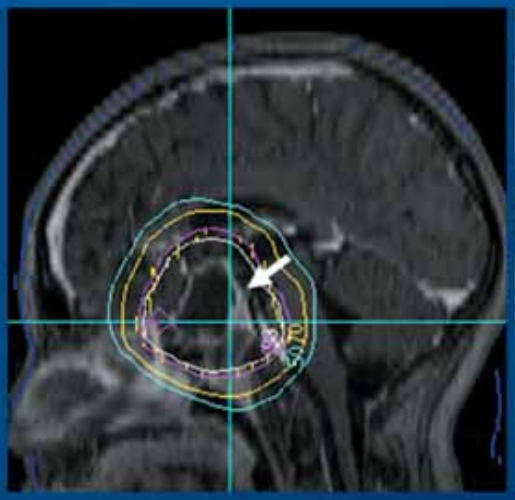
CINDY L. SCHWARTZ
WENDY L. HOBBIE
LOUIS S. CONSTINE
KATHLEEN S. RUCCIONE
Editors

Survivors of Childhood and Adolescent Cancer

PEDIATRIC ONCOLOGY



A Multidisciplinary Approach

Springer

Cindy L. Schwartz · Wendy L. Hobbie
Louis S. Constine · Kathleen S. Ruccione
(Eds.)

Survivors of Childhood and Adolescent Cancer

A Multidisciplinary Approach

Second Edition

With 49 Figures and 61 Tables

Springer

Cindy L. Schwartz
The Sidney Kimmel Cancer Center
at Johns Hopkins
Johns Hopkins Hospital
600 North Wolfe Street
Baltimore, MD 21287-5001
USA
Phone: 410-955-7385
E-mail: schwaci@jhmi.edu

Wendy L. Hobbie
Childrens Hospital of Philadelphia
Division of Oncology
34th St. & Civic Ctr. Blvd.
Philadelphia, PA 19104
USA
E-mail: hobbie@email.chop.edu

Louis S. Constine
University of Rochester Medical Center
Radiation Oncology and Pediatrics
601 Elmwood Avenue/Box 647
Rochester, NY 14642
USA
E-mail: louis_constine@urmc.rochester.edu

Kathleen S. Ruccione
Childrens Hospital Los Angeles
Center for Cancer and Blood Diseases
4650 Sunset Boulevard
Los Angeles, CA 90027
USA
E-mail: kruccione@chla.usc.edu

Library of Congress
Control Number 2005920312
ISBN 3-540-40840-1
Springer Berlin Heidelberg New York
ISSN 1613-5318

Originally published in 1994 by Mosby-Year Book, Inc.,
St. Louis, Missouri, USA
Title: Survivors of Childhood Cancer:
Assessment and Management

Medical Editor: Dr. Julia Heidelmann, Heidelberg, Germany
Desk Editor: Meike Stoeck, Heidelberg, Germany
Cover design: Erich Kirchner, Heidelberg, Germany
Layout: Bernd Wieland, Heidelberg, Germany
Production: Marina Litterer, ProEdit GmbH,
Heidelberg, Germany
Reproduction and typesetting: AM-productions GmbH,
Wiesloch, Germany

21/3150 – 5 4 3 2 1 0
Printed on acid-free paper

Dedication

To the memory of those children
for whom our knowledge
was insufficient;
to those children who have been cured
but must approach adult life
with the residua of treatment;
and to the children of the future
who will benefit from scientific advances
that may limit
treatment toxicity
so as to truly approachre cure.

Foreword

It was not long ago that clinicians would say, "study the late complications of cancer treatments we give to children? You must be joking! We can start worrying about that when we start curing them! Meanwhile, cure must be our only aim." These practitioners were only partially correct in what seemed to be a glaring truth, for, in fact, increasing numbers of children were beginning to survive their malignancy, and the long-term consequences of therapy would soon become critical.

It is well to remember that the delayed consequences of a cancer treatment delivered to developing organisms were first studied long ago. It has been 100 years since Perthes reported in 1903 that growth was impaired in juvenile creatures (chicks) that were irradiated [6]. During radiation therapy, strategies to circumvent this problem were set in motion, with the judicious placement of treatment fields as a first step [5].

It was not, however, until the 1940s that chemical agent-induced remissions of childhood leukemia and responses of solid tumors, such as nephroblastoma, were reported [2,3]. The focus, nonetheless, remained the same, and rightly so: namely, finding how best to integrate surgery, radiation and, later, chemotherapy in ways that would *cure* cancer. As strides were made with increasingly successful combined modality regimens, short-term toxicities began to become the object of study, and soon they were identified. Continued advances in treatment resulted in dramatic increases in long-term survival, drawing attention to late effects.

The first large-scale meeting to deal with issues related to toxicity was convened by the National Cancer Institute in 1975 [7]. Pediatric oncology had not been idle prior to this, of course, as several papers presented at the 1975 meeting revealed. Among them was one based on data collected by the Late Effects Study Group, an international consortium that consisted initially of five, then ten, pediatric centers. This was the first large scale, cooperative unit of its kind, organized specifically for the purpose of studying the late effects of cancer therapy (the study of delayed complications had been included as part of the original design in the National Wilms Tumor Study launched in 1969) [1]. These historical notes demonstrate that the epidemiologic, statistical and record-keeping mechanisms necessary for studying long-term survivors effectively were in the process of being established decades before the meeting in 1975.

History is fine, but one may still wonder: why should we study the late effects that might follow treatment of children 30 years ago? Those treatments are now antiquated, if not obsolete. The answer is that these patients must be followed for a lifetime to ascertain the true late effects of their therapies, and this is important regardless of what is being used today. The reason is because, even though treatments have been refined, it does not follow that the lower doses of radiation therapy or of the various chemotherapeutic agents currently used are free of potential late effects. Consider the cardiotoxic anthracyclines, for example. While it is true that no congestive heart failure excesses have been noted in patients given the current low doses of doxorubicin specified in certain current Wilms tumor treatment regimens [4], the follow-up of these patients is relatively short, a maximum of twenty years. What will happen in the next twenty years? Will 40-, 50- and 60-year olds who received therapy decades before show latent damage?

The evolution of late effect studies has been extremely useful in working out in considerable detail

practical and efficient research methods and techniques. Just as the treatments used in the past and those currently used have benefited from the early studies, so, too, will future treatments benefit from current studies. It is very likely that in the future many of the therapies will be completely new or very different from any currently in the armamentarium. The established epidemiologic and statistical techniques used to measure outcomes, and the means of tracking long-term survivors for late follow-up examinations, will be invaluable as the years roll by. For, no matter how new the treatments, it is likely that there will always be side effects, at least until the ultimate discovery of the "magic bullets" that affect singularly and precisely only the malignant cells, leaving nearby normal cells unscathed.

Let us not lose sight of the reason these studies are pursued: it is to inform the survivors themselves and their families of what to expect as the years go by. This volume brings together relevant invaluable material in a practical, easily understood form, with information extracted from the thousands of articles dealing with the chronic adversities of therapy. A recent survey showed that more than twenty-five hundred articles concerned with late effects have been published in the last five years alone. The readers of this volume, therefore, owe the editors a debt of gratitude for enlisting the multi-disciplinary array of contributing authors. Physicians, nurses, experts from other professions and lay persons all have assisted in condensing and bringing order out of this very complex matrix of information. These outstanding authorities offer up-to-date information on many different topics related to the late effects of juvenile cancer treatments. Together, they afford the reader a comprehensive, definitive overview of this compelling aspect of pediatric oncology.

The ultimate goal of pediatric oncology has been – and remains – to ensure not only the health, but also the psychosocial and economic well-being of children cured of malignant diseases. Parents have questions concerning all these issues, and what the future holds for their sons and daughters. So do the young men and women who themselves were treated successfully for cancer years before.

This book provides answers to their many questions.

Giulio J. D'Angio, MD
Hospital of the University of Pennsylvania,
Radiation Oncology, 2 Donner Building,
3400 Spruce Street, Philadelphia, PA 19104–4238

References

1. Evans AE, Norkool P, Evans I, Breslow N, D'Angio GJ. Late effects of treatment for Wilms tumor. A report from the National Wilms Tumor Study Group. Cancer 1991; 67:331–336
2. Farber S, Diamond LK, Mercer RD, et al. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). NEJM 1948; 328:787–793
3. Farber S, Toch R, Sears EM, Pinkel D. Advances in chemotherapy in cancer in man. Adv Cancer Res 1956; 4:1
4. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms tumor. A report from the National Wilms Tumor Study Group. J Clin Oncol 2001; 19:1926–1934
5. Neuhauser, EBD, Wittenborg MH, Berman CZ, Cohen J. Irradiation effects of roentgen therapy on the growing spine. Radiology 1952; 59:637–650
6. Perthes G. Ueber den Einfluss der Roentgen-Strahlen auf epithelial Gewebe insbensondere auf das Carcinom. Archiv Fuer Klinische Chirurgie 1903; 71:955–982
7. Proceedings of the National Cancer Institute Conference on the Delayed Consequences of Cancer Therapy. Proven and Potential. Cancer 1976; 37:999–1936

Acknowledgements

Ten years ago we embarked on the mission of creating a text that would foster a more complete understanding of the long-term toxicity of cancer therapy. Although progress has been impressive in the last decade, and long-term survivorship programs have been established at most pediatric oncology institutions, we still are on a journey toward the goal of optimizing the quality of survival for children with cancer.

Our personal families have matured in the years since the first edition was written. The joy we receive from observing the achievements of our children (Jaffa, Adam, Tali, Jonathan, Sarah, Alysia, Joshua and Daniel) encourage our work to provide all children with the chance for a healthy life, filled with opportunity. Our spouses (Howard, Danny and Sally) continue to be the unwavering supports that have enabled this work to proceed. As we have struggled to nurture our children, we are also even more appreciative of the role our own parents (Ruth, Jerry, Catrine, Michael, Mike, Nancy and Louis) have played in our efforts to reach our goals.

Indeed, it is often parents who are the greatest advocates for their children, and this is particularly true for children with cancer. We may provide advice, but it is they who sit at the bedside after hours during the child's therapy, and it is they who, once the child is cured, help him or her tackle the world. Their success is now visible in the new cohort of advocates: the survivors themselves. One in 500 young adults had cancer before the age of 20. These young adults not only support each other, they work together to ensure an even better future for those now affected.

In the previous edition we thanked our own mentors for teaching us the importance of long-term survivorship and for supporting our efforts. Just as parents nurture their children and are proud to watch them engage the future, we are proud to acknowledge our appreciation of the many young physicians, nurses, social workers and others who are focused on improving the lives of survivors of childhood and adolescent cancer. We hope that this second edition of our text will provide them with the background to achieve even greater success. With their collective intelligence, dedication and caring, we know that children diagnosed with cancer in the next era can look forward to happier and more productive lives than ever before.

