang et al. 1998). Recovery of spermatogenesis may occur in up to 50 % of this latter group (Anserini et al. 2002). There is evidence that the post-pubertal (adult) testes are more susceptible to infertility from alkylating agents and irradiation than the prepubertal organs (Chemaitilly and Sklar 2007; Greven and Paunesku 2006).

7.6 Ovaries

In women, the use of HD alkylators, irradiation, and older age are factors which increase the risk of ovarian failure (Brennan and Shalet 2002; Sanders 2004, 2008; Tauchmanovà et al. 2002, 2003; Chemaitilly and Sklar 2007; Mertens et al. 1998; Sanders et al. 1983, 1988, 1996). The dose of irradiation which will cause lethality in 50 % (LD_{50}) of oocytes is <4 Gy (single dose) (Greven and Paunesku 2006). The ovaries are relatively radioresistant compared to the proliferating granulosal cells which surround the oocytes which are very radiosensitive. Loss of the supporting granulosal cells leaves the oocytes without support and the monthly Graffian follicles will not be formed leading to menopause and infertility (Greven and Paunesku 2006). The radiation dose at which this occurs is greatly dependent on the age at the time of HCT. Low radiation doses of 4–7 Gy (over 1–4 fractions) can lead to permanent menopause in 100 % women over 40 years of age but only 30 % in younger women (Greven and Paunesku 2006; Ash 1980). A fractionated dose of over 20 Gy is necessary to produce the same affect in younger woman (Greven and Paunesku 2006). Sanders and colleagues showed that in patients prepared with CY and TBI, the probability of restoration of ovarian function declined by a factor of 0.8/year of age and those patients who were treated with fractionated TBI compared with single fraction were 4.8 times more likely to have return of ovarian function (Sanders et al. 1988). These results as well as other reports suggest that ovarian failure occurs in most post-pubertal women who receive fractionated TBI and some ovarian recovery is likely in approximately 50 % of prepubertal girls (Chemaitilly and Sklar 2007; Mertens et al. 1998; Sanders et al. 1988; Sarafoglou et al. 1997). The age relationship of ovarian failure and subsequent infertility is likely due to the number of germ cells (eggs) present at the time of the insult.

Alkylating agents are known to be particularly toxic to the ovaries and damage both oocytes and the dividing granulosal cells (Sanders 2004; Chemaitilly and Sklar 2007; Tauchmanovà et al. 2007; Averette et al. 1990). The toxicity from CY has been well documented and is related to cumulative dose as well as age at the time of drug administration (Averette et al. 1990; Blumenfeld 2007; Wetzels 2004). Cumulative doses of >500 mg/kg or 15 g will lead to approximately 60 % gonadal dysfunction in woman over 40 years of age versus 10 % if <30 years (Sanders et al. 1988; Averette et al. 1990; Wetzels 2004). Recovery of ovarian function occurs in practically all women who are conditioned with CY (200 mg/kg) alone (Sanders et al. 1988). The addition of BU (16 mg/kg) to CY, either with 120 mg or 200 mg/kg CY leads to permanent ovarian failure in virtually all women (Brennan and Shalet 2002; Sanders et al. 1996; Tauchmanovà et al. 2003). The addition of TBI to CY increases the risk of ovarian failure in almost all women >25 years of age at the time of HCT with approximately a 10 % recovery rate in younger women (Sanders et al. 1988).

In addition to causing ovarian failure, TBI in childhood may also affect uterine function in adult life. It has been demonstrated that prepubertal girls treated with TBI may have impaired uterine growth and decreased uterine blood flow (Bath et al. 1999; Critchley and Wallace 2005; Holm et al. 1999). These affects are intensified, if the patient has received previous abdominal irradiation (Critchley and Wallace 2005). Whole pelvic doses as low as 10–12 Gy have induced infertility in children treated for Wilms Tumor (Kalapurakal et al. 2004). Successful births after TBI preparative regimens have been reported (Grigg et al. 2000; Wang et al. 1998; Sanders et al. 1996; Blumenfeld 2007; Liu et al. 2008), but an increased rate of spontaneous abortions, preterm deliveries, and low-birth weight infants have also been documented in those women (Sanders et al. 1996; Salooja et al. 2001).

7.7 Summary

Most male patients receiving TBI as part of HCT, whether given as a single dose or fractionated, will be infertile regardless of age at the time of treatment. Testosterone production typically remains normal unless previous testicular irradiation has been administered. In contrast, the recovery of ovarian function is dependent of the age at which TBI is delivered. Women who are older than 25–30 years of age are unlikely to preserve ovarian function, while in approximately 10–30 % of prepubertal girls recovery of function occurs. Practically, all women who are

conditioned with CY (200 mg/kg) will have recovery, but the addition of TBI or BU in older women generally induces ovarian dysfunction with resultant infertility. Although pregnancy may occur after HCT, it is not the norm and those patients who do become pregnant are at increased risk for having spontaneous abortions, preterm babies, and low-birth weight infants.

8 Bone Density

Survivors of HCT are at risk for developing reduced bone mineral density (BMD) in later life (Chemaitilly and Sklar 2007; Bhatia et al. 1998; Nysom et al. 2000; Schimmer et al. 2001; Ebeling et al. 1999; Välimäki et al. 1999) in addition to the affects on growth that were discussed above. The incidence of reduced BMD is variable from study to study and is dependent on many factors including site of measurement, method of measuring BMD, and time point from HCT at which measurements were obtained. Reduced BMD has been reported in pediatric HCT patients (Bhatia et al. 1998; Nysom et al. 2000), however, the magnitude of loss does not appear to be as great as it is in older aged patients, where BMD may be decreased by a factor of 2–3 times compared to the normal population (Nysom et al. 2000; Schimmer et al. 2001). The major factors that are associated with a decrease in BMD appear to be the use of glucocorticoids and cyclosporine A for the treatment of GVHD and hypogonadism in both men and woman (Chemaitilly and Sklar 2007; Bhatia et al. 1998; Schimmer et al. 2001; Ebeling et al. 1999; Välimäki et al. 1999; Savani et al. 2007). In addition, patients who had previously received CI were more likely to have reduced BMD possible representing a decrease in GH secretion (Chemaitilly and Sklar 2007; Nysom et al. 2001; Nysom et al. 1998). Neither the cytotoxic agents or the use of TBI were associated with an increased likelihood of lowered BMD (Bhatia et al. 1998; Schimmer et al. 2001; Savani et al. 2007).

9 Oral Cavity

During HCT patients are at high risk of having oral complications including stomatitis, xerostomia, gingivitis, and alteration of the normal bacterial flora (Leiper 2002b; Barker 1999; Dahllöf et al. 1997a) and may result in tooth and gum disease. Preparative regimens containing TBI increase the risk of having acute oral effect (Barker 1999; Dahllöf et al. 1997a). Once myelosuppression has abated and the hematological status is returned to normal levels, the oral cavity returns to a fairly normal state in adults unless prior irradiation was administered to the oral cavity (Barker 1999). Late effects, however, are common in children and are directly linked to the age at the time of HCT (Dahllöf et al. 1997b, 1988; Hölttä et al. 2005a, b). Long-term dental abnormalities which occur include disturbed root development of permanent teeth, complete root or dental agenesis or microdontia, enamel hypoplasia, shortened or misshapen V-shaped dental roots, and craniomandibular dysfunction (Leiper 2002b; Dahllöf et al. 1989, 1997a, b, 1988, 1994; Hölttä et al. 2005a, b; Nasman et al. 1997). The most severe and extensive abnormalities were found in patients treated with TBI and CY who were under the age of 6 years at the time of HCT (Dahllöf et al. 1997b; Nasman et al. 1997). The most common abnormality is root hypoplasia or short V-shaped roots and may occur in nearly all children under the age of 12 years who have received TBI versus 20 % for children conditioned with chemotherapy only regimens (Nasman et al. 1997). In addition, salivary gland function may not only be reduced acutely but also for years after the TBI containing HCT (Dahllöf et al. 1997a, b). An alteration in normal mouth bacterial flora occurs as a result of diminished saliva production but appears not to increase dental caries in these children (Dahllöf et al. 1997a).

10 Neuropsychological

In contrast to the rather large body of literature for the long-term consequences of most other organ systems, the literature describing neurological and neuropsychological (NP) (including neurocognitive and neurobehavioral) late effects is comparatively sparse, particularly for adults. The deleterious effects of HCT on the central nervous system have long been known but the consistent measurement and documentation of those deficits often suffers from a lack of standardized testing and reporting. Both HD chemotherapy and CNS irradiation are known causes of delayed CNS toxicity in both adults and children (Leiper 2002a; Plotkin and Wen 2003; Graus et al. 1996; Friedman and Constine 2005; Bleggi-Torres et al. 2000; Andrykowski et al. 1990). Other complications of HCT including cGVHD and its treatment, opportunistic infections, CNS hemorrhages, and disease relapse may additionally impact the long-term NP functioning of these patients.

There are very few studies which have examined NP consequences in a prospective, longitudinal manner by using a solid battery of neurocognitive and neurobehavioral tools in adults. Andrykowski et al. (1992) showed that a minority of adult patients had NP impairment, specifically memory and cognitive processing, prior to HCT and were due to treatment-related factors including CRT or CNS disease treated with IT chemotherapy. Those studies that have documented baseline NP status prior to HCT suggest that if NP deficits occur they are mild in nature (Harder

et al. 2002, 2007; Sostak et al. 2003; Meyers et al. 1994; Wenz et al. 2000). The domains which were most frequently impaired included selective attention and executive function, information processing speed, and memory (Harder et al. 2002, 2007; Syrjala et al. 2005). TBI in single HD fractions was associated with an increased NP impairment (Andrykowski et al. 1990).

Childhood survivors of HCT potentially are at a much greater risk than adults of developing long-term NP deficits after brain insults due to the immaturity of the CNS throughout early childhood (Leiper 2002a; Friedman and Constine 2005; Roman and Sperduto 1995; Cousens et al. 1988). The deficits which may occur in children following HCT include a decrease in overall intelligence, shortened attention span, slowing of short-term memory and executive functioning, long-term memory deficits, reduced academic performance, and reduced visual-spatial and fine motor skills (Leiper 2002a; Friedman and Constine 2005; Moretti et al. 2008; Shaw and Robbins 2006; Kupst et al. 2002; Phipps et al. 2008; Shah et al. 2008; Arvidson et al. 1999). Among the agents used in conditioning regimens, TBI has been a primary focus, but other cytotoxic agents are potentially neurotoxic as well as TBI. The largest body of evidence for the neurocognitive effects of cancer treatment in children is from the leukemia literature. It is generally accepted from this data that cranial irradiation (CRT), young age at the time of treatment, CNS involvement, and increasing length of follow-up all have a negative impact on cognitive functioning in children treated for ALL (Leiper 2002a; Friedman and Constine 2005; Roman and Sperduto 1995; Cousens et al. 1988). Other factors which may influence CNS toxicity in this group include intrathecal and systemic methotrexate (MTX), female gender, and CI dose (Leiper 2002a; Friedman and Constine 2005; Roman and Sperduto 1995; Cousens et al. 1988). The dose of CRT used for prophylaxis in the early ALL trials (24 Gy at 2 Gy per daily fraction) lowered IQ scores of the order of 8–10 points (Roman and Sperduto 1995; Cousens et al. 1988). However, declines in scores have also been reported for patients treated with IT-MTX alone and the addition of either 18 or 24 Gy CI did not impact the decrease (Mulhern et al. 1991). It is not clear as to whether the reduction in the cranial dose from 24 to 18 Gy has reduced the toxic consequences with conflicting data existing (Friedman and Constine 2005; Roman and Sperduto 1995; Mulhern et al. 1991). An age <3 years at the time of CI appears to correlate with a steeper decline in IQ scores in most reports (Leiper 2002a; Friedman and Constine 2005; Roman and Sperduto 1995; Cousens et al. 1988; Mulhern et al. 1992; Cool 1996; Leung et al. 2000b; Sanders et al. 2005b). Furthermore, the probability of developing academic difficulties in <3-year olds increases dramatically with decreasing age by month (Leung et al. 2000b). The NP deficits may be observed shortly after CI but are more likely to manifest years after the insult (Leiper 2002a; Roman and Sperduto 1995; Cousens et al. 1988; Phipps et al. 2008, 2000; Arvidson et al. 1999; Mulhern et al. 1992; Leung et al. 2007).