Contents

Contributors

David Abramson M.D., F.A.C.S.
Clinical Professor of Ophthalmology
Weill Cornell Medical Center
New York-Presbyterian Hospital, 70 East 66th Street
New York, NY 10021, USA

M. Jacob Adams MD, MPH
Assistant Professor of Community
and Preventive Medicine
The University of Rochester School of Medicine
and Dentistry, 601 Elmwood Avenue
Box 644, Rochester, NY 14642, USA

Tithi Biswas
Department of Radiation Oncology
University of Rochester School of Medicine
and Dentistry, Strong Memorial Hospital/
The University of Rochester Medical Center
601 Elmwood Avenue, Box 647, Rochester
NY 14642, USA

Nancy Bunin
Professor of Pediatrics
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399, USA

Yuhchyau Chen
Associate Professor of Radiation Oncology
University of Rochester School of Medicine
and Dentistry, Strong Memorial Hospital/
The University of Rochester Medical Center
601 Elmwood Avenue, Box 647, Rochester
NY 14642, USA

Louis S. Constine MD
Professor of Radiation Oncology and Pediatrics
University of Rochester School of Medicine
and Dentistry, Strong Memorial Hospital/
The University of Rochester Medical Center
601 Elmwood Avenue, Box 647, Rochester
NY 14642, USA

Matthew R. DiCaprio MD
Department of Orthopedics
University of Florida Health Science Center
Gainesville, Florida, USA

Constance DiDomenico MSN, CRNP
Professor of Pediatrics
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399, USA

Sarah A. Duffy MS
Senior Research Associate
Department of Pediatrics, University
of Miami School of Medicine, P.O Box 016820
Miami, Florida 33101, USA

Debra A. Eshelman RN, MSN, CPNP
University of Texas Southwestern Medical Center
at Dallas, TX, and Children's Medical Center
Dallas, TX, the After the Cancer Experience (ACE)
Young Adult Program, 6263 Harry Hines Blvd.
Dallas, TX 75390-9067, USA

Debra L. Friedman
Children's Hospital and Regional
Medical Center
Assistant Professor
Children's Hospital & Regional Medical Ctr
4800 Sand Point Way NE; Mailstop 6d-1
Seattle, WA 98105, USA

Kathy Gamble RN
Pediatric Hematology/Oncology
University of Florida Health Science Center
Gainesville, Florida, USA

Jill P. Ginsberg MD
Children's Hospital of Philadelphia
34th & Civic Center Blvd.
4th Floor, Wood Building
Philadelphia, PA 19104, USA

Virginia Guzikowski MSN, CRNP
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399, USA

Barbara Anne Hieb MSN, CRNP
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399, USA

Andrea S. Hinkle MD
Division of Pediatric Hematology/Oncology
Golisano Children's at Strong
University of Rochester Medical Center
Box 777, 601 Elmwood Ave
Rochester, NY 14642, USA

Wendy L. Hobbie
Children's Hospital of Philadelphia
Division of Oncology
34th St. & Civic Ctr. Blvd.
Philadelphia, PA 19104, USA

Barbara Hoffman, J.D.
9 Madison Drive, Princeton Junction
NJ 08550, USA

Della Howell MD
Department of Pediatrics
Division of Hematology/Oncology
Emory University and Children's
Healthcare of Atlanta, Atlanta, GA 30322, USA

Melissa Hudson
St. Jude Children's Research Hospital Memphis
Pediatric hematology/oncology
332 North Lauderdale Street
Memphis, Tn 38105, USA

Anne E. Kazak PhD, ABPP
Childrens Hospital of Philadelphia
Division of Oncology
324 South 34th Street
Philadelphia, PA 19104, USA

Mary Koshy MD
Department of Radiation Oncology
Emory University and Emory Clinic
Atlanta, GA 30322, USA

Wendy Landier RN, MSN, CPNP, CPON
Pediatric Nurse Practitioner
City of Hope National Medical Center, Duarte
California, Assistant Clinical Professor
UCLA School of Nursing, Los Angeles
California, 1500 E. Duarte Rd., MOB-4, Duarte
CA 91010-3000, USA

Dieter M. Lindskog MD
Department of Orthopedics
University of Florida Health Science Center
Gainesville, Florida, USA

Steven E. Lipshultz MD
Professor and Chairman of Pediatrics
Professor of Public Health and Epidemiology
Professor of Medicine, University of Miami School of Medicine, P.O Box 016820
Miami, Florida 33101, USA

Wing Leung
St. Jude Children's Research Hospital Memphis
Hematology/Oncology
332 North Lauderdale Street
Memphis, Tn 38105, USA

Nina S. Kadan-Lottick MD, MSPH
Assistant Professor, Pediatrics Department
of Pediatrics, Section of Pediatric Hematology-Oncology, Yale University School of Medicine
333 Cedar St, LMP 2073, New Haven, CT 06520

Amit Maity MD
Department of Radiation Oncology
Hospital of the University of Pennsylvania
195 John Morgan Building
University of Pennsylvania School of Medicine
3620 Hamilton Walk
Philadelphia, PA 19104, USA

Robert B. Marcus, Jr. MD
Department of Radiation Oncology
Emory Healthcare, 1365 Clifton Road
Atlanta, GA 30322, USA

Lawrence Marks MD
Box 3085 Duke Univ Med Ctr
Durham NC 27710, USA

Brian E. McGrath MD
Department of Orthopedics
State University of New York at Buffalo
100 High Street, Buffalo, NY 14203, USA

Anna T. Meadows MD
Children's Hospital of Philadelphia
34th & Civic Center Blvd.
4th Floor Wood Building
Philadelphia, PA 19104, USA

Thomas E. Merchant DO, PhD
Chief, Division of Radiation Oncology
Department of Radiologic Sciences
St. Jude Children's Research Hospital
Memphis, Tennessee, 332 North Lauderdale Street
Memphis, TN 38105, USA

Ann Mertens PhD
Department of Pediatrics
University of Minnesota
MMC 715, 420 Delaware St, SE,
Minneapolis, MN 55455, USA

Joseph P. Neglia MD
Division of Pediatric Hem/Onc
Room D 557 Mayo Bldg./MMC 484
420 Delaware St., SE
Minneapolis, MN 55455, USA

Michael Ober MD
(e-mail: obermike@aol.com)
Fellow, Vitreo-Retinal Surgery
Columbia College of Physicians
and Surgeons, Edward S. Harkness Eye Institute
635 West 165th Street, New York, NY 10032, USA

Kevin C. Oeffinger MD
Department of Family Practice and Community Medicine, University of Texas Southwestern
Medical Center at Dallas, 6263 Harry Hines Blvd.
Dallas, TX 75390-9067, USA

Susan K. Ogle MSN, CRNP
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399, USA

Arnold C. Paulino MD
Department of Radiation Oncology, A1300
1365 Clifton Road, N.E., Atlanta, GA 30322, USA

Cindy Proukou RN, CPNP
Special Care Nursery
Highland Hospital
1000 South Avenue
Rochester, NY 14620, USA

Susan R. Rose MD
Professor of Pediatrics and Endocrinology
Cincinnati Children's Hospital Medical Center
and University of Cincinnati
3333 Burnet Avenue
Cincinnati, Ohio 45229-3039, USA

Mary T. Rourke PhD
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399, USA

Kathleen S. Ruccione MPH, RN
Childrens Hospital Los Angeles
Center for Cancer and Blood Diseases
4650 Sunset Boulevard
Los Angeles, CA 90027, USA

Mark Scarborough MD
Department of Orthopedics
University of Florida Health Science Center
Gainesville, Florida, USA

Cindy L. Schwartz MD
The Sidney Kimmel Cancer Center
at Johns Hopkins
Johns Hopkins Hospital
600 North Wolfe Street
Baltimore, MD 21287-5001, USA

Camille A. Servodidio RN, MPH
70 East 66th Street, New York, NY 10021, USA

Yutaka Yasui PhD
Cancer Prevention Research Program
Division of Public Health Sciences
Fred Hutchinson Cancer Research Center
P.O. Box 19024, 1100 Fairview Ave. N., MP702
Seattle, WA 98109-1024, USA

Overview

Cindy L. Schwartz · Wendy L. Hobbie · Louis S. Constine · Kathleen S. Ruccione

In the 21st century, most children and adolescents with cancer can be cured. This resounding success story has been written over the past several decades by visionary pediatric oncology care providers and researchers, together with courageous patients and families. Today, because more than three quarters of young people with cancer survive, the population of childhood and adolescent cancer survivors is large and growing, with about 270,000 survivors of childhood cancer in the United States [1]. However, the sobering correlates of this success are the long-term consequences of therapy that can profoundly compromise quality of life and even survival. As more children with cancer survive, the obligation grows for the critical assessment of the adverse effects of therapy on the physical, intellectual, psychological and social development of these patients. The complexity of these adverse consequences demands involvement of a multidisciplinary team, ideally consisting of nurse practitioners, pediatric oncologists, radiation oncologists, and psychosocial personnel. In addition, the expertise of sub-specialists from related disciplines, such as cardiology, endocrinology, orthopedics, and pulmonary medicine, is vital to the success of the adult healthcare provider.

In 1990, when the first edition of this book was conceived, recognition of the need for organized, ongoing follow-up of cancer survivors was just emerging. Those healthcare providers responsible for hands-on care of the early survivors had to review the scant available literature and make individual judgments as to screening approaches. This state of affairs prompted our decision to compile a compendium of knowledge from a variety of experts, a "how to" guide, as it were, of assessment and management that would allow for the delivery of expert care throughout the pediatric oncology community and facilitate the development of long-term follow-up programs.

Fortunately, since the publication of the first edition, survivorship issues, both medical and psychosocial, have received increased attention. Three groups have played a major role in advancing the knowledge of the implications for child and adolescent survivorship over the past decade. The Office of Cancer Survivorship (OCS) (http://dccps.nci.nih.gov/ocs/), established in 1996 at the National Cancer Institute (NCI), has disseminated knowledge, supported survivorship research, and promoted the development of a cadre of young investigators dedicated to the needs of cancer survivors. The data that has emerged from the Childhood Cancer Survivor Study (CCSS) (http://www.cancer.umn.edu/ltfu) has recognized and substantiated the impact of cancer on the health and quality of life of approximately 15,000 childhood cancer survivors, mandating advocacy on their behalf. The Children's Oncology Group (COG) has similarly embraced the effort to assess long-term outcomes in the context of the COG therapeutic trials, working with the NCI to ensure that the new CTC-AE criteria that report toxicities of cancer therapy now include a specific section related to the effects of therapy on growth and development [2]. The *Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* were developed in 2003 [3], based upon evidence in the literature that linked exposures to particular late effects. The guidelines are available at www.survivorshipguidelines.org. They provide screening recommendations determined by the collective clinical experience of an expert panel

and are critical to providing a uniform approach to long-term surveillance, particularly in the context of the COG clinical trials. An analysis of the status of childhood cancer survivors by the National Cancer Advisory Board resulted in the 2003 publication, *Childhood Cancer Survivorship: Improving Care and Quality of Life*. This report, disseminated by the Institute of Medicine (IOM), was the result of a systematic review of the policy implications of the changing landscape of survivorship after cancer in childhood and adolescence. It addresses the needs for evidence-based follow-up guidelines for care, systems of care responsive to survivors' healthcare needs, survivor awareness of late effects, and professional education and training. It also focuses on strengthening public programs serving childhood cancer survivors, improving access to healthcare services, and increasing research on childhood cancer survivorship [4]. Two other recent publications also disseminate knowledge, define priorities and recommend strategies to ensure adequate resources for survivors [5, 6].

The purpose of our current book, *Survivors of Childhood and Adolescent Cancer: A Multi-disciplinary Approach*, is to update our understanding of the long-term consequences of cancer therapy and address issues related to pathophysiology, clinical manifestations, detection, screening and interventions. Providing this information necessary to assist in achieving recommendations of the IOM report.

Chapter 2 provides a compilation of algorithms specific for each of the common pediatric malignancies. Common treatments are noted, as well as late effects and screening methodologies.

Chapter 3, details the chronic effects by organ system, outlining suitable evaluations and management options. The chapter also lists the late effects, causative treatments, signs and symptoms, screening and diagnostic tests, and the management and intervention techniques. Our goal was to provide a concise yet comprehensive approach that facilitates care in the clinical setting.

Chapters 4–16 cover the side-effects of the treatment of specific organs and organ systems. A comprehensive approach is taken in each chapter, which addresses normal physiology, pathophysiology, treatment-specific effects, clinical manifestations and detection and screening, as well as the management of established problems.

Chapter 19, "Methodological Approach to Survivorship," describes the scientific approaches necessary to facilitate high-quality outcomes research.

Chapter 21 covers stem cell transplantation while chapter 18 reviews secondary malignance.

The provisions of psychosocial care and support for navigating the legal implications of cancer survivorship are essential components of any program and are addressed in Chapters 19 and 20. These chapters have been dramatically expanded based on the growing body of knowledge in this area over the past decade.

Chapter 22, "Transition Issues," was added in view of the fact that, a decade after our original book was published, many long-term survivors of childhood cancer are now adults and must obtain healthcare in the adult medical community. Healthcare models in various settings are examined, with an analysis of the benefits and difficulties involved in providing comprehensive care.

Survivorship care is a young science. Major progress has been made over the past decade, but much remains unknown about the future of the ever-enlarging, vulnerable and aging population of childhood cancer survivors. Although this book cannot describe every possible complication that may arise, we hope that the information we present will enable healthcare providers to better understand the etiology of late effects and to recognize the impact of childhood and adolescent cancer therapy. We hope to encourage systematic, thoughtful and risk-based approaches to treatment for both individuals and cohorts of survivors. Our goal, like that of Dr. D'Angio, is that "the children of today don't become the chronically ill adults of tomorrow" [7]. We look forward to the day when our understanding of the long-term consequences of therapy allows for mitigation in those already affected by therapy and prevention of injury in children who require treatment.