The data regarding the NP consequences of children after HCT are less abundant than that described for ALL and extrapolating from the ALL data one might anticipate a similar impact on HCT patients. The data, however, are conflicting but the majority of reports suggest that the impact of HCT treatment on neurocognition is rather minimal even when TBI is part of the preparative regimen (Kupst et al. 2002; Phipps et al. 2008; Leung et al. 2007; Barrera and Atenafu 2008). Table 5 displays the largest and most pertinent longitudinal studies evaluating neurocognition after transplant. Several factors appear to influence both the incidence and magnitude of cognitive loss in these longitudinal studies and other cross sectional reports. Prior CRT was found to result in lower IQ scores and academic performance (Leung et al. 2000a; Arvidson et al. 1999; Cool 1996; Sanders et al. 1994). PreHCT testing suggested that previously irradiated children were exhibiting declining IQ scores after CRT but before HCT (Cool 1996). Sanders et al. demonstrated a greater drop in full scale IQ in children conditioned with a TBI containing regimen and having prior CRT >16 Gy compared with children conditioned with either CTX alone or CTX + TBI (Sanders et al. 1994). These data are in keeping with the previously discussed data from ALL patients receiving CRT. For the most part, children who have not received CRT prior to transplant have little or no deterioration in NP functioning whether or not TBI is part of conditioning (Kupst et al. 2002; Phipps et al. 2008; Arvidson et al. 1999; Barrera and Atenafu 2008; Sanders et al. 1994; Simms et al. 1998). The data from Phipps and colleagues at St. Jude suggest that TBI doses <14 Gy are unlikely to cause significant cognitive declines which concur with the Seattle data (Shaw and Robbins 2006; Phipps et al. 2008; Sanders et al. 1994). The potential effect of age on NP outcome is less certain as the data are sparse and conflicting. The data from several centers suggest that children approximately <3 years of age at the time of HCT are at more risk of developing learning difficulties than older children (Leung et al. 2007; Phipps et al. 2000; Smedler et al. 1995; Smedler and Winiarski 2008). In contrast, with longer follow-up, the St. Jude group (Phipps et al. 2008) did not find age to be a significant predictor of NP outcome which is in agreement with several other reports (Kupst et al. 2002; Sanders et al. 2005b; Simms et al. 1998; Kramer et al. 1997). Conditioning regimens that omit TBI appear to be less neurotoxic in the extremely

Table 5 Longitudinal Studies of cognitive ability at baseline following stem cell transplant

Study	Sample (n)	Conditioning	Duration of FU (years)	Results
Phipps (Phipps et al. 2008)	123[a]	CTX ± TBI	1–5	No significant changes
Sanders (Sanders et al. 1994)	231	CTX ± TBI	1–14	No significant changes unless previous CRT
Cool (1996)	76	CTX ± TBI	1–4	PIQ increased; VIQ decreased
Kramer (Kramer et al. 1997)	67	CTX ± TBI	1–5	Significant decline in IQ[b, c]
Simms (Simms et al. 1998)	51	CTX ± TBI	1	No significant changes
Shah (Shah et al. 2008)	38[d]	CTX ± TBI	1–5	Significant decline
Kupst (Kupst et al. 2002)	105[e]	CTX + TBI	1–2	No significant changes
Barrera (Barrera and Atenafu 2008)	46	CTX ± TBI	2	No significant changes[f]

PIQ performance IQ, *VIQ* verbal IQ, *CRT* cranial radiotherapy
[a] 1-year; 100 patients—3 year; 80 patients—5-year
[b] No relationship with TBI dose or age
[c] Mean IQ decrease of six points over 1 year; no further changes at 3 years
[d] 1-year; 23 patients—3-year; 12 patients—5-year; all leukemia or lymphoma; decline worse if previous CRT
[e] 1-year follow-up; 70 patients—2 year follow-up
[f] PIQ, FSIQ, PIQ same, decreased perceptual organization; decreased spelling (WRAT); all patients >3 years

young child (Leung et al. 2000b; Smedler and Winiarski 2008), while prior CRT and TBI is particularly toxic (Leung et al. 2000b). The interval over which NP deficits occur is not known with several studies suggesting that deficits begin to stabilize after approximately 3 years (Phipps et al. 2008; Kramer et al. 1997), while others suggest ongoing decrements at 5 years (Shah et al. 2008).

10.1 Summary

Neuropsychological impairment following HCT in adults occurs in a minority of patients. The magnitude of the deficits if they occur is minor and of little clinical significance even when predisposing factors such as CRT or neurotoxic drugs are present. Impairment in children is most likely to be observed in younger children, particularly those <3 years of age, and in those who were treated with CRT in addition to TBI. The NP deficits may not occur until years after therapy so it is imperative to follow these children long term.

11 Secondary Malignant Neoplasms

It is well established that a proportion of HCT survivors develop post-transplant (secondary) malignant neoplasms (SMN) (Friedman and Constine 2005; Baker et al. 2003; Lowe et al. 2007; Rizzo et al. 2009). Potential risk factors for SMN following HCT are numerous and include TBI as well as a number of host, disease, treatment, and post-treatment issues (Tables 6 and 7).

11.1 SMN Following Autologous HCT

The incidence of hematologic malignancies and solid tumors following autologous transplantation varies widely across studies, with actuarial risks estimated from <1 to 18 % (Deeg and Witherspoon 1993; Deeg and Socie 1998; Milligan 2000). Prior chemotherapy with large cumulative doses of alkylating agents as well as prior conventional radiotherapy are important risk factors for treatment-related or secondary MDS or leukemia (t-MDS, t-AML). In addition, patient age at transplant and the use of TBI in the preparative regimen have been identified as risk factors. In some studies, patients transplanted with peripheral blood stem cells after chemotherapy priming showed a higher risk of t-MDS or t-AML than patients transplanted with cells isolated from the bone marrow without priming (Pedersen-Bjergaard et al. 2000). The incidence appears highest in patients treated for Hodgkin or non-Hodgkin lymphoma, an experience similar to that reported after conventional chemo- and radiotherapy for those diseases.

Metayer and colleagues (2003) conducted a case-control study of 56 patients with t-MDS/AML and 168 matched controls within a cohort of 2,739 patients receiving autologous transplants for Hodgkin or non-Hodgkin lymphoma. In multivariate analyses, pretransplant alkylating agent type and intensity and the use of TBI at doses of 12 Gy or less did not appear to increase the leukemia risk, but TBI doses of 13.2 Gy or higher increased the risk significantly. In a series of 493 patients treated for NHL at The University of Texas M.D. Anderson Cancer Center, 22 patients developed tMDS or tAML. Multiple logistic regression analyses showed that TBI was independently associated with an increased risk of developing tMDS/tAML, as well as the

Table 6 General risk factors for post-transplant malignancies

Host	Disease	Treatment	Post-transplant complications	Exogenous exposures
Genetic predisposition	Lymphoma > others	Pretransplant therapy	Graft versus host disease	Ultraviolet light
Age at transplant Gender		Total body irradiation	Viral infections	Tobacco
		Immunosuppressive agents		Alcohol
		Stem cell source		Other carcinogens

Table 7 Post-transplant SMN specific risk factors

Type of SMN	Host	Primary disease	Treatment	Post-transplant complications
MDS/AML	Older patient age	Lymphoma	Alkylating agents	GVHD
			Topoisomerase II inhibitors	
			Nitrosureas	
			Peripheral blood stem cell source	
			TBI	
			Pretransplant radiotherapy	
Hodgkin lymphoma	Unknown	Leukemia	Unknown	Acute GVHD
				Therapy for chronic GVHD
Skin and buccal mucosa	Male gender	Aplastic anemia	TBI	Acute or chronic GVHD
	Older or younger patient age			
Female breast cancer	Younger patient age	Lymphoma	TBI	None known
	Increased time since transplant			
Other Solid tumors	Male gender	Aplastic anemia	TBI	Chronic GVHD
	Older or younger patient age		Azathioprine	
	Female donor			

concurrent use of etoposide in the conditioning regimen (Hosing et al. 2002).

11.2 SMN Following Allogeneic HSCT

Risks for specific types of SMN following allogeneic HSCT range from 3- to 25-fold that of the general population, with cumulative incidences reaching 3–11 % at 10–15 years (Deeg and Witherspoon 1993; Deeg and Socie 1998; Hosing et al. 2002; Bhatia et al. 2001, 1996; Curtis et al. 1997; Deeg et al. 1996; Socie et al. 2000). In particular, the risks of melanoma and nonmelanoma skin cancer and cancers of the oral cavity, liver, cervix, central nervous system, thyroid, bone, and connective tissue are particularly elevated (Bhatia et al. 2001, 1996; Curtis et al. 1997). Risk factors include the underlying diagnosis, pretransplant therapy, transplantation for refractory or recurrent disease, and the use of TBI and immunosuppressive agents and GVHD (Deeg and Witherspoon 1993; Deeg and Socie 1998; Bhatia et al. 2001, 1996; Curtis et al. 1997; Deeg et al. 1996; Socie et al. 2000). Host factors include younger age at diagnosis in some series (Curtis et al. 1997; Socie et al. 2000) and, for squamous cell carcinoma (SCC) of the buccal cavity and skin, male gender (Curtis et al. 1997; Deeg et al. 1996). A recent series by Gallagher found older age at transplant and female donor to be a risk factor for the development of secondary solid tumors (Gallagher and Forrest 2007).

Several large studies illustrate these risks. Among 2,129 patients, who had undergone transplantation for hematologic malignancies at the City of Hope National Medical Center between 1976 and 1998, 29 developed solid cancers, which represent a two-fold increase in risk relative to a comparable normal population. The estimated cumulative incidence (±SE) for the development of a solid cancer was 6.1 ± 1.6 % at 10 years. Cancers of the thyroid gland, liver, and oral cavity occurred primarily among patients who received TBI. Risk continued with ongoing time since transplant (Bhatia et al. 2001).

The risk of SMNs was reported by Curtis and colleagues in 19,229 patients who received allogeneic (97.2 %) or syngeneic transplants between 1964 and 1992 at one of 235

centers reporting to the International Bone Marrow Treatment Registry or the FHCRC. Among patients who survived 10 years or more, the risk of SMN was 8.3 times that of the general population. The cumulative incidence was 2.2 % (95 % CI 1.5, 3.0 %) at 10 and 6.7 % (95 % CI 3.7, 9.6 %) at 15 years. The risk was significantly elevated for malignant melanoma, buccal cavity, liver, CNS, thyroid, bone, and connective tissue cancers. In multivariate analyses, higher doses of TBI were associated with an increased risk. Chronic GVHD and male gender were strongly associated with an excess risk of squamous cell cancers of the buccal cavity and skin (Deeg and Witherspoon 1993).

Among 700 patients with severe aplastic anemia or Fanconi Anemia (FA), who received allogeneic HSCT at the Fred Hutchinson Cancer Research Center (FHCRC) or at Hôpital St. Louis in Paris, 23 developed malignancies at a median of 7.6 years after transplantation, with a cumulative incidence of 14 % at 20 years. In univariate analysis, risk factors for solid tumors included the diagnosis of FA ($p = 0.0002$), use of azathioprine ($p < 0.0001$), radiotherapy ($p = 0.0002$), cGVHD ($p = 0.009$), acute GVHD ($p = 0.01$), and male gender ($p = 0.05$). In multivariate analysis, azathioprine therapy ($p < 0.0001$) and the diagnosis of FA ($p < 0.0001$) were statistically significant. Radiotherapy was statistically significant ($p = 0.004$) as a predictor only if the time-dependent variable azathioprine was not included in the analysis. Among non-FA patients, azathioprine ($p = 0.004$), age ($p = 0.03$), and radiotherapy ($p = 0.04$) were significant (Deeg et al. 1996).

In an analysis of SMNs from the FHCRC, which included both allogeneic and autologous transplant, in a cohort of 5,806 patients treated with transplant and who survived beyond 100 days, 381 SMNs were reported, excluding benign tumors, cancer in situ, or post-transplant lymphoproliferative disease. Using Cox proportion models, dose and fraction of TBI were analyzed, as well as the use of pretransplant conventional radiotherapy. The analysis was adjusted for gender and age and found TBI to be a significant risk factor. The hazard of SMN among patients receiving TBI was 1.64 times that of patients who did not receive TBI. Furthermore, use of TBI in a single dose increased the hazard by a factor of 2.3 relative to patients receiving no TBI. Incorporation of the likelihood of pretransplant radiation did not markedly increase the hazard ratio compared to TBI only. The overall incidence of SMNs in our cohort was 17, 6, and 13 % at 10, 20, and 25 years, respectively. Patients with TBI exposure had a 25-year incidence of SMN of 21 %, compared to 10 % among patients not exposed to TBI. Of particular interest, for patients $\geq$10 years of age at HSCT, those with TBI exposure had a 25-year incidence of SMN of 19 %, compared to 5 % among patients not exposed to TBI. For patients >10 years of age at HSCT, those with TBI exposure had a 25-year incidence of SMN of 21 %, compared to 11 % among patients not exposed to TBI (Friedman et al. 2004).

In the largest study to date to evaluate risk factors for solid cancers following allogeneic transplant, within a multi-institutional cohort of 28,874 allogeneic transplant recipients, there were 189 solid malignancies. The SIR for second solid tumors was 2.1 (95 % CI 1.8–2.5). The risk increased with longer time since transplant k reached threefold among patients followed for 15 years or more after transplantation. The risk of developing a non-SCC following TBI was highly dependent on age at exposure. Among patients irradiated at ages under 30 years, the relative risk of non-SCC was nine times that of nonirradiated patients, while the comparable risk for older patients was 1.1 (p interaction <0.01). Chronic GVHD and male sex were the main determinants for risk of SCC.

The impact of patient-, disease-, treatment-, and toxicity-related factors on risk of basal cell carcinoma (BCC) and SCC was determined in 4,810 patients who received allogeneic HCT at the FHCRC and who survived for at least 100 days. In this cohort, 237 developed at least one skin or mucosal cancer. Twenty-year cumulative incidences of BCC and SCC were 6.5 and 3.4 %, respectively. Total body irradiation was a significant risk factor for BCC, most strongly among patients younger than 18-years old at HCT. Light-skinned patients had an increased risk of BCC. Acute GVHD increased the risk of SCC, whereas cGVHD increased the risk of both BCC and SCC (Leisenring et al. 2006).

In a subsequent analysis of BCC in the FHCRC cohort, in a Poisson regression analysis to examine age at time of BBC, BCC risk in non-TBI patients increased with attained age and the rate of age-related increase was higher for more recent birth cohorts and among Caucasians (Schwartz et al. 2009). For patients treated with TBI, the crude BCC incidence rates in TBI patients increased with age at HCT; however, for those transplanted at younger ages, the crude rates were markedly higher than the corresponding rates for non-TBI patients. When all TBI patients were combined and compared to non-TBI patients, there was a significant radiation-related risk, with TBI patients having an overall Absolute Excess Risk (AER) of 24.3 cases per 10,000 person-years. However, the AER decreased with age at exposure, while sharply increasing with attained age. After accounting for the effects of attained age and age at transplant, there was no significant difference in AER between whites and nonwhites in those treated with TBI (Schwartz et al. 2009).

A combined analysis at the FHCRC and the European Bone Marrow Transplant Registry evaluated the risk of breast cancer among 3,337 female 5-year survivors who underwent allogeneic hematopoietic cell transplantation. Fifty-two survivors developed breast cancer at a median of

12.5 (range: 5.7–24.8) years following HCT (SIR = 2.2). Twenty-five year cumulative incidence was 11.0 %, higher among survivors who received TBI (17 %) than those who did not receive TBI (3 %). In multivariable analysis, increased risk was associated with longer time since transplantation (hazard ratio [HR] for 20 + years after transplantation = 10.8), use of TBI (HR = 4.0), and younger age at transplantation (HR = 9.5 for HCT < 18 years). Hazard for death associated with breast cancer was 2.5 (Friedman et al. 2008).

11.3 Radiation Exposure and Sensitivity

There is interindividual variation in radiation sensitivity, evidenced by different degrees of skin erythema, fibrosis, and telangiectasia following radiotherapy (West and Hendry 1992). It is therefore likely that a number of genetic elements work in concert to determine individual response to radiotherapy. Radiation sensitivity assays on fibroblasts and lymphocytes from apparently normal individuals have established at least a threefold range in interindividual sensitivity. Radiosensitivity is distributed normally in the population (West and Hendry 1992; Mossman 1997). There is growing evidence that variation in the degree of radiation sensitivity is genetically determined. Family members of radiosensitive individuals are more likely to be radiosensitive than unrelated individuals (Roberts et al. 1999; Thacker 1989). There are also data to suggest that individuals who develop malignancies are radiation-sensitive (Baria et al. 2001; Berwick et al. 2001; Bondy et al. 2001; Buchholz and Wu 2001; Hannan et al. 2001; Papworth et al. 2001; Scott 2000). Furthermore, there is evidence of a correlation between radiation sensitivity and susceptibility to cancer (Hall 1994; Bennett 1999; Okayasu et al. 2000; Yu et al. 2001). What remains unclear is who is at risk for cancer following radiation therapy, what proportion of patients with SMNs have increased radiation sensitivity, what genetic elements contribute to sensitivity, and how sensitivity is most effectively characterized.

11.4 Summary

The proportion of second cancers among all cancers in the United States has more than doubled in the past 20 years. With improving survivorship, this percentage is likely to increase. The role of genetic risk factors remains relatively unknown and is best evaluated in the context of treatment and disease-related risk factors, as well as health-related risk behaviors known to promote cancer, such as smoking, alcohol exposure, sun exposure, and dietary risk factors. Identifying markers of cancer susceptibility after exposure to carcinogenic therapeutic agents can result in several important outcomes. Patients who harbor a genetic predisposition to subsequent cancers can be more closely monitored during their lifetime, and counseled regarding avoidance of potential cocarcinogens that may share similar metabolic pathways. Treatment for primary malignancies may be altered in those with identified inherited high-risk genotypes. Family members may be at a similarly increased risk of specific malignancies, when exposed to specific carcinogens and may require more targeted preventive strategies and lifetime monitoring for development of malignancy. Specific emphasis can be directed toward the interaction between environmental and therapeutic exposures and genetic susceptibility. The knowledge gained from these lines of investigation will, in part, be applicable to the larger population of cancer survivors, treated with conventional radiotherapy and at risk for SMN, and at the very least will generate hypotheses.

12 Future Directions

Several emerging technologies in TBI delivery have been employed in attempts to mitigate the deleterious effects of TBI. Schneider and colleagues reported their results using a technique of static intensity-modulated TBI which uses compensators to deliver a more homogeneous dose to the patient (Schneider et al. 2008). They showed a decrease in pneumonitis by constraining the dose to the lungs to 11 Gy. Another emerging technology has been the use of image-guided tomographic intensity-modulated radiotherapy or helical tomotherapy. Schultheiss and colleagues (2007; Wong et al. 2006) demonstrated a substantial reduction in dose to visceral organs by using this method with no decrease in rates of engraftment.

Another avenue of investigation has been the use of monoclonal antibodies against hematopoietic cells linked to radioactive substances in an effect to omit TBI altogether, at least for nonmyeloablative HCT. The use of radioimmunotherapy in conjunction with conventional conditioning regimens (TBI containing) has been studied using linked β-emitters and shown to add 10–24 Gy to the marrow dose without much added toxicity (Bethge et al. 2006; Bunjes et al. 2001; Matthews et al. 1999; Pagel et al. 2006). In an attempt to further decrease toxicity, α-emitters with higher energies and shorter path lengths than β-emitters (40–90 μm for α vs. 1–4 mm for β) have been utilized. Bethge and his colleagues (Bethge et al. 2004, 2003) in Seattle have linked bismuth-213 to either anti-CD45 or anti-TCR$\alpha\beta$ (T cell receptor) and shown the feasibility of those compounds for nonmyeloablative allogeneic HCT in a canine model with minimal toxicity. Unfortunately, the cost of producing bismuth has been prohibitive for use in

humans. Other radioactive species are actively being investigated which hopefully will lead to more feasible compounds.

13 Conclusions

As the number of HCT increases worldwide and the survival continues to improve, the late deleterious consequences of HCT will increasingly become paramount. As outlined in the sections above, the late effects of HCT and in particular TBI are manifest in practically every organ system and may have significant impact on the quality of life of surviving patients years after transplantation. Patients must be followed meticulously and appropriate interventions executed to minimize the impact of late treatment effects. Continued exploration of alternative preparative regimens and supportive care of transplant patients will be necessary to improve the long-term quality of life in this cohort of patients.

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Lymph Nodes, Thymus, Spleen, and Lymphatics

Jennifer C. Jones and Susan J. Knox

Contents

Abstract

- The effects of radiation on these tissues is determined by the response of the constituent immune cells to radiation, and these range from highly sensitive conventional T cells to relatively radioresistant plasma cells, with the stromal supporting cells being relatively resistant to the effects of radiation.
- Lymphatic vessels connect the lymphoid organs and these lymphatics are therefore critical for the systemic antigen sampling and filtering functions of the lymphoreticular system.
- Plasma cells then migrate into the medullary cords in the center of the lymph node where they produce antibodies, which flow out through the medullary sinuses.
- T and B lymphocytes have distinct patterns of survival after radiation, with T cells demonstrating greater radiation sensitivity than the B cells.
- In addition to promoting cytokine production and stimulating cell proliferation and/or recruitment, radiation also modulates the expression of costimulatory and coinhibitory molecules, such as CD28 and CTLA-4, respectively.
- Damage to the lymphorecticular system after RT can lead to acute cytopenias and immune compromise, which can increase the risk of infection.
- Historically lymphangiograms, and more recently nuclear medicine modalities, such as PET are being investigated.
- High doses of radiation destroy the parechyma of lymph nodes and other organized lymphatic tissue, leaving the stroma, blood vessels, mature plasma cells and phagocytic cells.
- Sparing of a strip of medial skin/lymphatics in the design of extremity fields will minimize the risk of lymphedema. TBI and TLI fields used for transplantation conditioning or immunomodulation are usually treated to total doses of approximately 1200–1320 cGy and 800–1200 cGy, that are often hyperfractioned for TBI.

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- Hormesis is the paradoxical augmentation of certain immune responses by low doses of irradiation due to shifts in the relative ratios of immune cell subsets with distinct radiosensitivity profiles.

Abbreviations

AHS	Adult health study samples
CTV	Clinical target volumes
HSCT	Hematopoetic stem cell transplantation
MLR	Mixed lyphocyte reactions
NK	Natural killer
PHA	Phytohemagglutinin
TBI	Total body irradiation
TLI	Total lymphoid irradiation

1 Introduction

The lymphoreticular system is a complex network of cells and tissues that control immune responses, circulate lymphatic fluid, and filter particulate material such as senescent erythrocytes. The primary role of this system is to generate and regulate adaptive immune responses to foreign antigens. Certain components of the lymphoreticular system are highly sensitive to radiation, while others are relatively radioresistant, and a clear picture of these distinct sensitivities is important to understanding the various late effects that follow irradiation of lymphoid organs and the lymphoid circulatory system connecting these organs.