References

1. Ries LA, Eisner M, Kosary C et al (eds) (2002) SEER cancer statistics review, 1973–1999. National Cancer Institute, Bethesda MD
2. National Cancer Institute (2003) Cancer therapy evaluation program, common terminology criteria for adverse events v3.0 (CTCAE), accessed from the internet (http://ctep.cancer.gov/reporting/ctc.html), 1 July 2004
3. Landier W, Bhatia S, Eshelman D et al (2004) Development of risk-based guidelines for childhood cancer survivors: the children's oncology group long-term follow-up guidelines. J Clin Oncol (in press)
4. Institute of Medicine, National Research Council of the National Academies (2003) Childhood Cancer Survivorship: Improving Care and Quality of Life. The National Academies Press, Washington DC
5. Reuben SH for The President's Cancer Panel (2004) Living beyond cancer: finding a new balance, 2003–2004 annual report. National Cancer Institute, National Institutes of Health, Washington DC
6. Centers for Disease Control and Prevention and Lance Armstrong Foundation (2004) A national action plan for cancer survivorship: advancing public health strategies, Atlanta
7. D'Angio G (1975) Pediatric cancer in perspective: cure is not enough. Cancer Suppl 35:867–870

Algorithms of Late Effects by Disease

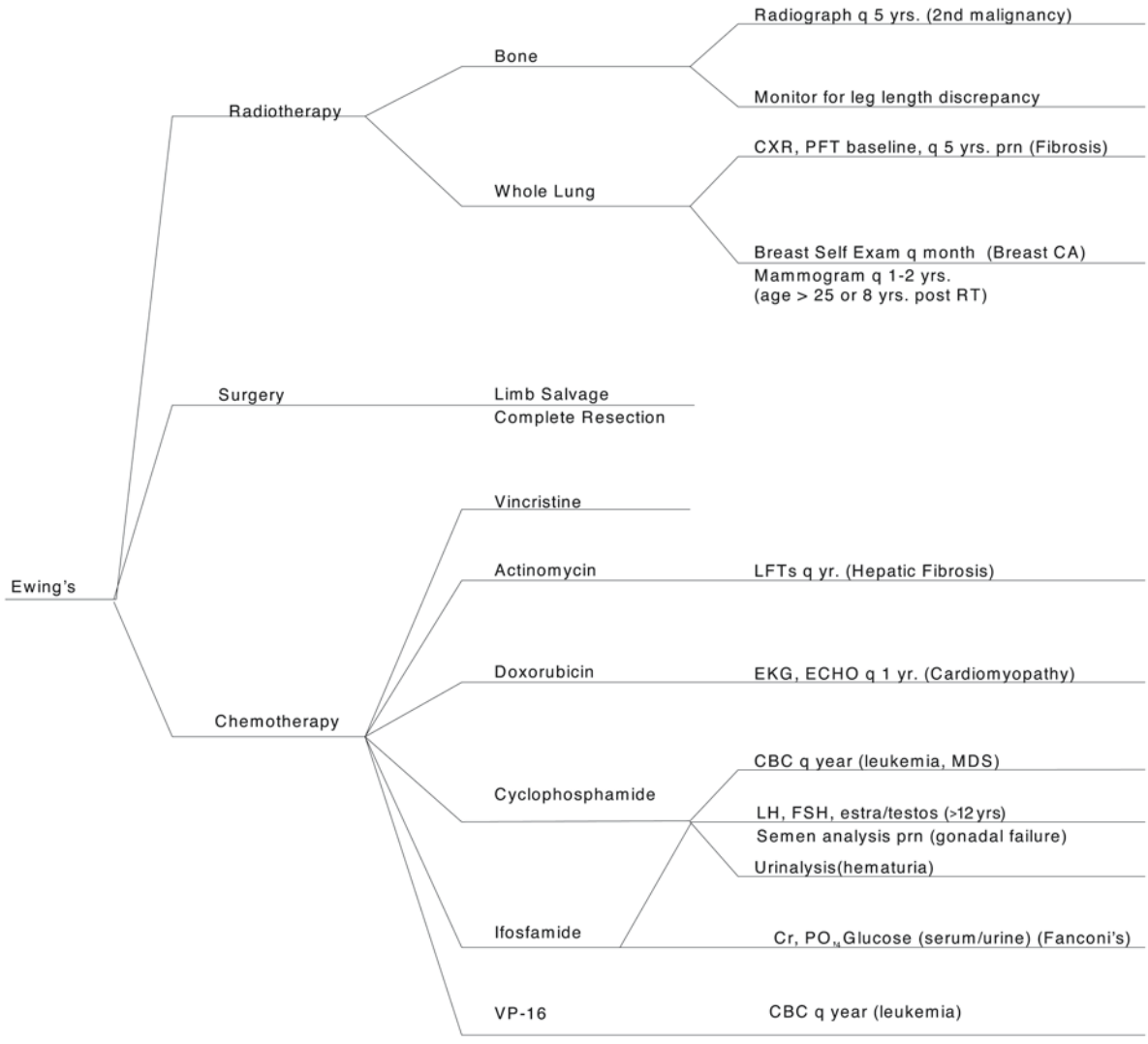
Cindy L. Schwartz · Wendy L. Hobbie · Louis S. Constine

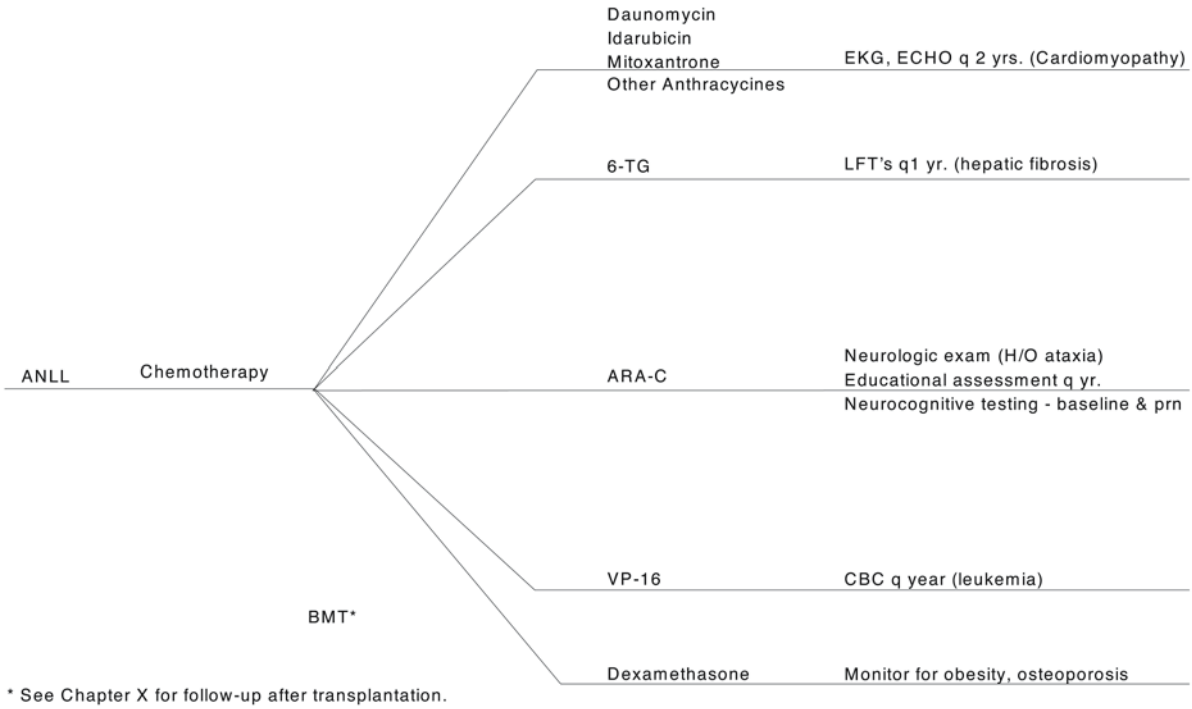
This chapter provides algorithms designed to facilitate understanding of subsequent chapters. By locating the tumor type, information can be accessed from the algorithms regarding standard tumor therapies, common late effects, and methods of detection. Since the algorithms are relatively inclusive, not all patients will have received all therapies. Availability of the treatment record can assist in determining potential risk and streamlining screening procedures.

Of course, the clinical acumen of the healthcare professional cannot be replaced by algorithms. The recommendations should be used only as guidelines to potential risks. Information provided in subsequent chapters regarding specific organs is intended to deepen the healthcare provider's understanding of the pathophysiology, manifestations and methods of detecting late effects.

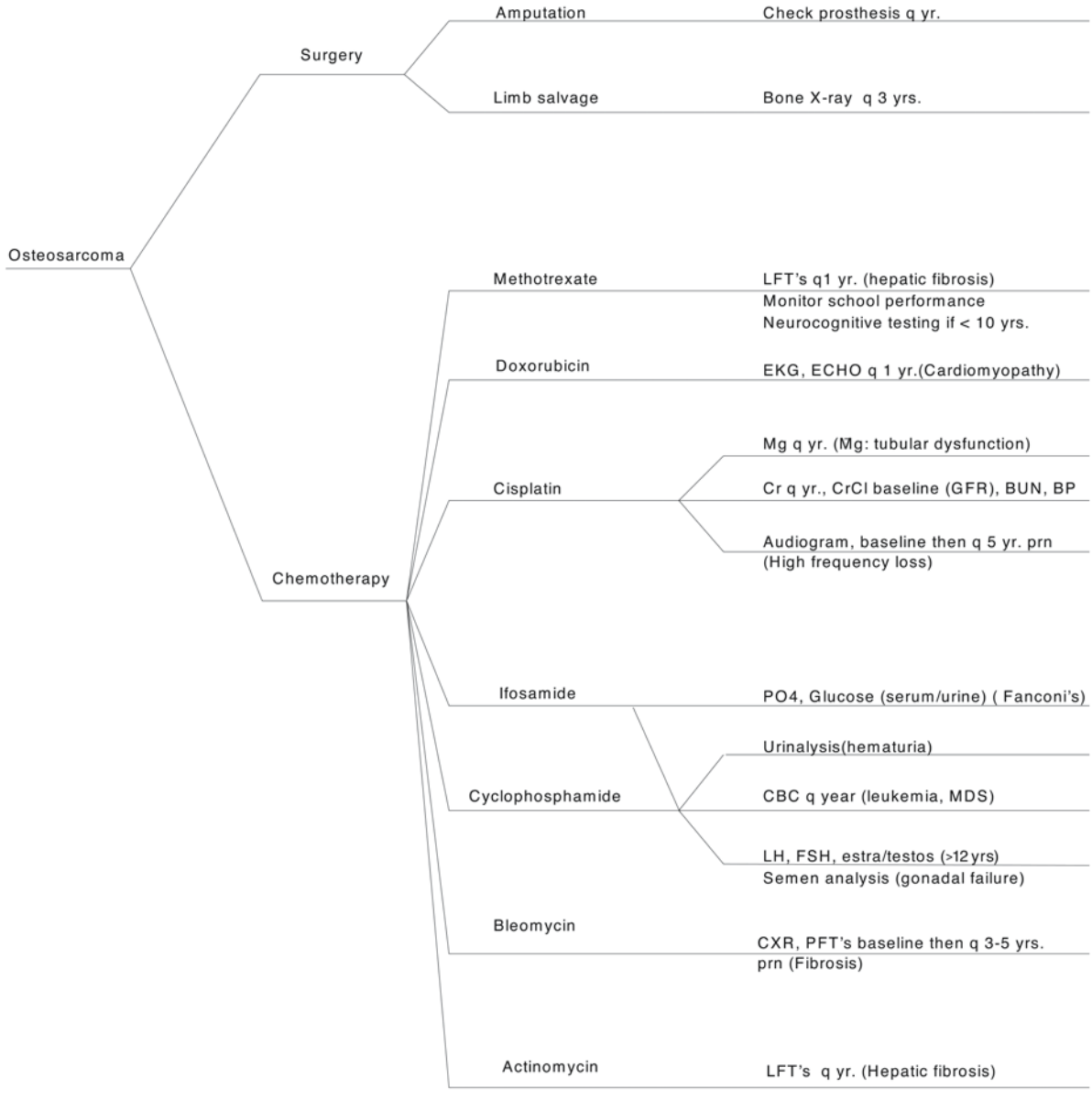
Abbreviations commonly used in the algorithms are listed below.

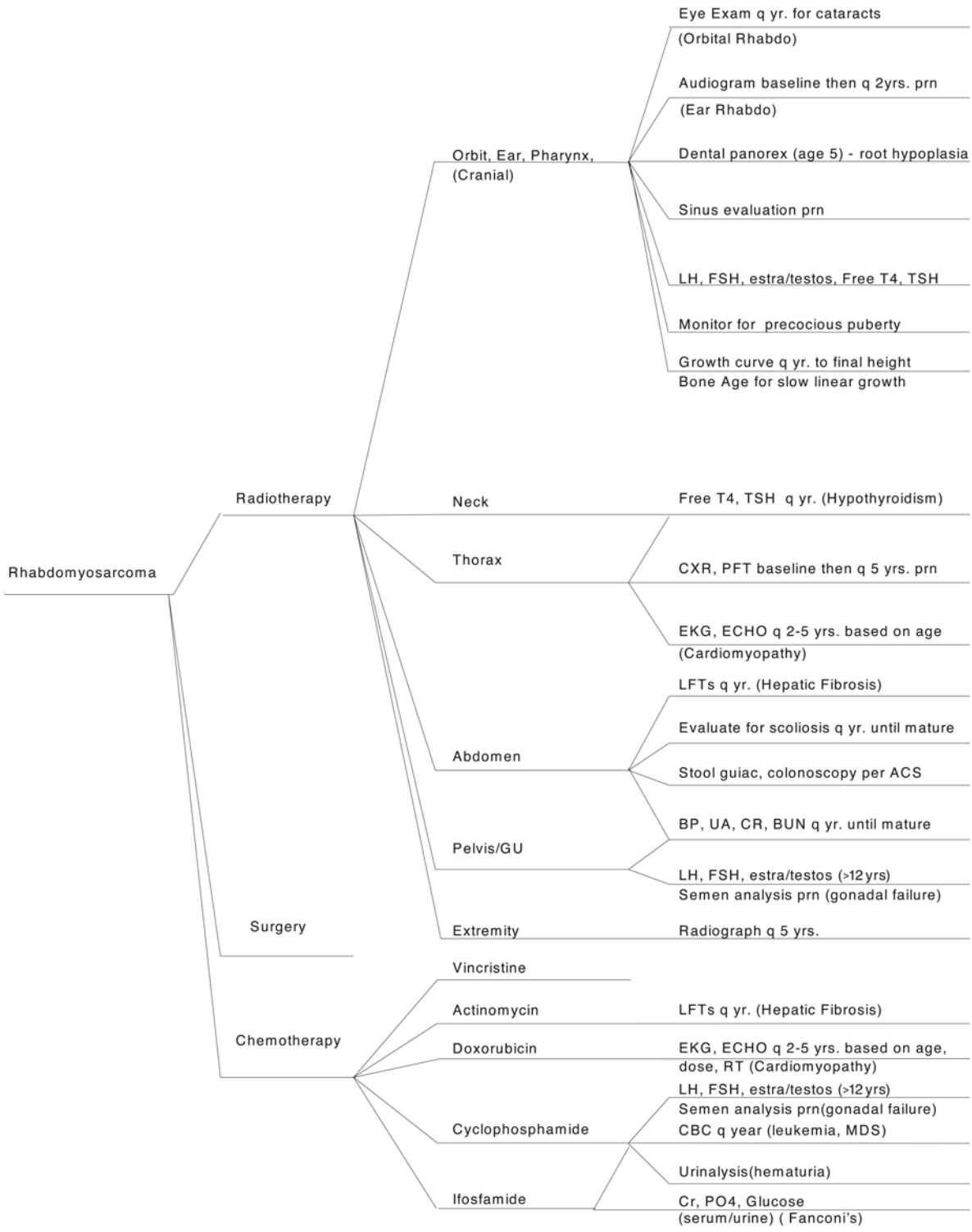
ACS	American Cancer Society
ALL	Acute lymphoblastic leukemia
ANLL	Acute nonlymphocytic leukemia
ARA-C	Cytosine arabinoside
BMT	Bone marrow transplant
BP	Blood pressure
BUN	Blood urea nitrogen
CA	Carcinoma
CBC	Complete blood count
CCNU	Chloroethyl cyclohexyl nitrosourea
BCNU	1, 3-Bis (2 chloroethyl-1 nitrosourea)
Cr	Creatinine
CrCl	Creatinine clearance
CXR	Chest radiograph
DTIC	Dacarbazine
ECHO	Echocardiogram
EKG	Electrocardiogram
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
GFR	Glomerular filtration rate
GU	Genitourinary
HiB	*Hemophilus influenzae* type B (vaccine)
H/P	Hypothalamic/pituitary
IT	Intrathecal
LFT's	Liver function tests
PFT's	Pulmonary function tests
PO_4	Phosphate
6-TG	Thioguanine
TSH	Thyroid-stimulating hormone
UA	Urinalysis
VP-16	Etoposide
Mg	Magnesium
HD	High Dose

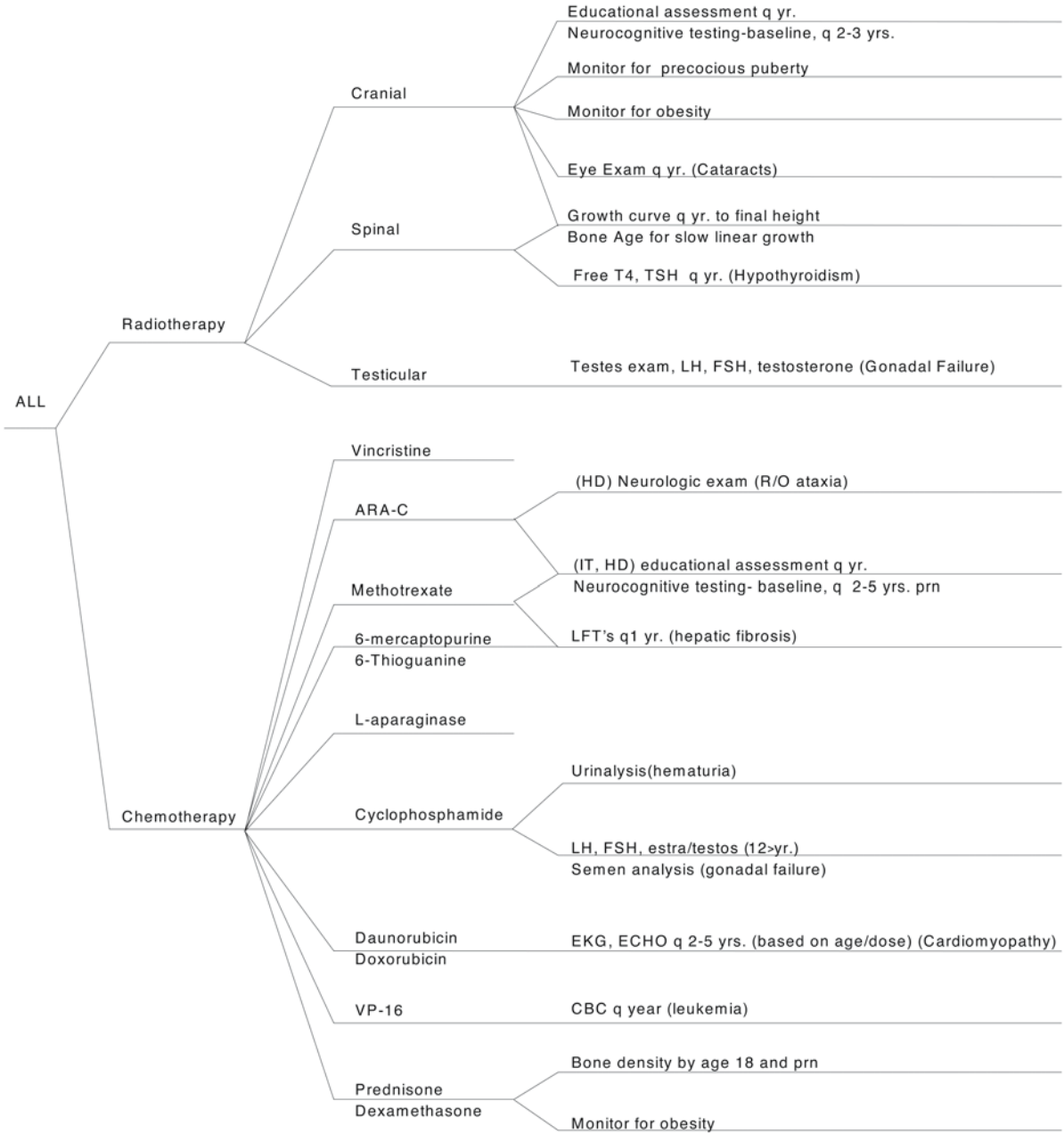

Ewing's
Radiotherapy
Bone
Radiograph q 5 yrs. (2nd malignancy)
Monitor for leg length discrepancy
Whole Lung
CXR, PFT baseline, q 5 yrs. prn (Fibrosis)
Breast Self Exam q month (Breast CA)
Mammogram q 1-2 yrs.
(age > 25 or 8 yrs. post RT)
Surgery
Limb Salvage
Complete Resection
Chemotherapy
Vincristine
Actinomycin
LFTs q yr. (Hepatic Fibrosis)
Doxorubicin
EKG, ECHO q 1 yr. (Cardiomyopathy)
Cyclophosphamide
CBC q year (leukemia, MDS)
LH, FSH, estra/testos (>12 yrs)
Semen analysis prn (gonadal failure)
Urinalysis(hematuria)
Ifosfamide
Cr, PO4, Glucose (serum/urine) (Fanconi's)
VP-16
CBC q year (leukemia)