Lymphoid tissues are commonly treated with radiation therapy (RT), whether the lymphoid tissues are a primary target, as with involved field treatments for lymphoma, or as an area of involvement (actual or at risk) with tumor from solid tumor primary sites. Less commonly, lymphoid tissues are also treated for immunomodulatory purposes. The effects of radiation on these tissues is determined by the response of the constituent immune cells to radiation, and these range from highly sensitive conventional T cells to relatively radioresistant plasma cells, with the stromal supporting cells being relatively resistant to the effects of radiation.

When designing radiation treatment plans with curative intent, clinical target volumes (CTV) encompass the detectable tumor (or tumor bed) and the anatomic areas at risk for metastatic spread or microscopic involvement. Thus, the CTV commonly includes neighboring lymph node echelons. Lymphoid organs, such as the spleen, thymus, or tonsils may also be indirectly included in planning target volumes due to proximity to at risk structures. The primary structures of the lymphoreticular system, which are discussed in this section include: the lymph nodes, spleen, thymus, appendix, tonsil, and lymphatic vessels. Lymphoid tissues, due to the inherent radiosensitivity of lymphoid cells, are sensitive to radiation, but the acute and long term immunological sequelae of this sensitivity are most significant for the spleen. Acutely, dose and fractionation of the radiation to the spleen may be limited by cytopenias, while long term, splenic compromise warrants careful consideration of vaccination and antibiotic prophylaxis, since procedures, such as dental work may introduce gram negative organisms into the circulation. Locally, damage to the dermal lymphatics can impact fluid circulation, such that flow from the extremities is impaired and causes edema, but this topic is addressed separately in chapter 38 (skin).

The lymphoreticular system is a complex network of structures which consist of multiple cell types and play an important role in the reguation of T cell development, and the coordination of immune responses. These immune functions depend upon precise coordination of several cell types and highly specialized microenvironrnents.

Acute effects of radiation are dramatic, with rapid apoptotic loss of conventional T cells, while macrophages and plasma cells persist despite relatively high doses of radiation. Since these cells arise from stem cells and committed progenitors, which populate areas beyond the radiation field, repopulation happens within a matter of days. Longer term sequelae and alteration of immune function reflect more permanent effects on the microenvironment of the lymphoreticular organs, such that repopulation after radiation may consist of a shift in the representation of different immune cell subsets as compared to pretreatment.

The early effects of radiation on the lymphoreticular sites is rapid, with apopotic death of lymphocytes occurring within hours of radiation exposure. Later phenotypic changes in surviving cells and repopulating cells are characterized in certain situations by a brief period of hyperresponsiveness, before homestasic mechanisms renormalize the system. Ultimately, higher doses of radiation can also result in fibrosis of lymphatic vessels and lymphoreticular organ reconstitution with fibrous or adipose tissue, rather than immune cells with their associated microenvironments. Our understanding of the cellular and biochemical changes that occur in lymphoid tissues after RT is limited by the small number of studies performed after the current concepts of cellular immunology and immune cell subsets began to mature during the past few decades. Our understanding of RT effects on the immune system and the lymphoid organs which comprise the immune system will continue to evolve as our understanding of the relevant constituent elements and cell subsets evolves.

Generally, concerns about radiation-induced immune/lymphoreticular dysfunction secondary to irradiation of lymphoreticular structures are not a major consideration in treatment field design or prescribed doses. Because immune function is controlled by a network of tissues and cells distributed throughout the body, localized radiation treatments seldom have clinically significant effects on the lymphoid system. Field modifications, however, are commonly considered when treating extremities if the doses and fields are substantial, due to the risk that lymphatic circulation can be compromised after radiation and lead to edema of extremities distal to the irradiated lymphatics. Therefore, it is standard practice to consider sparing tissue laterally or medially when treating extremities to a relatively high dose in order to spare a conduit of lymphatic drainage and minimize the risk of lymphedema.

Although the immune effects of irradiation of lymphoid organs rarely demonstrates significant effects on immune functions, certain potential long term sequelae of radiation on the lymphoreticular system shoud be considered in patients' follow-up care, as pneumococcal vaccinations for patients after splenic radiation can help to offset theoretical RT-related susceptibility to infection. Typically, the immunological compromise after radiation is self-limited in time and extent, and routine vaccination protocols and simple precautions can provide further protection from infectious complications. Dose/volume parameters have been not been defined that predict functional lymphoid organ recovery after radiation. However, some basic parameters relating to dose effects on these tissues are known, largely from animal experiments, and although our knowledge of the effects of RT on the lymphoreticular and immune systems require further study, the management of these effects is generally straightforward and is not commonly associated with long term health consequences. In this chapter we will review the many facets of RT-induced lymphoreticular injury and clinically useful information for the clinician.

2 Anatomy and Histology

Tissues of the lymphoid system are distributed throughout the body and take several basic forms. Lymphatic nodules, such as Peyer's patches in the ileum, are found primarily in the lamina propria of the digestive, upper respiratory and urinary tracts. They do not have a connective tissue capsule, may occur in aggregates and consist of a mixture of lymphoblasts, lymphocytes and plasma cells, with a central germinal center comprised primarily of activated lymphocytes (immunoblasts). In contrast, lymph nodes are encapsulated, and are distributed along lymphatic vessels. Blood vessels, lymphatic vessels and nerves pass through the hilum. Below the capsule is a cortical region with dense aggregates of lymphocytes and reticular cells that make up nodules (Fig 1).

Lymph nodes filter tissue fluid and play an important role in the regulation of immune responses. Antigen sampling from the peripheral tissues is localized to the lymph nodes, where immature dendritic cells in the periphery sample antigen, mature, and migrate from the periphery into the regional lymph nodes. Sinuses within the lymph node facilitate filtering of particulate and antigenic material. Antigen and debris are removed by phagocytosis primarily by macrophages. Some antigen is trapped and processed by dendritic cells for presentation to immune cells, such as B lymphocytes. B lymphocytes that recognize the presented antigen become activated and migrate to the germinal center where they undergo transformation into plasma cells. The plasma cells then migrate into the medullary cords in the center of the lymph node where they produce antibodies, which flow out through the medullary sinuses. Thus the medullary cords are primarily involved in humoral immune responses. T lymphocytes, on the other hand, are located primarily in the paracortical zones, where the T lymphocytes interact with a variety of other immune cell subsets. Antigen specific and memory T lymphocytes in these paracortical areas regulate cellular immune responses.

The thymus is a central lymphoid organ in the mediastinum that is essential for the development of T lymphocytes and the regulation of self- versus non-self antigen recognition by these T cells via the T cell receptor. The lobules of the thymus are partially separated by connective tissue and each lobule possesses a histologically distinct cortex and medulla. (Fig 2a, b) Unlike lymph nodes, the thymus has no afferent lymphatics or nodules. The peripheral zone of dense cortical lymphoid tissue is primarily composed thymocytes or T lymphocytes, while the central medullary zone is predominantly composed of loose connective tissue and characteristic specialized groups of epithelial cells, Hassall's corpuscles. Other, less prominent, populations of cells, including B cells, macrophages, interdigitating dendritic cells, mast cells, eosiniphils, and Langerhans cells are also found in the thymus. The process of thymic lymphocyte development results in apoptosis of the majority of lymphocytes as part of a regulatory system that eliminates potentially autoreactive T cells before they enter the systemic circulation. The thymus spontaneously involutes with age, leaving a residual of retricular cells, Hassell's corpuscles, some lymphocytes and connective tissue. Prior to thymic involution, the thymus is the site of the development of the majority of the T cells that populate the thymus-dependent paracortical zone of lymph nodes and the periarterial sheaths in the white pulp of the spleen.

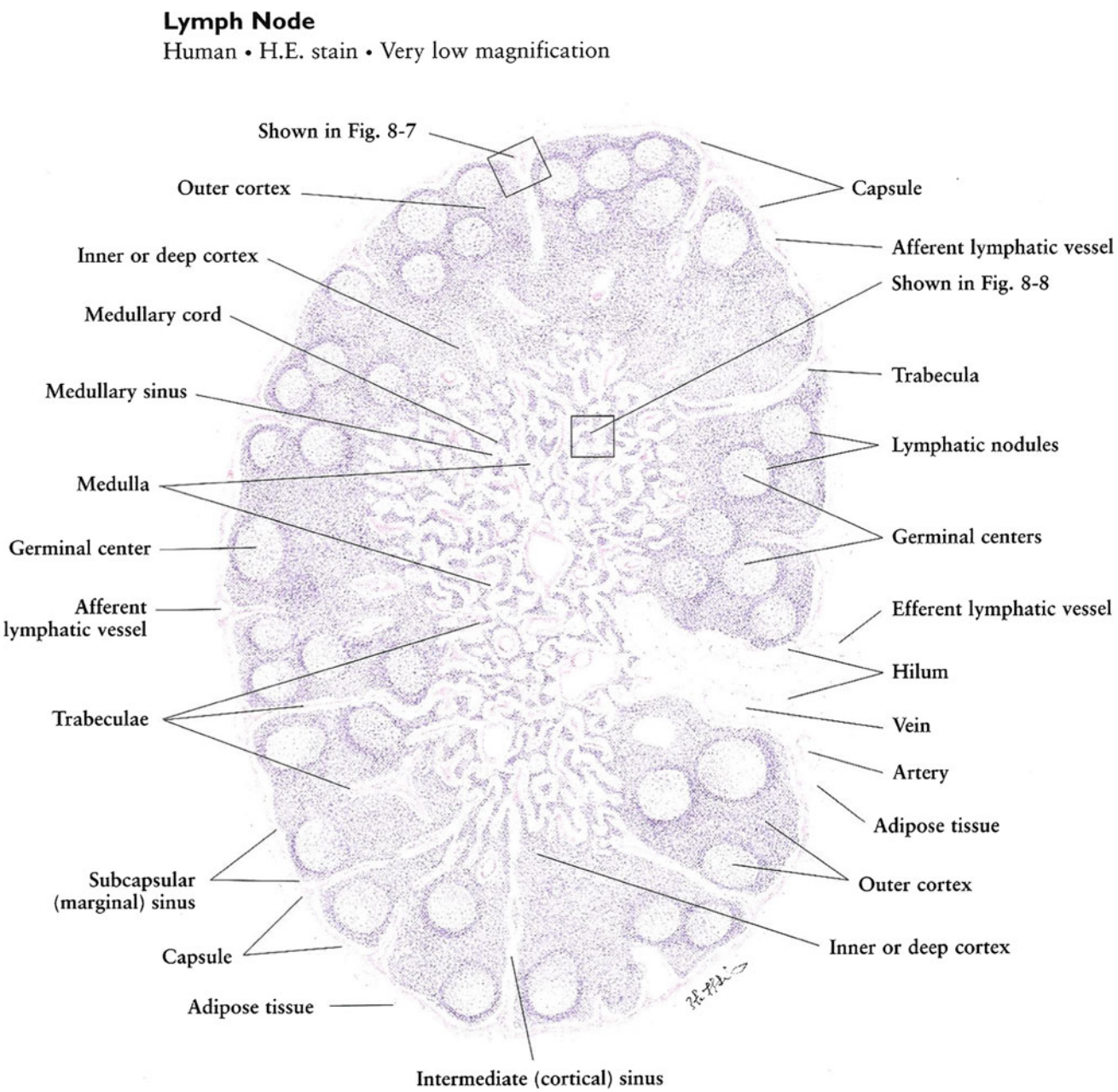


Fig. 1 Histologic structure of a lymph node (with permissions from Zhang 1999)

The spleen is the largest lymphoid organ in the body and plays an important role in the production of blood cells, filtering of erythrocytes, blood storage, and generation of immune responses. The filtering functions of the spleen occur in the red pulp, while the immune functions of the spleen primarily occur in the white pulp. Beneath its thick capsule, the spleen has trabeculae that divide the parenchyma into incomplete sections with (1) lymphatic nodules in the white pulp along vessels, (2) a marginal zone with sinuses, loose connective tissue and many macrophages and dendritic cells between the white pulp and red pulp, and (3) red pulp with sinusoids. Immunity to infectious microorganisms in the systemic circulation is promoted by the interactions between B and T lymphocytes and antigen presenting cells in the white pulp. Even low doses of radiation can significantly deplete radiosensitive immune cell subsets and, to a lesser degree, affect immunocompetency.