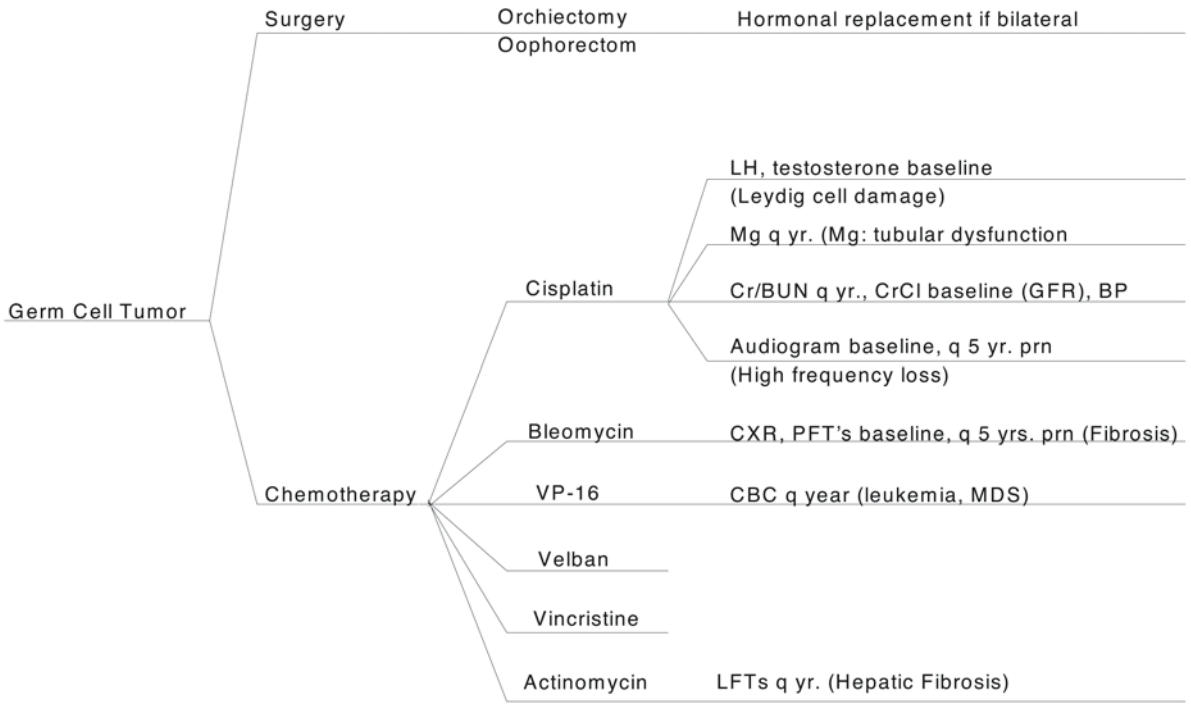


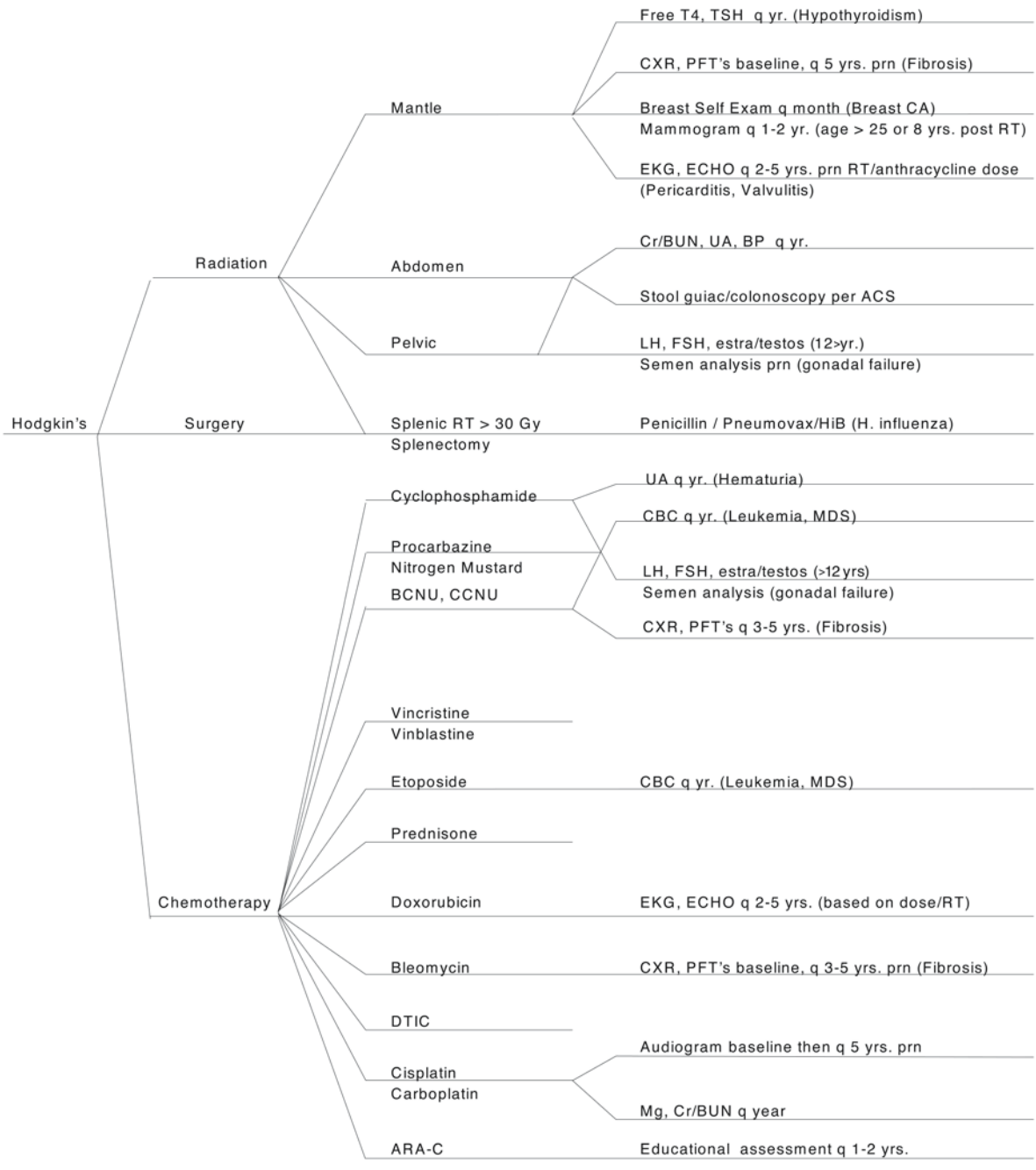
* See Chapter X for follow-up after transplantation.

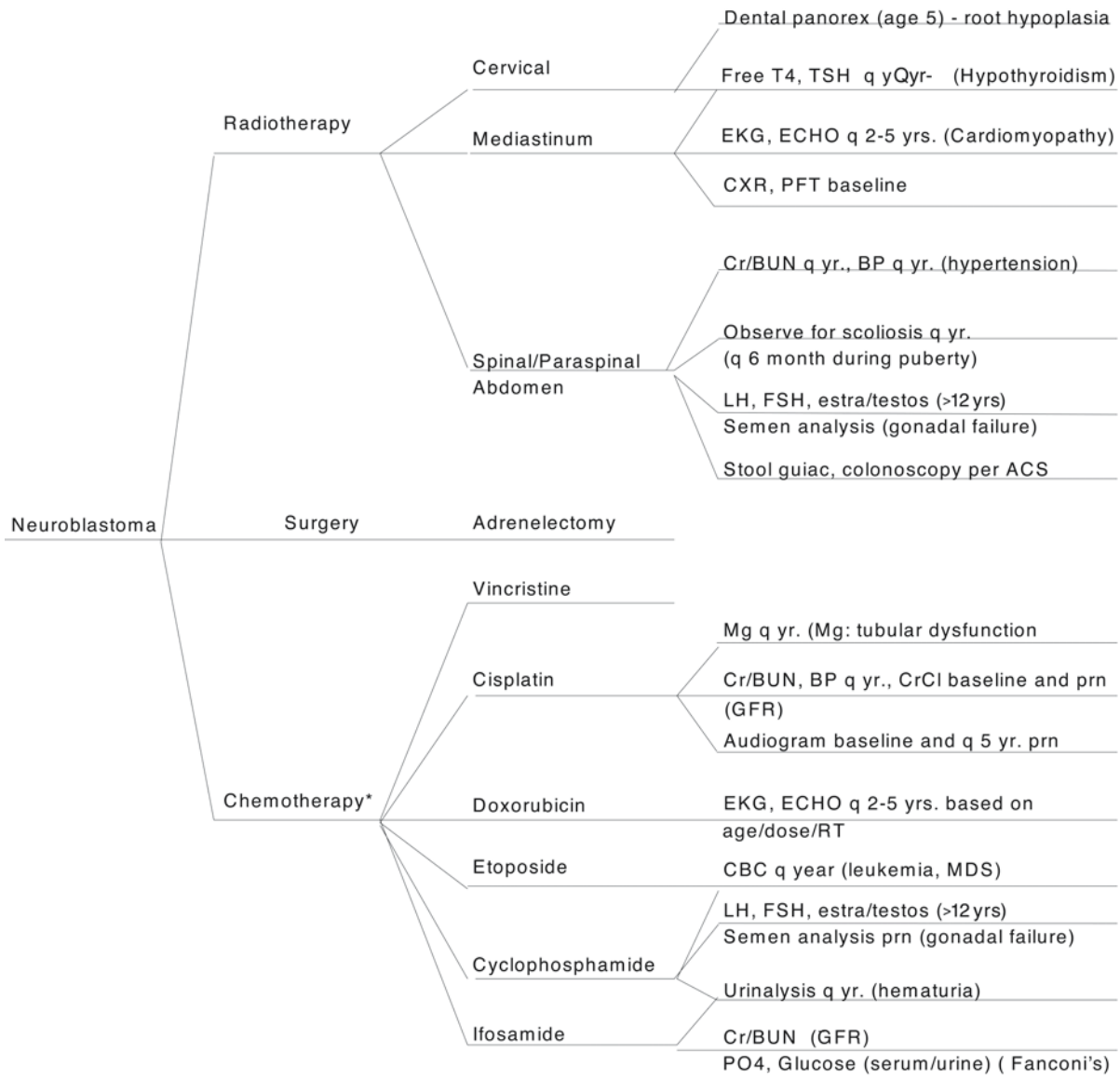

Osteosarcoma
Surgery
Amputation
Check prosthesis q yr.
Limb salvage
Bone X-ray q 3 yrs.
Chemotherapy
Methotrexate
LFT's q1 yr. (hepatic fibrosis)
Monitor school performance
Neurocognitive testing if < 10 yrs.
Doxorubicin
EKG, ECHO q 1 yr.(Cardiomyopathy)
Cisplatin
Mg q yr. (Mg: tubular dysfunction)
Cr q yr., CrCl baseline (GFR), BUN, BP
Audiogram, baseline then q 5 yr. prn
(High frequency loss)
Ifosamide
PO4, Glucose (serum/urine) (Fanconi's)
Cyclophosphamide
Urinalysis(hematuria)
CBC q year (leukemia, MDS)
LH, FSH, estra/testos (>12 yrs)
Semen analysis (gonadal failure)
Bleomycin
CXR, PFT's baseline then q 3-5 yrs.
prn (Fibrosis)
Actinomycin
LFT's q yr. (Hepatic fibrosis)


Rhabdomyosarcoma
Radiotherapy
Surgery
Chemotherapy
Orbit, Ear, Pharynx, (Cranial)
Neck
Thorax
Abdomen
Pelvis/GU
Extremity
Vincristine
Actinomycin
Doxorubicin
Cyclophosphamide
Ifosfamide
Eye Exam q yr. for cataracts
(Orbital Rhabdo)
Audiogram baseline then q 2yrs. prn
(Ear Rhabdo)
Dental panorex (age 5) - root hypoplasia
Sinus evaluation prn
LH, FSH, estra/testos, Free T4, TSH
Monitor for precocious puberty
Growth curve q yr. to final height
Bone Age for slow linear growth
Free T4, TSH q yr. (Hypothyroidism)
CXR, PFT baseline then q 5 yrs. prn
EKG, ECHO q 2-5 yrs. based on age
(Cardiomyopathy)
LFTs q yr. (Hepatic Fibrosis)
Evaluate for scoliosis q yr. until mature
Stool guiac, colonoscopy per ACS
BP, UA, CR, BUN q yr. until mature
LH, FSH, estra/testos (>12yrs)
Semen analysis prn (gonadal failure)
Radiograph q 5 yrs.
LFTs q yr. (Hepatic Fibrosis)
EKG, ECHO q 2-5 yrs. based on age,
dose, RT (Cardiomyopathy)
LH, FSH, estra/testos (>12yrs)
Semen analysis prn(gonadal failure)
CBC q year (leukemia, MDS)
Urinalysis(hematuria)
Cr, PO4, Glucose
(serum/urine) (Fanconi's)