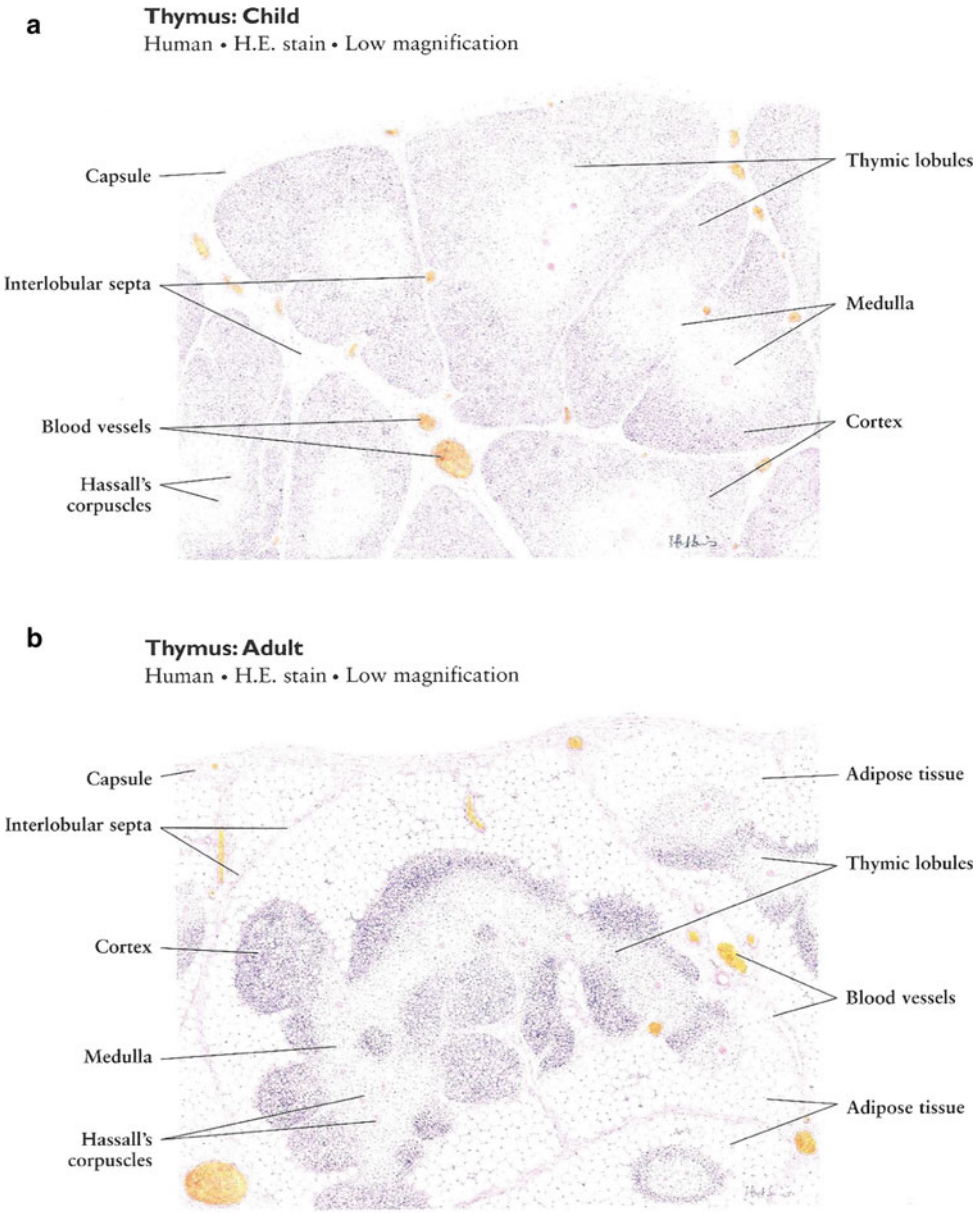


Fig. 2 Histologic structure of: **a** the thymus of a child, and **b** the thymus of an adult (with permissions from Zhang 1999)

Lymphatic vessels connect the lymphoid organs and these lymphatics are therefore critical for the systemic antigen sampling and filtering functions of the lymphoreticular system. Typical lymphatic vessels have an intimal layer (a monolayer of epithelium) with scant adventitia. Peripheral lymphatic vessels are found throughout the body. Afferent lymphatic vessels are found in lymph nodes, but not the thymus and spleen. Lymph circulates from the thymus, spleen, and lymph nodes via efferent lymph nodes. High doses of radiation can not only affect the microenvironment of lymphoid organs, but also lead to changes in lymphatic vessel structure and function. Because patency of the lymphatic channel is important for normal flow of lymph, damage to the lymphatics may lead to regional lympedema.

3 Biology, Physiology, and Pathophysiology

3.1 Cellular Dynamics and the Radiation Response

RT-induced tissue injuries in general have traditionally been divided into two phases: an early inflammatory phase and a late fibroproliferative phase. For certain cell subsets and organs of the lymphoreticular system, there may be an early phase, a recovery phase, and a late phase. The acute phase occurs within hours after radiation exposure and is primarily characterized by apoptosis of lymphoid cells.

Depending on the doses and fields involved, this acute lymphoid depletion is followed by reconstitution from marrow-derived hematopoetic progenitor elements and homestatic proliferation of locally surviving immune cells. Ultimately, this process results (From Kataoka 1975) in a renormalization and homeostasis, which may be distinct from the preirradiation lymphoid state, due to long lasting changes related to regional tissue scarring and local microenvironment changes which impair complete reconstitution.

3.2 Physiology and Pathophysiology: Basic Radiobiology of the Immune System

Just as the early clinical applications of radiation preceded the scientific understanding of the cytotoxic effects of radiation, so too has the use of radiation to manipulate the immune system far out paced our understanding of the basic biology of these effects. During the 1970s and 1980s, investigators applied classical radiobiological methods to the study of recently identified immune cell subsets, such as B and T cells. In 1974, Han et al. used T and B cell lines to demonstrate that T and B lymphocytes have distinct patterns of survival after radiation, with T cells demonstrating greater radiation sensitivity than the B cells (Fig. 3a, b). Kataoka in 1975 delineated these differences in native T and B cells in spleens of mice after radiation (Fig.3b). Radiobiologically, these investigators determined the parameters characterizing the survival curve of B lymphocytes: Do = 200 cGy and $n = 1.0$. The T lymphocytes, on the other hand, were shown to consist of two distinct subpopulations with respect to their radiosensitivity. The radiobiological parameters of the radiosensitive fraction of T lymphocytes were Dq = 185 cGy, Do = 195 cGy and $n = 2$–50. The Do value of the radioresistant T lymphocyte subpopulation was practically unmeasurable, and approximately eight percent of the T lymphocytes present in the spleen belonged to this radioresistant subpopulation. Lymphocytes are especially sensitive to radiation induced apoptosis. This correlates with the unique features of lymphocytes that allow the development of a diverse immune repertoire by NHEJ mediated DNA recombination, which is mediated by their distinct expression levels of DNA repair enzymes.

Radiation resistance in immune cells also varies with cellular activation. The figure below demonstrates that phytohemagglutinin (PHA) stimulation can enhance T cell survival after radiation (Fig. 4a). Similar enhancement of lymphocyte survival has also been reported after ConA and PWM lectin stimulation. The impact of PHA stimulation on cell survival after radiation relates to enhanced DNA repair capacity in stimulated cells (Fig. 4b). Numerous investigators have also demonstrated that these types of simple lymphocyte survival curves can be used to determine individual persons' hereditary susceptibility to the effects of radiation, especially in persons with DNA repair deficits.

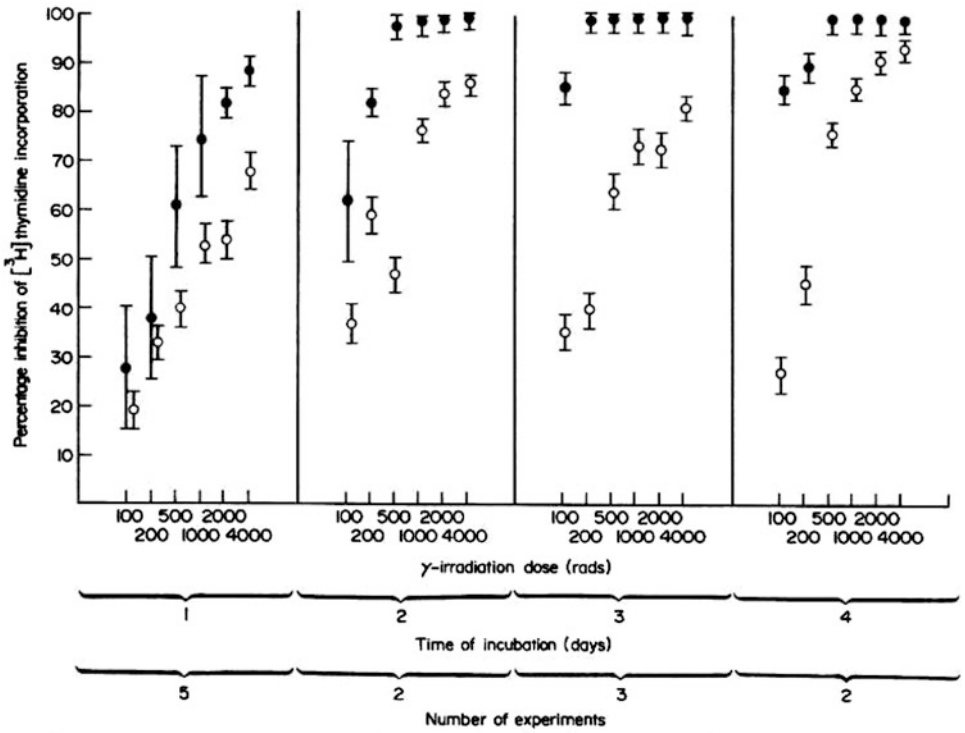
Early observations of immune stimulation at low doses of radiation have been confirmed in modern studies, using flow cytometry to delineate cell numbers of T, Natural Killer (NK) and NKT cells after low dose whole body irradiation (Ren et al. 2006). After low dose total body irradiation (20 cGy x 4, delivered QOD), despite an initial drop in total monocyte and lymphocyte counts at d 10, total numbers of NK, NKT, and T cells are increased, and show an increase in pro-inflammatory cytokine expression, as measured by IFN-γ and IL-12 (Ren et al. 2006). Interestingly, in addition to NKT cells, there appears to be another relatively radioresistant cell subset, a thymic medullary population, that is associated with the development of regulatory T cells. NKT radioresistance is associated with relatively lower bax:bcl-2 ratios and lower propensities to undergo apoptotic death after irradiation (Yao et al. 2009).

In addition to promoting cytokine production and stimulating cell proliferation and/or recruitment, radiation also modulates the expression of costimulatory and coinhibitory molecules, such as CD28 and CTLA-4, respectively. This change in costimulatory receptor expression is associated with shifts in cytokine expression that would be expected, i.e., IL-10 expression is enhanced concurrently with a rise in CTLA-4 expression (Usui et al. 2006). MLR responses to irradiated DC are also influenced by XRT, but this has only been shown at one dose, 30 Gy (Cao et al. 2004).

4 Clinical Endpoints

Damage to the lymphorecticular system after RT can lead to acute cytopenias and immune compromise, which can increase the risk of infection. If these changes persist long term, they could potentially compromise the ability of the immune system to recognize transformed cells and increase the risk of malignancy in these patients. Laboratory studies in such patients would demonstrate profound lymphopenia, with other cell types less affected. A subset analysis might demonstrate an alteration in the relative proportion of cells, such as CD4 and CD8 T cells.

CTC v4 provides guidelines for the assessment of side effects (Table 1). Few radiological studies have been used to assess lymphoreticular injury. Historically, lymphangiograms, and more recently, other imaging methods are being



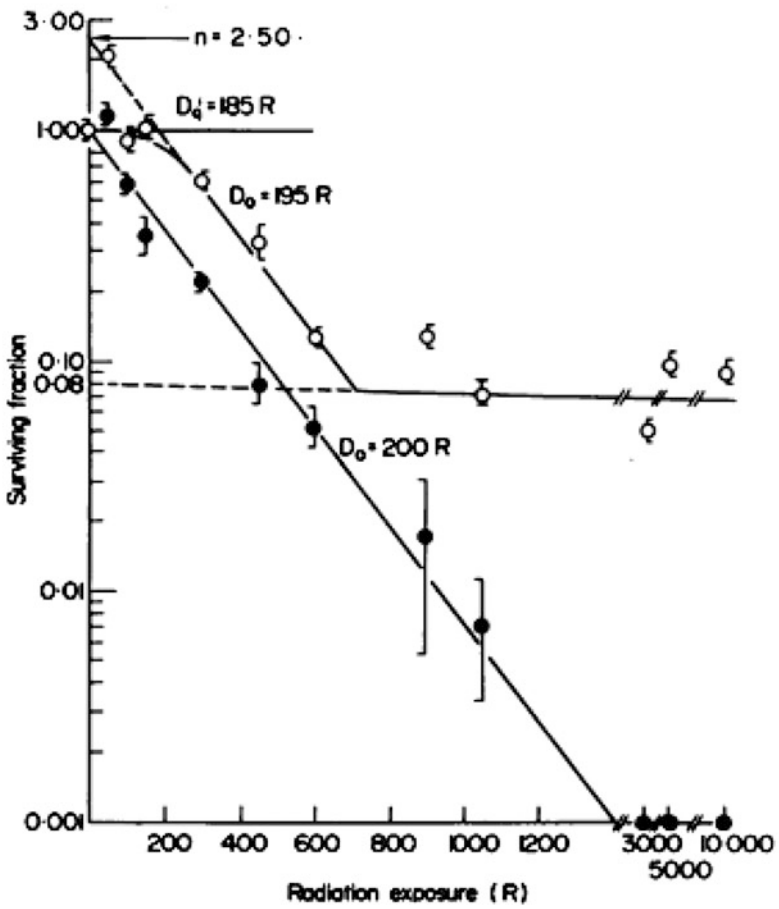


Fig. 3 **a** Comparison of cytotoxic effect of irradiation on human T (●) and B lymphoid cell lines (○). The mean ± s.d. is shown in each case. **b** Survival curves of T and B lymphocytes 3 days after various doses of γ-rays. (○) T lymphocytes. (●) B lymphocytes (From Han et al. 1974)

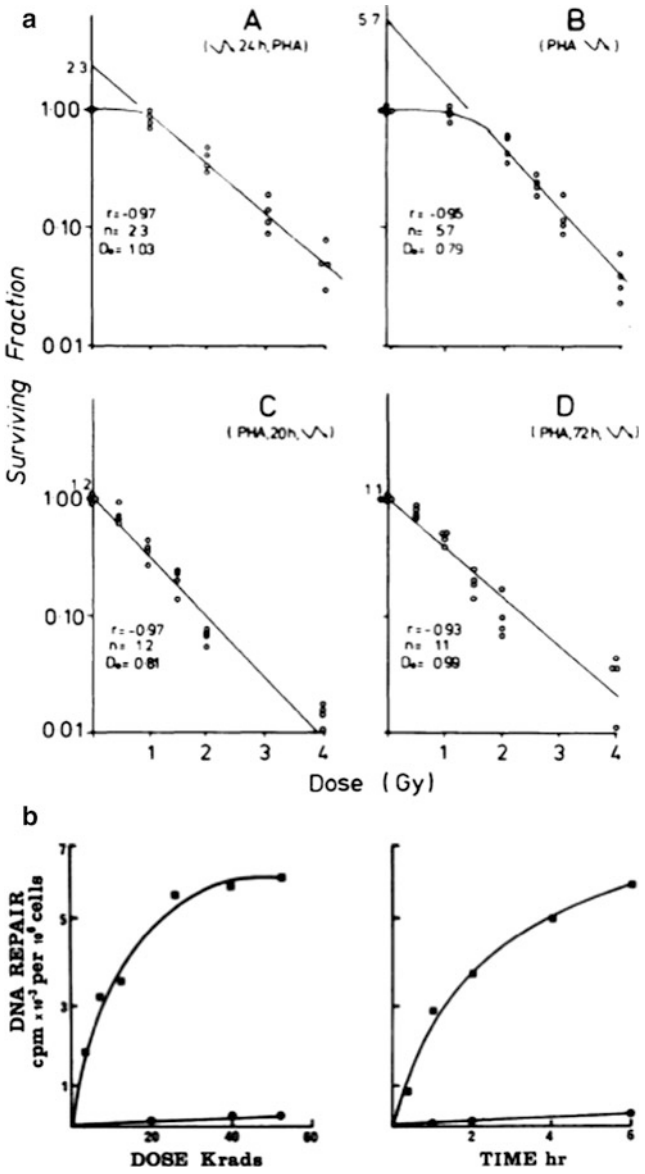


Fig. 4 **a** Enhancement of T cell survival after irradiation when stimulated by phytohemagglutinin. Survival curves produced for T-colony formation when the cells were irradiated at different stages of activation. (A) Irradiation 24 h prior to PHA exposure; scheme A, (B) Irradiation immediately prior to PHA exposure; (C) Irradiation 20 h after PHA exposure; scheme C, Fig. 1. (D) Irradiation 3 days after PHA exposure; Each point represents the surviving fraction. The results of four experiments are shown. **b** Enhancement of DNA repair in phytohemagglutinin stimulated cells. (*left*) DNA repair in human lymphocytes with increasing dose of ionizing radiation. Unstimulated cells (*black circle*), irradiation (*black square*). The result presented represent the mean values of 11 experiments (*right*). Time course of DNA repair in phytohemagglutinin stimulated lympocytes irradiated with 65 Krads. Cells were incubated with phytohemagglutinin for 5 days. Unstimulated cells (*black circle*), cells stimulated with phytohemagglutinin (*black square*) (From Kataoka 1975)

investigated, but none have demonstrated significant clinical utility. The sensitivity of these radiological modalities varies tremendously, with lymphangiograms being the most useful for showing patency of flow in lymphatic channels, as well as the size, architecture and filling properties of lymph nodes.

5 Radiation Tolerance

5.1 Therapeutic Lymphoreticular Irradiation

Areas of lymphoid tissues are encompassed within most standard radiation therapy treatments, whether as a therapeutic target or neighboring structure. Instances of direct targeting of the lymphoid system include total lymphoid irradiation, total body irradiation, splenic irradiation, or the treatment of nodal tissues with or at risk for involvement by tumor.

The entire lymphoid system is irradiated with total body irradiation (TBI), as used as part of a preparatory regimen for bone marrow or peripheral stem cell transplantation. The major lymph node bearing regions and spleen are included in total or subtotal lymphoid irradiation (TLI/sTLI) fields used in transplantation protocols and occasionally for the treatment of organ rejection and severe, medically refractory autoimmune disease. The spleen may be intentionally irradiated (e.g. for the treatment of Hodgkin's disease or severe splenomegaly in myelodysplastic syndromes), or receive dose during the course of the treatment of certain abdominal or thoracic tumors. Lastly, specific lymph node regions are often treated as part of the PTV for solid tumors or involved or extended field RT for lymphomas.

Depending upon the particular protocol, TBI and TLI fields used for hematopoetic stem cell transplantation (HSCT) conditioning or immunomodulation are usually treated to total doses of approximately 1,200–1,320 cGy and 800–1,200 cGy, respectively in 80–120 cGy fractions, that are often hyperfractionated for TBI. Treatment of Hodgkin's disease uses higher doses (e.g. 3,000-4,400 cGy) to the spleen and lymph nodes. Fields used for the treatment of lymphomas or solid tumors are standard (total dose and fractionation) for the particular clinical indication and tumor type. Fraction sizes of 150–200 cGy are commonly used in the treatment of lymphoma, and total doses range from four Gy for the treatment of certain cases of radiosensitive and indolent lymphomas, such as follicular lymphoma, to more than 40–55 Gy for the treatment highly aggressive and radioresistant lymphomas, such as nasal

Table 1 CTCAE 4.02

Grade	0	1	2	3	4
Immune system disorders - other, specify	None	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Blood and lymphatic system disorders					
Spleen disorder	None	Incidental findings (e.g., Howell-Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	–	Life-threatening consequences; urgent intervention indicated
Blood and lymphatic system disorders - Other, specify	None	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Vascular disorders					
Lymph leakage	None	–	–	–	–
Lymphedema	None	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	–
Lymphocele	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	–

NKT cell lymphomas. Irradiation of nodal volumes that are involved with or at risk for involvement with solid tumor metastases commonly follow the dose and fractionation standards for the specific solid tumor primary site. Acute and late toxicity is related to volume, dose, fractionation, and dose rate. Dose rate effects are most dramatic in the setting of TBI, with low dose rates (e.g. 6–25 cGy/min) used for routine TBI for HSCT conditioning.

5.2 Effects of Radiation on lymphoid Tissues

Most immune cells in lymphoid tissue behave as early-responding normal tissues with a high α/β ratio and steep initial slope on radiation survival curves. In contrast, connective tissue and supportive stromal elements in lymphoid tissue microenvironments behave more like late-responding tissues, with low α/β ratios and a shallow initial slope on the survival curve. These characteristics are pertinent to the tolerance of lymphoid tissues to radiation and secondary toxicity. The majority of immune cells in lymph nodes and the thymus are very radiosensitive and undergo radiation-induced apoptosis at relatively low doses, resulting in cellular subpopulation shifts, as described above, and thymic involution. Whole body exposures to doses as low as 25 cGy significantly reduce circulating lymphocyte numbers. Lymphocyte morphological and motility changes have been observed at doses of 5 R and 2 R, respectively. Animal studies demonstrate that a dose of 100 cGy is associated with a 25 % reduction in peripheral lymphocyte levels.

High doses of radiation destroy the parnechyma of lymph nodes and other organized lymphatic tissue (e.g. splenic white pulp, Peyer's patches, appendix, tonsil, thymus), leaving the stroma, blood vessels, mature plasma cells and phagocytic cells relatively intact. Scattered, but few, lymphocytes remain in the cortex and germinal centers (Congdon 1966). In contrast to parenchyma, lymphatic vessels are relatively radioresistant and are not significantly affected by doses up to 40 Gy (Hauer-Jensen 1990; Engaset 1964; Van den Brenk 1957; Sung et al. 2006). By 7–8 days following high dose irradiation, there is marked dilation of lymphatics (Zweifach and Kivy-Rosenbery 1965). Both inflammation and direct damage to lymphatic vessels may contribute to fibrotic constriction of lymph vessels and

obstructed lymphatic flow (Hauer-Jensen 1990). Lymphatic regeneration is inhibited after irradiation with doses in excess of 20 Gy (Van den Brenk 1957), but parenchyma can regenerate, providing the microenvironment is intact. Collections of cortical lymphocytes appear first, followed by germinal centers (Congdon 1966). Some evidence from adult mice suggests that functional regeneration of the lymphoid system after irradiation requires the presence of an intact thymus (Cross et al. 1964).

After splenic irradiation at doses commonly used to treat lymphoma, patients are functionally asplenic. Acutely after splenic irradaition, there is decreased celluarity, alterations in the relative composition of constituent splenic cell populations, and decreased responsiveness to mitogen (Harrington et al. 1997). Late effects of splenic irradiation were studied in an autopsy series of patients 1–8 years following a mean dose of 3,899 cGy fractionated over 5–6 weeks. Most of the irradiated spleens were small, with thick capsules, often with focal hemorrhage. There was also collapse of parenchyma, close opposition of trabeculae and diffuse fibrosis of the red pulp, with lymphocyte depletion (Dailey et al. 1981). These findings have profound implications in terms of immunocompetency, the ability to resist infection and the potential efficacy of immunization.