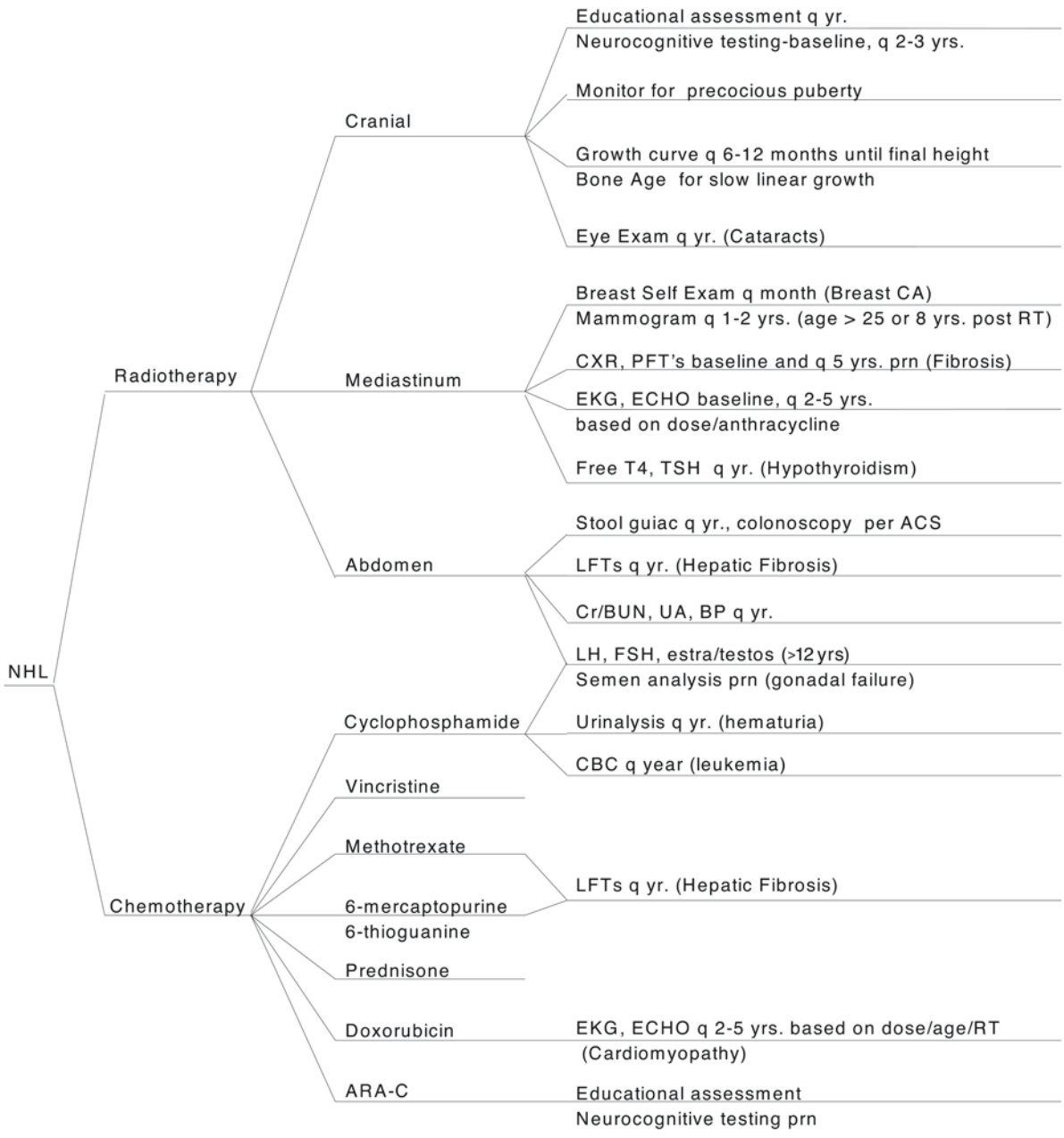

ALL
Radiotherapy
Cranial
Educational assessment q yr.
Neurocognitive testing-baseline, q 2-3 yrs.
Monitor for precocious puberty
Monitor for obesity
Eye Exam q yr. (Cataracts)
Spinal
Growth curve q yr. to final height
Bone Age for slow linear growth
Free T4, TSH q yr. (Hypothyroidism)
Testicular
Testes exam, LH, FSH, testosterone (Gonadal Failure)
Chemotherapy
Vincristine
ARA-C
(HD) Neurologic exam (R/O ataxia)
Methotrexate
(IT, HD) educational assessment q yr.
Neurocognitive testing- baseline, q 2-5 yrs. prn
6-mercaptopurine
6-Thioguanine
LFT's q1 yr. (hepatic fibrosis)
L-aparaginase
Cyclophosphamide
Urinalysis(hematuria)
LH, FSH, estra/testos (12>yr.)
Semen analysis (gonadal failure)
Daunorubicin
Doxorubicin
EKG, ECHO q 2-5 yrs. (based on age/dose) (Cardiomyopathy)
VP-16
CBC q year (leukemia)
Prednisone
Dexamethasone
Bone density by age 18 and prn
Monitor for obesity

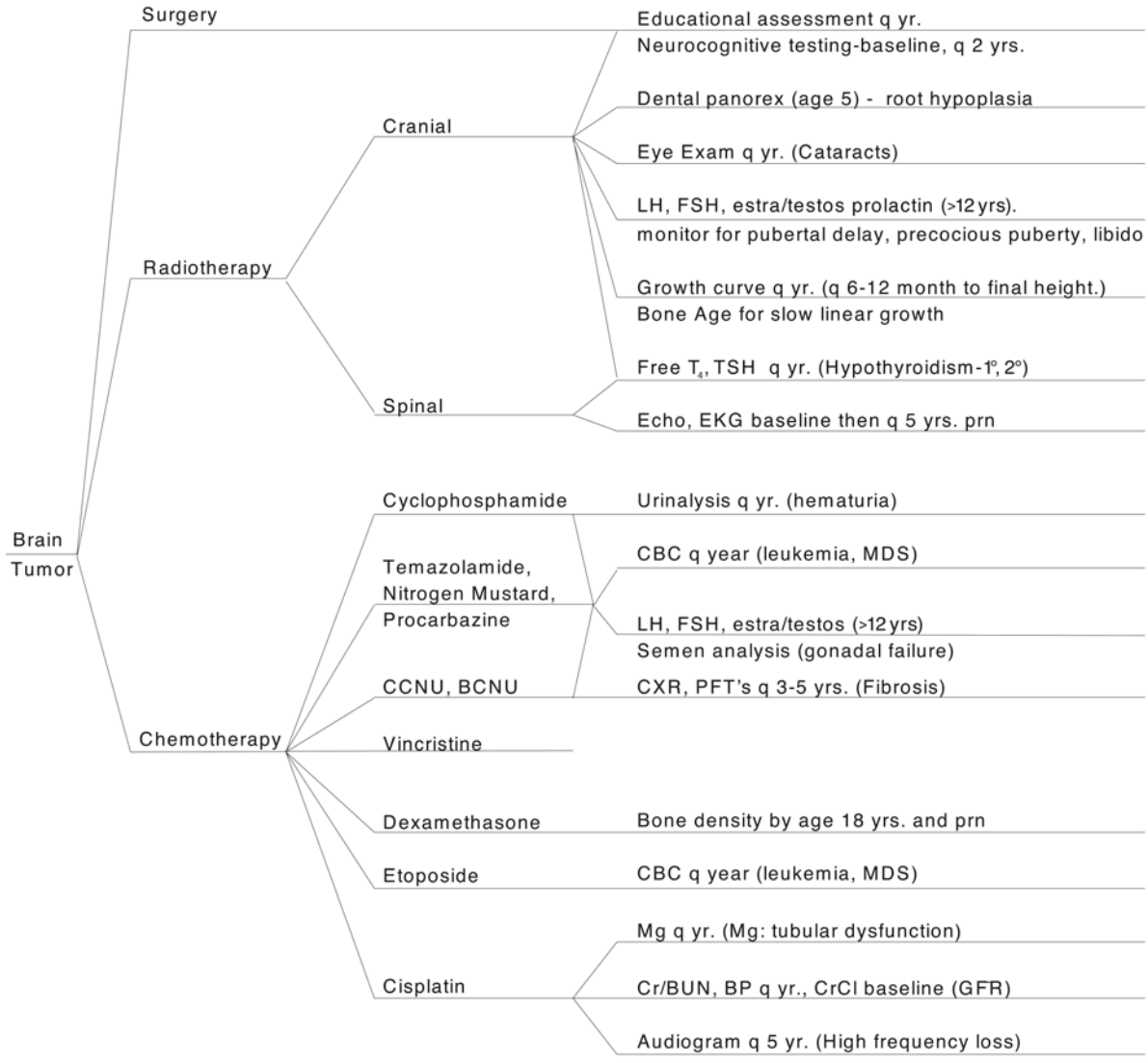

Germ Cell Tumor
Surgery
Orchiectomy
Oophorectom
Hormonal replacement if bilateral
Chemotherapy
Cisplatin
LH, testosterone baseline
(Leydig cell damage)
Mg q yr. (Mg: tubular dysfunction
Cr/BUN q yr., CrCl baseline (GFR), BP
Audiogram baseline, q 5 yr. prn
(High frequency loss)
Bleomycin
CXR, PFT's baseline, q 5 yrs. prn (Fibrosis)
VP-16
CBC q year (leukemia, MDS)
Velban
Vincristine
Actinomycin
LFTs q yr. (Hepatic Fibrosis)

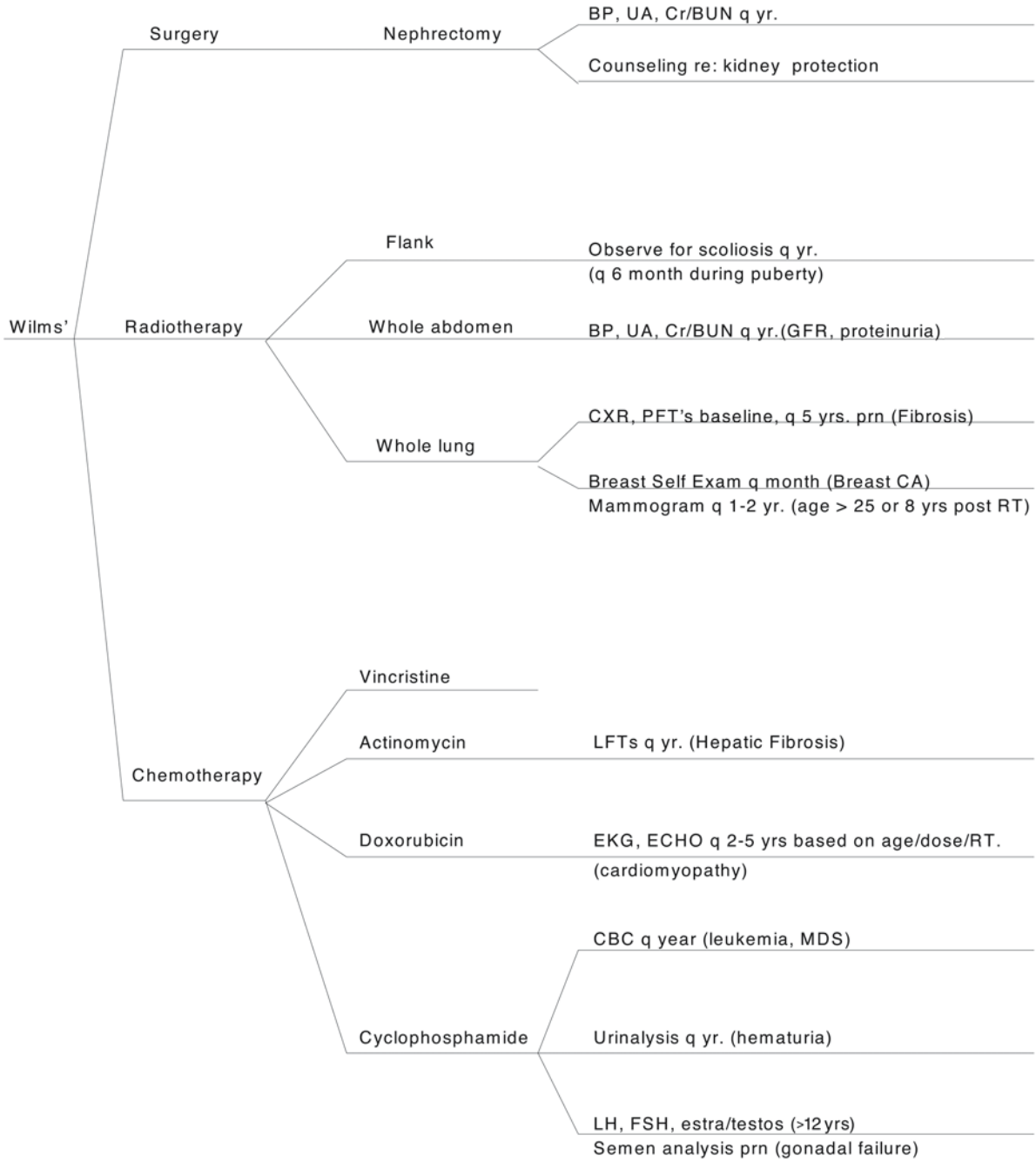

Hodgkin's
Radiation
Surgery
Chemotherapy
Mantle
Abdomen
Pelvic
Splenic RT > 30 Gy
Splenectomy
Cyclophosphamide
Procarbazine
Nitrogen Mustard
BCNU, CCNU
Vincristine
Vinblastine
Etoposide
Prednisone
Doxorubicin
Bleomycin
DTIC
Cisplatin
Carboplatin
ARA-C
Free T4, TSH q yr. (Hypothyroidism)
CXR, PFT's baseline, q 5 yrs. prn (Fibrosis)
Breast Self Exam q month (Breast CA)
Mammogram q 1-2 yr. (age > 25 or 8 yrs. post RT)
EKG, ECHO q 2-5 yrs. prn RT/anthracycline dose
(Pericarditis, Valvulitis)
Cr/BUN, UA, BP q yr.
Stool guiac/colonoscopy per ACS
LH, FSH, estra/testos (12>yr.)
Semen analysis prn (gonadal failure)
Penicillin / Pneumovax/HiB (H. influenza)
UA q yr. (Hematuria)
CBC q yr. (Leukemia, MDS)
LH, FSH, estra/testos (>12yrs)
Semen analysis (gonadal failure)
CXR, PFT's q 3-5 yrs. (Fibrosis)
CBC q yr. (Leukemia, MDS)
EKG, ECHO q 2-5 yrs. (based on dose/RT)
CXR, PFT's baseline, q 3-5 yrs. prn (Fibrosis)
Audiogram baseline then q 5 yrs. prn
Mg, Cr/BUN q year
Educational assessment q 1-2 yrs.