The effects of radiation on cellular and humoral immune parameters have been studied in some detail in the survivors of atomic bomb and nuclear accidents, especially in survivors from Nagasaki and Hiroshima followed in the adult health study samples (AHS) (Akiyama 1995). (Tables 2, 3) Although the effects of radiation exposure on immune cell and biomarker levels are evident in these populations, an association with infectious disease has been more difficult to demonstrate. The range of effects on distinct immune cell subsets and parameters reflects the complexity of the immune system, where radiosensitivity is influenced by many factors, including cell type, history of antigen exposure, age at irradiation, gender, individual variation, and hormesis. Hormesis is the paradoxical augmentation of certain immune responses by low doses of irradiation, due to shifts in the relative ratios of immune cell subsets with distinct radiosensitivity profiles. Such shifts in lymphocyte subsets may have long term effects on immune profiles, because resistant lymphocytes that survive the acute radiation exposure may recirculate for decades.

T cell changes are the most pronounced long term changes in the peripheral blood immune profiles of these survivors. Doses of more than 1.5 Gy are associated with increased numbers of rare CD4-CD8- alpha beta + (double negative T cells), and with decreased proportions of mature CD3 + cells and CD4 + CD45 + naïve cells. T cell functional responses are also diminished in these survivors, as measured by in vitro cell culture assays including mitogen (phytohemagglutinin, PHA) responses, mixed lymphocyte reactions (MLR). Cytotoxic T cell frequencies and IL-2 production were not affected. Dose correlations with immune changes were observed after the Chernobyl accident. In the exposed Russian workers, increased total T cell numbers and increased titers of autoantibodies to thymic reticuloendothelial cell were noted in groups of exposed workers, across the estimated dose exposure range examined (0.1 Gy–9 Gy). Low doses (0.1 Gy–0.5 Gy) were associated with decreased CD8 + cells, while higher doses (4 Gy–9 Gy) were associated with decreased CD4 + cell counts.

Dose distribution influences T cell survival and function profiles. TLI promotes tolerance to histoincompatible grafts and this effect is associated with proportionately greater survival of potentially tolerogenic NKT cells and gamma delta T cells compared to conventional CD4 and CD8 T cell populations during and following the conditioning regimen. TLI, as compared with TBI, causes a rapid and relatively selective depletion of T cells. B cells are lost after TLI as well, however, B cell counts recover more rapidly and more completely than T cells after TLI. T cell levels may remain suppressed chronically, and this has been associated with changes in DTH reactions as assayed by skin testing, but it has not been associated with susceptibilities associated with other causes of T cell immunosuppression, such as HIV infection.

Changes in B cell numbers in the peripheral circulation were not noted in one AHS group, but a decrease was noted in another. B cell production of IgG was not affected in these populations, but IgM and IgA production were be increased in AHS survivors (Fujuwara et al. 22). Selected autoantibodies (rheumatoid factor, anti-parietal cell antibody, and anti-kidney) are also increased in AHS survivors, while no changes in other autoantibodies have been found. Despite the increase in certain autoantibodies in these survivors and those in the Chernobyl accident, no increase in autoimmune disease incidence has been identified. It is important to note that alterations in barrier permeability (i.e. gut) in individuals after whole body radiation exposure may contribute to these alterations in immune parameters.

Lymphatic vessels like other vessels are highly susceptible to radiation damage. Atrophy, fibrosis, luminal narrowing, and loss of elasticity characterize the chronic changes observed after irradiation of lymphatic vessels. These changes along with changes in adjacent arterial and venous tissues may lead to regional edema and pain.

Table 2 Effect of radiation on general cellular and humoral immunity among atomic bomb survivors

Parameter	Study cohort (number of subjects)	Study period	Effect of radiation	References
Total lymphocytes:				
Spleen index	Life span study (1433)	1963–1970	None	Doughty (1973)
No. of lymphocytes	Adult health study (12,354, 12,809, 10,733)	1958–1972	None	Osterle (1981)
NK cells:				
No. of cells	AHS (1316)[b]	1983–1986	None	Kusunoki (1988)
No. of cells	AHS (400)[h]	1987–1991	None	Kusunoki (1994)
K activity	AHS (1316)[b]	1983–1986	None	Bloom (1988)
Interferon production	AHS (486)[b]	1983–1986	None	Bloom (1988)
Killer-cell activity (ADCC)	AHS (1040)[b]	1983–1986	None	Kusunoki (1986)
T cells:				
No. of cells	AHS (900)	1974–1977	Decreased[c] ($p < 0.05$)	Akiyama (1983)
No. of cells	AHS (1328)	1983–1986	Decreased in older cohorts ($p < 0.05$)	Kusunoki (1988)
No. of cells	AHS (400)	1987–1991	Decreased	Kusunoki (1994)
PHA response	AHS (683)	1974–1977	Decreased in older cohorts ($p < 0.05$)	Akiyama (1983)
MLC response	AHS (139)	1984–1985	Decreased in older cohorts ($p < 0.05$)	Akiyama (1989)
Cytotoxic T cell frequency	AHS (68)	1989–1991	None	Kusunoki (1994)
IL-2 production	AHS (547)	1983–1986	None	Bloom (1988)
B cells:				
No. of cells	AHS (1328)	1983–1986	None	Kusunoki (1988)
No. of cells	AHS (400)	1987–1991	Decreased	Kusunoki (1994)
IgG				
	AHS (803)	1968–1969	None	Hall (1973)
	AHS (2043)	1970–1971	None	King (1973)
	AHS (2061)	1987–1989	None	Fujiwara (1994)
IgA				
	AHS (803)	1968–1969	None	Hall (1973)
	AHS (2043)	1970–1971	None	King (1973)
	AHS (2061)	1987–1989	Increased (females) ($p < 0.01$)	Fujiwara (1994)
IgM				
	AHS (803)	1968–1969	None	Hall (1973)
	AHS (2043)	1970–1971	None	King (1973)
	AHS (2061)	1987–1989	Increased ($p < 0.0001$)	Fujiwara (1994)
IgE				
	AHS (803)	1968–1969	–	Hall (1973)
	AHS (2043)	1970–1971	–	King (1973)
	AHS (2061)	1987–1989	None	Fujiwara (1994)

Source after Akiyama 1983

Table 3 Effects of radiation on T and B cell subpopulations among atomic bomb survivors

Cell phenotype	Radiation effect
NK-cell subpopulations:	
$CD16^+$	None
$CD16^+$ $CD57^{+\ or-}$	None
$CD56^+$ $CD3^-$	None
T cell subpopulations:	
$CD2^+$	Decreased ($p < 0.05$)
$CD3^+$	Decreased ($p < 0.1$)
$CD3^+$ $CD4^+$ $TCR\alpha\beta^+$	Decreased ($p < 0.05$)
$CD3^+$ $TCR\alpha\beta^+$ (= $TCR\alpha 8$)	None
$CD3^+4$-8-$TCR\alpha\beta^+$	Increased ($p < 0.05$)
$CD5^+$ $CD20^-$	Decreased ($p < 0.05$)
$CD4^-$	Decreased ($p < 0.01$)
$CD4^+$ $CD45RA^+$	Decreased ($p < 0.01$)
$CD4^+$ $CD45RA^-$	None
$CD4^+$; $CD8^{hi}$; 8^{hi}; $CD11b^{+\ -or\ -}$	None
$CD4^+$ $CD57^-$; $CD3^+$ $CD57^-$; $CD3^+$ $CD56^+$	None
B cell subpopulations:	
$CD20^+$	Increased ($p < 0.01$)
$CD20^+$ $CD5^{+\ or\ -}$	Increased ($p < 0.01$)
$CD20^+$ $CD23^+$ $DC^{\ or\ -}$	Increased ($p < 0.01$)

Source after Akiyama 1983

6 Prevention and Management

Although potential radioprotectors have been studied in preclinical models, there are no FDA approved drugs or biological response modifiers for the prevention of radiation damage to lymphoid tissues.

The process of treatment planning and field design provide several opportunities to consider for limiting the exposure of uninvolved lymphoid tissues to radiation, where appropriate. For example, when possible, the use of advanced imaging (e.g. PET CT), image merging, and the use of highly conformal planning methods, such as IMRT, may allow for minimization of field size and inclusion of lymphoid tissue in the PTV for the treatment of solid tumors. Fractionation and low dose rate irradiation with TBI help to minimize normal tissue toxicity. Sparing of a strip of skin/lymphatics in the design of extremity fields will also minimize the risk of lymphedema.

Irradiation of lymphoid tissue has profound effects on both humoral and cellular immunity. The greatest risk of lymphoid tissue irradiation is overwhelming infection. However, this is very rarely seen, except with splenic irradiation and immunosuppressive treatments such as TLI and TBI. Patients for whom splenic irradiation is planned (such as patients with Hodgkin's disease who require splenic radiation) are at increased risk of septicemia due to encapsulated bacteria such as Streptococcus pneumoniae. Humoral immunity and seroconversion after vaccination typically takes several days to weeks, so patients at risk for post-irradiation functional asplenia should receive the pneumococcal vaccine and other immunizations as clinically indicated as early as possible prior to the initiation of radiation therapy to the spleen. Formal guidelines for the administration of these vaccines prior to radiation have not been established. Following radiation to the spleen, patients should be vigilant about avoiding exposure to infection, and should notify their physician for any signs/symptoms and significant fever suggestive of infection. Antibiotic prophylaxis prior to dental work is also recommended, as per the broader guidelines established for asplenia in general. Compression devices and a variety of investigational approaches may be useful in the setting of lymphedema.

7 Future Directions

Radiation of the lymphatic system can be used to intentionally manipulate the immune response in order to optimize transplant conditioning for stem cell transplant, by selectively depleting radiosensitive subpopulations of immune cells, while enriching for more radioresistant subpopulations, which can have a variety of effects, including optimizing the balance between GVHD and GVL. TLI has been used to induce tolerance to transplanted organs and self antigens in autoimmune diseases. More recently, radiation is being used as a component of tumor vaccine strategies to release tumor antigens in combination with adjuvants of targeted immunotherapy. Elucidation of specific effects of radiation (dose, fractionation and dose rate) at the molecular level (e.g. up or down regulating co-stimulatory molecules on antigen presenting cells) and on signal transduction pathways will help with the design of future clinical trials in which radiation can be used to potentiate therapeutically advantageous immune responses or specifically abrogate undesirable and harmful immune responses. This is a very exciting and promising area for future clinical investigation.

8 History and Review of Literature and Landmarksigs

8.1 History

Early in the history of radiation therapy, lymphocytic malignancies and immunological disease were found to be especially responsive to radiation. Among the first

documented therapeutic effects of radiation were leukemic remissions (Pusey 1902a, b, 1904), diminished blood cell counts, and amelioration of rheumatologic conditions (Pusey 1900). The use of radiation for therapeutic purposes was initially strictly empiric, since clinical observations preceded precise scientific analysis of these effects of radiation by many years (Hayter 1998). Even today, although our understanding of the biological effects of radiation on the immune system has progressed, our current knowledge about this topic remains scant relative to our modern understanding of the general immunobiology of tumors and transplantation tolerance.

Between 1899 and 1904 several clinicians reported cases of leukemia treated with X-rays, each reporting a definite reduction in circulating leukocytes and clinical resolution of splenomegaly and lymphadenopathy after treatment. Contemporaneous treatments of individuals with autoimmune disorders, including rheumatoid arthritis and lupus, demonstrated significant improvement in patient symptoms (Pusey and Caldwell 1904), Table 4, Fig. 5. In these cases, clinical utilization of X-rays preceded and informed the basic research which soon followed.

The early histologic and cellular characterizations of the effects of radiation on the immune system are nicely reviewed by Taylor (Taylor et al. 1919), who notes that Heineke and Harvey were the first to make careful histological examinations of animals following X-ray exposures (Harvey 1908; Heineke 1914). The studies by Heinke and Harvey demonstrated that the lymphatic tissues of the body were primarily affected. Heinke found degeneration of the lymph follicles in the spleen and lymph glands, along with a concomitant decrease in circulating lymphocytes (Heineke 1914), while Helber and Linser examined blood counts of a rabbit before and after X-ray treatment and found a marked reduction in both the percentile and absolute number of circulating lymphocytes. Warthin confirmed Heineke's observations of the destructive action of X-rays on lymphoid tissues with experiments demonstrating that Malpighian bodies of the spleen to be first affected, followed by lymph nodes and bone marrow (Heineke 1914). Histologically, he observed fragmentation of the tissue lymphocytes, with the fragments being ingested by phagocytic cells which appeared to be more resistant to the effects of radiation. Morton and Murphy (1915b, JEM) discovered that resistance to cancer and tuberculosis in animals correlated with an increase in the number of the circulating lymphocytes and that this resistance, as well as the lymphocytosis, could be destroyed by X-rays (Hektoen 1915; Murphy and Morton 1915a, b). However, it was not feasible to accurately define the dose response relationships based on those early experiments because they were performed using radiation from gas tubes.

Table 4 First reported leukemic remission after radiation therapy

	March 6, 1902	April 9, 1902
Red blood-corpuseles	2,768,000	2,160,000
White corpuseles	74,300	12,000
Hemoglobin	45 %	43.0 %
Polymorphonuclears	14 %	41.1 %
Large mononuclears	5 %	4.2 %
Small mononuclears	80 %	53.3 %
Eosinophiles	1 %	1.1 %
Mast cells		0.3 %
Nucleated reds	A very few	1.0 %
Non-granular polymorphonucleas		

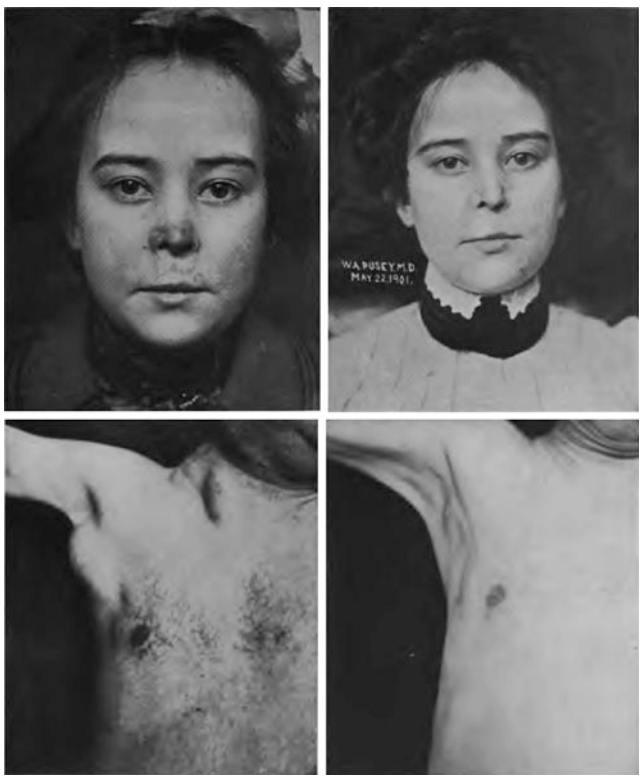


Fig. 5 Early photos of the use of radiation to treat lupus and leukemia (From Pusey and Caldwell 1904)

Taylor, Witherbee, and Murphy's publication in 1918 presented the first systematic analysis of the effects of radiation on the blood with more precise dose definitions (Taylor et al. 1919). Their experiments showed that X-rays in large doses affect lymphocyte counts before any other circulating cells. They delineated a biphasic pattern in the kinetics of the lymphocyte counts after effects within multiple animal species, and noted that total (rather than

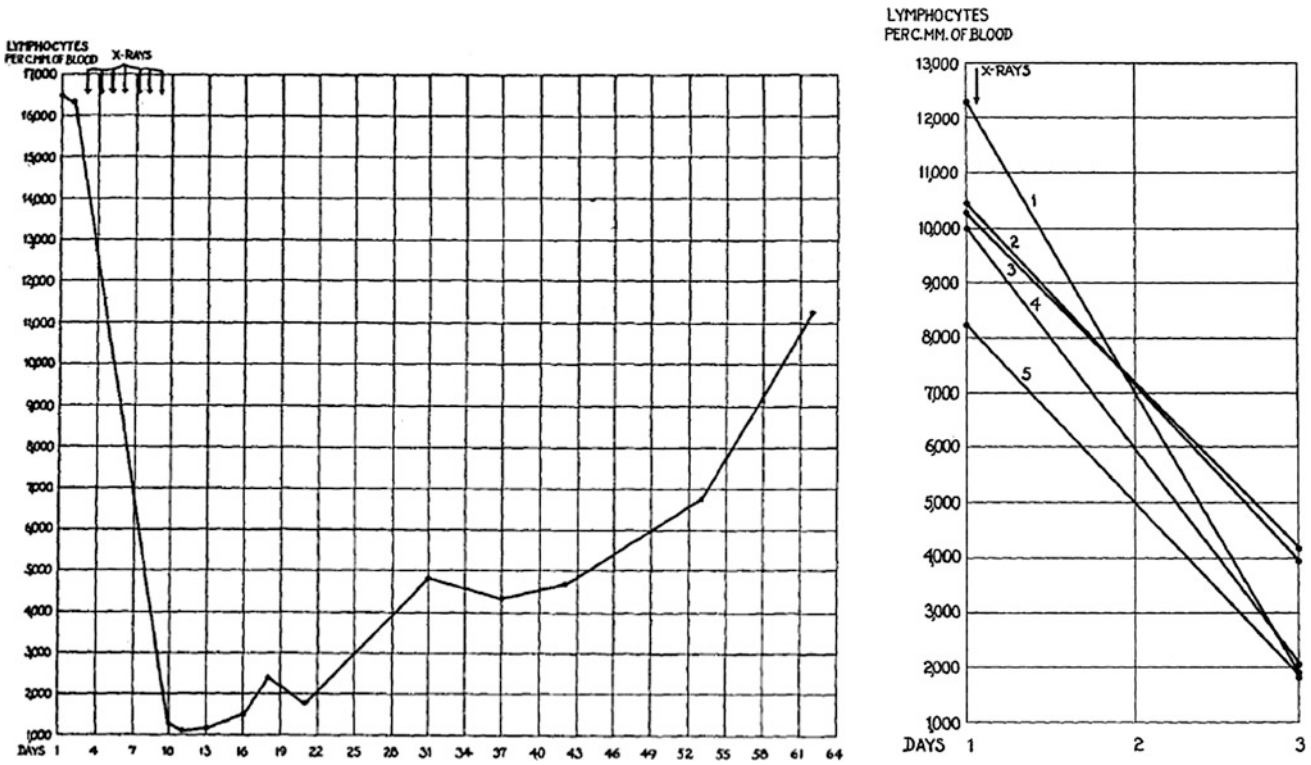


Fig. 6 First systematic analysis of lymphocyte kinetics after radiation exposure (from Taylor et al. 1919)

percentage) cell counts most accurately demonstrated the consistency of these quantitative effects (Fig. 6).

Murphy and Morton also noted in their early experiments (1915b) that although radiation at high doses produced a destructive effect on lymphocytes, low doses of radiation produced immunologically stimulatory effects (Taylor et al. 1919; Thomas et al. 1919). ln 1919 Thomas, Taylor and Witherbee systematically examined the effects of superficial (low penetration) X-ray and identified doses which produced a lymphocytosis (Fig. 7) (Thomas et al. 1919). In these experiments, the X-ray dose used was generated by a Coolidge tube and was of low penetration, with the spark-gap being under an inch. The use of a larger spark-gap with the same dose of X-rays did not lead to a lymphocytosis. The authors therefore deduced that the effect of radiation on the lymphoid organs is not the result of a direct action of the radiation, but rather is secondary to changes brought about either in the circulating blood or in the superficial tissues.

Further refinement in radiation techniques led to more precise radiation targeting, and it was noted that anatomic dose distributions influenced the immunological effects of irradiation. In 1964, Carston and Noonan demonstrated that the depression in leukocyte levels after whole body radiation was more severe and prolonged than after a lethally equivalent exposure of the upper or lower body. These results demonstrated that the severity of lymphocyte depression after partial-body exposures was consistent with either a direct effect on circulating lymphocytes or abscopal effects.

Based on observations of immunological changes in Hodgkins disease patients receiving total lymphoid irradiation (TLI) at Stanford Hospital during the 1960s, Samuel Strober, in collaboration with Henry Kaplan, hypothesized that this form of radiation could be especially therapeutically beneficial in the newly pioneered field of transplantation and for treating life threatening autoimmune conditions. Their work demonstrated that the functional character of immune reactions could be influenced and manipulated with rational radiation field design. In their 1976 Science paper, they demonstrated that lymphocyte-mediated rejection of allogeneic skin grafts could be abrogated by the selectively immunosuppressive effects of TLI (Slavin et al. 1976). These results were among the first to demonstrate that radiation could be used to therapeutically redirect, rather than to simply inhibit or suppress the immune system.

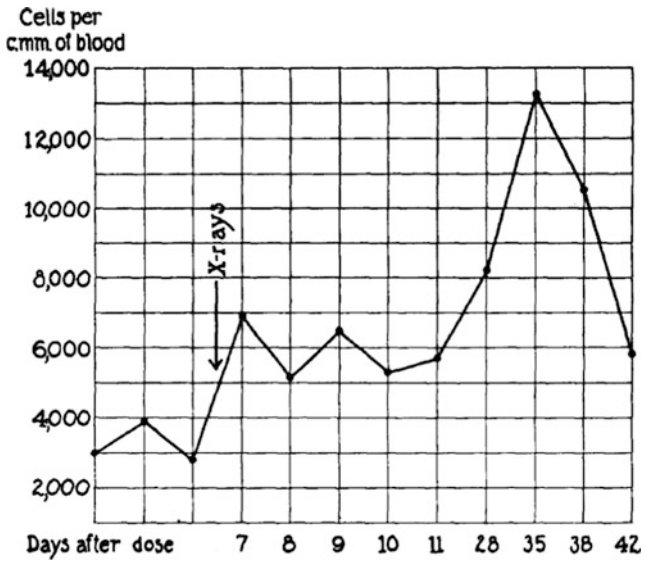


Fig. 7 First systematic analysis of lymphocytosis after low dose radiation exposure (from Thomas et al. 1919)

8.2 Literature Landmarks

1906 Warthin: Described the reduction of lymphoid tissue and fatty degenerative changes in lymph nodes of patients treated with radium.

1924 Jolly: Recorded changes in lymph nodes following irradiation of the knee nodes of rabbits similar to those described in whole-body irradiation.

1940 Sugarbaker and Sugiura: Noticed a slight increase in lymphatic permeability immediately after irradiation.

1948 DeBruyn: Followed sequentially the histologic effect on lymphoid tissue of total body irradiation with 600 R in rats.

1957 Treves: Presented a most detailed evaluation of the etiological factors of lymphedema following radical mastectomy.

1964 Engeset: Did an excellent and thorough review of the literature with meticulous and beautiful experimentation on irradiation of lymph nodes and vessels in rats, with important clinical implications for prophylactic preoperative irradiation of lymph nodes.

1966 Micklem and Loutit: Presented a well written statement of current views on radiation chimera, secondary disease and experimental application of total body irradiation as a method to study the immunologic mechanisms in tissue transplantation.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

2003 Trotti and Rubin: Modified and developed the Common Toxicity Criteria CTC V3.0 which applied similar scales to grade adverse effects of all major modalities—surgery and chemotherapy in addition to irradiation.

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