*Dental Panorex at age 5 (root hypoplasia)


NHL
Radiotherapy
Cranial
Educational assessment q yr.
Neurocognitive testing-baseline, q 2-3 yrs.
Monitor for precocious puberty
Growth curve q 6-12 months until final height
Bone Age for slow linear growth
Eye Exam q yr. (Cataracts)
Mediastinum
Breast Self Exam q month (Breast CA)
Mammogram q 1-2 yrs. (age > 25 or 8 yrs. post RT)
CXR, PFT's baseline and q 5 yrs. prn (Fibrosis)
EKG, ECHO baseline, q 2-5 yrs.
based on dose/anthracycline
Free T4, TSH q yr. (Hypothyroidism)
Abdomen
Stool guiac q yr., colonoscopy per ACS
LFTs q yr. (Hepatic Fibrosis)
Cr/BUN, UA, BP q yr.
LH, FSH, estra/testos (>12yrs)
Semen analysis prn (gonadal failure)
Chemotherapy
Cyclophosphamide
Urinalysis q yr. (hematuria)
CBC q year (leukemia)
Vincristine
Methotrexate
6-mercaptopurine
6-thioguanine
LFTs q yr. (Hepatic Fibrosis)
Prednisone
Doxorubicin
EKG, ECHO q 2-5 yrs. based on dose/age/RT
(Cardiomyopathy)
ARA-C
Educational assessment
Neurocognitive testing prn


Brain Tumor
Surgery
Radiotherapy
Chemotherapy
Cranial
Spinal
Cyclophosphamide
Temazolamide, Nitrogen Mustard, Procarbazine
CCNU, BCNU
Vincristine
Dexamethasone
Etoposide
Cisplatin
Educational assessment q yr.
Neurocognitive testing-baseline, q 2 yrs.
Dental panorex (age 5) - root hypoplasia
Eye Exam q yr. (Cataracts)
LH, FSH, estra/testos prolactin (>12 yrs).
monitor for pubertal delay, precocious puberty, libido
Growth curve q yr. (q 6-12 month to final height.)
Bone Age for slow linear growth
Free T4, TSH q yr. (Hypothyroidism-1°, 2°)
Echo, EKG baseline then q 5 yrs. prn
Urinalysis q yr. (hematuria)
CBC q year (leukemia, MDS)
LH, FSH, estra/testos (>12 yrs)
Semen analysis (gonadal failure)
CXR, PFT's q 3-5 yrs. (Fibrosis)
Bone density by age 18 yrs. and prn
CBC q year (leukemia, MDS)
Mg q yr. (Mg: tubular dysfunction)
Cr/BUN, BP q yr., CrCl baseline (GFR)
Audiogram q 5 yr. (High frequency loss)


Wilms'
Surgery
Nephrectomy
BP, UA, Cr/BUN q yr.
Counseling re: kidney protection
Radiotherapy
Flank
Observe for scoliosis q yr.
(q 6 month during puberty)
Whole abdomen
BP, UA, Cr/BUN q yr.(GFR, proteinuria)
Whole lung
CXR, PFT's baseline, q 5 yrs. prn (Fibrosis)
Breast Self Exam q month (Breast CA)
Mammogram q 1-2 yr. (age > 25 or 8 yrs post RT)
Chemotherapy
Vincristine
Actinomycin
LFTs q yr. (Hepatic Fibrosis)
Doxorubicin
EKG, ECHO q 2-5 yrs based on age/dose/RT.
(cardiomyopathy)
Cyclophosphamide
CBC q year (leukemia, MDS)
Urinalysis q yr. (hematuria)
LH, FSH, estra/testos (>12 yrs)
Semen analysis prn (gonadal failure)

Facilitating Assessment of Late Effects by Organ System

Cindy L. Schwartz · Wendy L. Hobbie · Louis S. Constine

Contents

This chapter provides charts by organ system that cover the late effects of various cancer treatments. The healthcare provider for a patient with cardiac symptomatology, for example, can review the cardiac chart to find the common late side effects, causative treatments (chemo, radiation or surgery), signs and symptoms, screening and diagnostic tests and appropriate intervention and management procedures. If further information is needed, the reader can refer to the chapter that covers the affected organ for a detailed discussion of the pathophysiology and clinical manifestations, as well as additional information regarding detection, screening, management and intervention.

The charts, in conjunction with the algorithms in chapter 2, should facilitate planning patient evaluations in preparation for accessing more detailed information in the chapters that follow.

Abbreviations used in this section are included in the glossary at the end.

Chemotherapy

ABVD	Adriamycin, Bleomycin, Vincristine, Actinomycin-D
Act-D	Actinomycin-D
Ara-C	Cytosine arabinoside
BCNU	1, 3-Bis (2 chloroethyl-1 nitrosourea)
BLEO	Bleomycin
Bus	Busulfan
CCNU	1, -(2-chloroethyl-3-cyclohexyl-1 nitrosourea)
CDDP	Cisplatin
Carbo	Carboplatin

DTIC	Dimethyl Triazine Imidazole Carboxamide
Doxo	Doxorubicin
Dnm	Daunomycin
HN_2	Nitrogen mustard
HU	Hydroxyurea
Ifos	Ifosfamide
IT	Intrathecal
MTX	Methotrexate
PCB, PCZ	Procarbazine
VCR	Vincristine
VP-16	Etoposide
5FU	5- Fluorouracil
6MP	6-Mercaptopurine
6TG	6-Thioguanine

Other Terms

Abd	Abdominal
ACTH	Adrenocorticotropic hormone
ASA	Aspirin
B/P	Blood pressure
BA	Barium swallow
BM	Bone marrow
BMT	Bone marrow transplant
BSE	Breast self examination
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
CMV	Cytomegalovirus
CNS	Central nervous system
CO_2	Carbon dioxide
Cr	Creatinine
CT	Computed tomography
CXR	Chest radiograph
DHEA	Dehydroepiandrosterone
DLCO	Diffusing capacity for carbon monoxide (pulmonary)
ECHO	Echocardiogram
EEG	Electroencephalogram
EKG	Electrocardiogram
FiO_2	Fractional inspired oxygen
FSH	Follicle-stimulating hormone
FS	Fractional shortening
GFR	Glomerular filtration rate
GI	Gastrointestinal
GU	Genitourinary
GVHD	Graft-versus-host disease
Gy	Grey (measure of radiation)
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
HD	High Dose
H/O	History of
H/P axis	Hypothalamic-pituitary axis
IOP	Intra ocular pressure
IQ	Intelligence quotient
IT	Intrathecal
IV	Intravenous
IVP	Intravenous pyelogram
LFT	Liver function tests
LH	Luteinizing hormone
MCV	Mean corpuscle volume
Mg	Magnesium
MRI	Magnetic resonance imaging
NPO	Nothing by mouth
PET scan	Positron emission tomography
PFT	Pulmonary function test
PO_4	Phosphate
PRN	As needed
PTU	Propylthiouracil
QTc	Corrected QT interval
RNA	Radionuclear angiography
R/O	Rule out
RT	Radiation therapy
SMN	Second malignant neoplasm
SPECT	Single photon emission computed tomography
T_3	Triiodothyronine
T_4	Thyroxine
Free T_4	Unbound thyroxine
TBI	Total body irradiation
TMJ	Temporomandibular joint
TSE	Testicular self examination
TSH	Thyroid-stimulating hormone
TRH	Thyrotropin-releasing hormone
U/A	Urinalysis
US	Ultrasound
UTI	Urinary tract infection
UV	Ultraviolet light
VA	Visual acuity
VF	Visual field
WBC	White blood count

Table 3.1. Evaluation of patients at risk for late effects: thyroid

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Overt hypothyroidism (Elevated TSH, decreased T_4)		>20 Gy to the neck, cervical spine >7.5 Gy TBI (total body irradiation)	Partial or completed thyroidectomy	Hoarseness Fatigue Weight gain Dry skin Cold intolerance Dry brittle hair Alopecia Constipation Lethargy Poor linear growth Menstrual irregularities Pubertal delay Bradycardia Hypotension	Free T_4, TSH annually Plot on growth chart	Thyroxine replacement Anticipatory guidance regarding symptoms of hyper-thyroidism/ hypothyroidism
Compensated hypothyroidism (Elevated TSH, normal T_4)		Same as *Overt hypothyroidism*	Same as *Overt hypothyroidism*	Asymptomatic	Free T_4, TSH annually Plot on growth chart	Thyroxine to suppress gland activity
Thyroid nodules		Same as *Overt hypothyroidism*		Same as *Overt hypothyroidism*	Free T_4, TSH annually Physical exam	Thyroid scan Biopsy/resection
Hyperthyroidism Decreased TSH, elevated T_4		Same as *Overt hypothyroidism*		Nervousness Tremors Heat intolerance Weight loss Insomnia Increased appetite Diarrhea Moist skin Tachycardia Exophthalmus Goiter	Free T_4, TSH annually Physical exam T_3, antithyroglobulin Antimicrosomal Antibody baselines, then prn symptoms	Refer to endocrinologist for PTU, propranolol, ^{131}I Thyroidectomy

Table 3.2. Evaluation of patients at risk for late effects: CNS effects

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Neurocognitive deficit	High-dose IV MTX IT MTX	>18 Gy	Resection of CNS tumor	Difficulty with: Reading, language, verbal/non-verbal memory, arithmetic, receptive and expressive language. Decreased speed of mental processing Attention deficit Decreased IQ Behavior problems Poor school attendance Poor hand-eye coordination	Neurocognitive testing: Psychoeducational Neuropsychologic	Psychoeducation assistance
Leukoencephalopathy	MTX: IT or IV IT Ara-C	>18 Gy		Seizures Neurologic impairment * Compare with premorbid status	CT/MR scan baseline and symptoms	Symptom management: Muscle relaxant Anticonvulsants Physical therapy Occupational therapy
Focal necrosis	MTX: IT or high-dose IV BCNU, CDDP	>50 Gy (especially with >21 Gy daily fraction)	Resection of tumor	Headaches Nausea Seizures Papilledema Hemiparesis/ other focal findings Speech, learning, and memory deficits	CT/MR scan baseline, PRN symptoms PET or SPECT scan	Steroid therapy Debulking of necrotic tissue
Large-vessel stroke		>60 Gy		Headache Seizures Hemiparesis Aphasia Focal neurologic findings	CT scan/MRI Arteriogram	Determined by specific Neurologic impairment
Blindness	Intraarterial BCNU, CDDP	RT (optic nerve chiasm, occipital lobe)	Resection of tumor	Progressive visual loss	Ophthalmic evaluation Visual-evoked response	Visual aids
Ototoxicity	CDDP Carboplatin	>50 Gy (middle/inner ear)		Abnormal speech development Hearing	Audiogram baseline prn symptoms	Speech therapy Hearing aid
Myelitis		>45–50 Gy	Spinal cord surgery	Paresis Spasticity Altered sensation Loss of sphincter control	MRI	Steroids Physical therapy Occupational therapy

Table 3.3. Evaluation of patients at risk for late effects: gastrointestinal

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Enteritis	Act-D, doxo, enhance RT effect	>40 Gy	Abdominal surgery enhances RT effect	Abdominal pain Diarrhea Decreased stool bulk Emesis Weight loss Poor linear growth	Height and weight q yr Stool guaiac q yr CBC with MCV q yr Total protein and albumin q 3–5 yr (Absorption tests, vitamin B_{12} level, and contrast studies)	Dietary management Refer to gastro-enter-ologist
Adhesions		RT enhances effect	Laparotomy	Abdominal pain Bilious vomiting Hyperactive bowel sounds	Abdominal radiograph	NPO Gastric suction Adhesion lysis
Fibrosis: Esophagus (stricture)	Doxo and Act-D (RT enhancers)	>40–50 Gy	Abdomen	Dysphagia Weight loss Poor linear growth	Height and weight q yr CBC q yr	Refer to GI
Fibrosis: Small intestines		>40 Gy	Abdomen	Abdominal pain Constipation Diarrhea Weight loss Obstruction	Height and weight q yr CBC q yr (BA swallow/ endoscopy prn)	Esophageal dilation Antireflux surgery
Fibrosis: Large intestine, colon		>40 Gy	Abdomen	Abdominal colic Rectal pain Constipation Melena Weight loss Obstruction	Height and weight q yr Rectal exam Stool guaiac q yr Lower GI Colonoscopy Sigmoidoscopy	Stool softeners High-fiber diet

Table 3.4. Evaluation of patients at risk for late effects: hepatic

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Hepatic Fibrosis/cirrhosis	MTX Act-D 6MP 6TG	>30 Gy	Major resection	Itching Jaundice Spider nevi Bruising Portal hypertension: Esophageal varices Hemorrhoids Hematemesis Encephalopathy	LFTs q yr (Hepatitis C screen) (Liver biopsy) (Endoscopy)	Hepatitis screen (hepatitis A,B,C, CMV) Diuretics Refer to hepatologist

Table 3.5. Evaluation of patients at risk for late effects: genitourinary

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Glomerular dysfunction	CDDP Carboplatin Ifos	>20 Gy or >15 Gy with chemo		Asymptomatic or Fatigue, Poor linear growth, Anemia, Oliguria	Creatinine, BUN q yr. Creatinine clearance baseline and q 3 yrs Annual: Blood pressure Height, weight Hemoglobin Urinalysis	Low-protein diet Dialysis Renal transplant
Hypoplastic kidney/renal arterio-sclerosis		20–30 Gy or 10–15 Gy with chemo		Fatigue Poor linear growth Hypertension Headache Edema Albuminuria Urinary casts	Same as *Glomerular dysfunction*	Same as *Glomerular dysfunction*
Tubular dysfunction	CDDP Carboplatin Ifos			Seizures (↓ Mg) Weakness (↓ Po_4) Glycosuria Poor linear growth	Mg, Ca, PO_4, Cr, BUN, Hg annually, BP/urinalysis q year 24 hour urine for Ca, Po_4 prn abnormalities	Mg supplement Po_4 supplement

Table 3.5. Continued

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Nephrotic syndrome		20–30 Gy		Proteinuria Edema	Serum protein, albumin, Cr, BUN, q year Urinalysis q yr Blood pressure q yr (24 hr urine for protein and Cr)	Low-salt diet Diuretics
Bladder: Fibrosis or Hypoplasia (reduced bladder capacity)	CPM Ifos Surgical referral	>30 Gy prepubertal >50 Gy postpubertal		Urgency Frequency Dysuria Incontinence (nocturia) Pelvic hypoplasia	Urinalysis q yr Cystoscopy, IVP/US; volumetrics	Exercises to increase bladder capacity
Hemorrhagic and non-hemorrhagic cystitis	CPM Ifos	>35 Gy Lower doses enhance chemotherapy effect		Hematuria, or Frequency, Urgency, Dysuria, Bladder tenderness	Urinalysis q yr Cystoscopy if hematuria on 2 exams Hg q year	Refer to urologist Maintain Hg Antispasmodics Counsel regarding risk of bladder cancer
Prostate		40–60 Gy (lower doses inhibit development; higher doses cause atrophy)		Decreased volume of seminal fluid Hypoplastic or atrophied prostate	Prostate Examination Annually of prostate gland. Semen analysis x 1 at maturity. Ultrasound	Counsel regarding: possible infertility due to inadequate seminal fluid Monitor prostate (exam and prostate-specific antigen)
Vagina: Fibrosis/ diminished growth	(Act-D), doxo enhance RT effect)	4–60 Gy (lower doses inhibit development; higher doses cause atrophy)		Painful intercourse Vaginal bleeding Small vaginal vault	Pelvic exam (possibly under anesthesia), baseline during puberty and then prn for symptoms	Dilations Reconstructive surgery Potential need for cesarean section
Uterus: Fibrosis/ Decreased growth		>20 Gy (prepubertal) >40–50 Gy (postpubertal)		Spontaneous abortion Low birth-weight infants	Pelvic examination, prn for symptoms or if planning pregnancy	Counsel regarding pregnancy Refer to Gynecologist if considering pregnancy

Table 3.5. Continued

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Ureter: Fibrosis		>50–60 Gy		Frequent UTIs Pelvic hypoplasia Hydronephrosis	Urinalysis q yr Urethrogram	UTI prophylaxis
Urethra: Strictures		>50 Gy	GU	Frequent UTIs Dysuria Stream abnormalities	Urinalysis q yr Voiding cystogram	UTI prophylaxis Surgical intervention

Table 3.6. Evaluation of patients at risk for late effects: head and neck

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Xerostomia (decreased salivary gland function)	Doxorubicin, Actinomycin D enhance RT effect	>30 Gy and >50% gland must be radiated		Decreased salivary flow Dry mouth Altered taste perception Dental decay Candida (thrush)	Dental examination Salivary flow studies Attention to early caries, periodontal disease	Encourage meticulous oral hygiene Saliva substitute Prophylactic fluoride Dietary counseling regarding avoiding fermentable carbohydrates Nystatin for oral candidiasis Pilocarpine
Intranasal scarring		>40 Gy		Chronic rhinosinusitis Nasal discharge Postnasal drip Facial pain Headache	Inspection of mucosa Nasopharyngoscopy	Decongestants Drainage procedures Antibiotics prn
Epilation (scalp)		>15–20 Gy		Thinning of hair Alopecia	Examination	Wigs Compensatory hair styling
Eyelash Eyebrow		>30 Gy >50 Gy				
Fibrosis		>40 Gy		Pain Constriction Facial asymmetry Limitation of jaw motion (TMJ fibrosis)	Examination	Prevention of infection (especially after trauma) "Stretching" exercises of TMJ

Table 3.6. Continued

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Osteo-necrosis		>50–60 Gy (or interstitial radiation)	Tooth extraction	Ulcers/necrosis	Examination	Prosthetic devices Surgical repair
Abnormal facial growth		>30 Gy		Facial asymmetry Hypoplastic development of orbit, maxilla, mandible	Examination	Prosthetic devices Surgical repair
Craniofacial deformity			Surgery		Examination	Surgical repair
Abnormal tooth and root development	(VCR, Act-D, CPM, 6MP, PCZ, HN_2)	≥10 Gy		Enamel appears pale Teeth appear small, uneven Malocclusion	Dental exam q6 months with attention to early caries, periodontal disease, and gingivitis. Panorex/ bite-wing radiographs baseline (age 5–6)	Careful evaluation prior to tooth extraction, endodontics, and ortho-dontics Fluoride Antibiotics prn risk of infection (e.g., trauma)
Chronic otitis		≥ 40–50 Gy		Dryness and thickening of canal and tympanic membrane Conductive hearing loss Perforation of TM	Otoscopic exam Audiometry	Antibiotic therapy Decongestants Myringotomy PE tubes Preferential seating in school Amplification
Sensorineural hearing loss	Cisplatin	≥ 35–40 Gy Cranial RT enhances the platinum effect		High frequency hearing loss (bilateral) Tinnitus Vertigo	Conventional pure tone audiogram baseline and then q 2–3 yr Bilateral, symmetrical, irreversible	Preferential seating in school Amplification
Decreased production of cerumen		≥ 30–40 Gy		Hard and encrusted cerumen in canal Hearing impairment Otitis externa	Examination of canal	Periodic cleaning of ear canal Cerumen-loosening agents Otic drops for otitis externa Keep ear dry: Ear plugs Drying solution
Chondritis		≥ 50 Gy		Cauliflower ear	Inspection of auricle	Antibiotics Surgical repair (Reconstruction may be hampered by poor blood supply)
Chondrone-crosis		≥ 60 Gy				

Table 3.7. Evaluation of patients at risk for late effects: integumentary/breast

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Alopecia		>40 Gy		Hair loss involving the scalp, eyelashes, or eyebrows	Examination	Wig management
Hyper-Pigmentation Skin	Bleo, Bus, DTIC	>30 Gy		Hyperpigmentation	Examine skin	Cosmetic intervention only
Increased benign or malignant melanocytic nevi		RT		Increased numbers of pigmented nevi in the field of radiation	Skin examination annually. Photograph involved areas to follow accurately	Refer to dermatologist for close follow-up of multiple or suspicious lesions. Biopsy of suspicious lesions
Basal cell carcinoma		RT		Lesion	Skin examination annually.	Excisional biopsy
Hypoplasia of soft tissue	(Effect enhanced by: Act-D Doxo)	>20 Gy (developing child)		Decreased elasticity Decreased tissue volume Local inability to sweat Dryness	Annual examination of skin elasticity and volume	Avoid sun exposure Use sunscreen in treated area Moisturizers
Telangiec-tasia	As above	>40 Gy	Enhances risk, compro-mises blood supply	Skin appears tight with woody texture Spidery pattern of small blood vessels	Annual examination of skin	Avoid sun exposure in treated areas. Avoid trauma
Skin fibrosis/ necrosis	As above	>40 Gy	Enhances risk, compromises blood supply	Contractures Discoloration of tissue	Annual skin exam Examination for tissue breakdown	Must be in the care of a dermatologist – may require surgery
Hypoplasia of breast tissue		>10 Gy Pubertal breast very sensitive		Reduced breast tissue Failure to lactate in treated breast	Annual breast examination Mammography at age 25 yrs or 8 years post-XRT baseline, then q 1–2 years (annually after age 40)	Teach BSE Anticipatory guidance re: Breast nodules Impaired lactation

Table 3.8. Evaluation of patients at risk for late effects: musculoskeletal

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Muscular hypoplasia		>20 Gy (growing child) Younger children more sensitive	Muscle loss or resection	Asymmetry of muscle mass when compared with untreated area Decreased range of motion Stiffness and pain in affected area (uncommon)	Careful comparison and measurement of irradiated and unirradiated areas Range of motion	Prevention: Exercise program: Range of motion Muscle strengthening
Spinal abnormalities Scoliosis Kyphosis Lordosis Decreased sitting height		For young children, RT to hemi-abdomen or spine (especially hemi-vertebral) 10 Gy (minimal effect) >20 Gy (clinically notable defect)	Lami-nectomy	Spinal Curvature Back pain Hip pain Uneven shoulder height Rib humps or flares Gait abnormalities	Standing by stadiometer. During puberty examine spine q 6 months until growth is completed Spinal films baseline during puberty, then prn curvature (COBB technique to measure curvature)	Refer to orthopedist if any curvature is noted, especially during a period of rapid growth
Length discrepancy		>20 Gy		Lower back pain Limp Hip pain Discrepancy in muscle mass and length when compared with untreated extremity Scoliosis	Annual measurement of treated and untreated limb (completely undressed patient to assure accurate measurements) Radiograph baseline to assess remaining epiphyseal growth Radiographs annually during periods of rapid growth	Contralateral epiphysiodesis Limb-shortening procedures
Pathological fracture		>40 Gy	Biopsy	Pain Edema Ecchymosis	Baseline radiograph of treated area to assess bone integrity, then prn symptoms	Consider limitation of activities (e.g., contact sports) Surgical repair of fracture; may require internal fixation

Table 3.8. Continued

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Osteo-necrosis	Steroids	>40–50 Gy (more common in adults)		Pain in affected joint Limp	Radiograph, CT scan prn symptoms	Symptomatic care Joint replacement
Osteo-cartilaginous exostoses		RT		Painless lump/ mass noted in the field of radiation	Radiograph baseline and prn growth of lesion	Resection for cosmetic Functional reasons Counsel regarding 10% incidence of malignant degeneration
Slipped capito-femoral epiphysis	High-dose steroids	>25 Gy (at young age		Pain in affected hip Limp Abnormal gait	Radiograph baselines to assess integrity of the treated joint(s), then prn symptoms	Refer to orthopedist for surgical intervention

Table 3.9. Evaluation of patients at risk for late effects: ophthalmology

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Lacrimal glands: Decreased tear production	5FU	>40 Gy		Dry, irritated red eye Foreign-body sensation	Eye exam/slit lamp exam Fluorescein staining	Tear replacement Occlude lacrimal puncta
Lacrimal duct: Fibrosis	5FU	>50 Gy		Tearing	Ophthalmic exam	Dilation of duct
Eyelids: Ulceration		50 Gy		Blepharitis Bleeding/crusted lesion Previous infections	Eye exam	Topical/oral steroids Skin balm Teach: Lid hygiene Radiosensitizing drugs
Telangiectasia		50 Gy		Enlarged, tortuous blood vessels Pigmentary changes	Slit lamp	UV protection Avoid trauma, Harsh soaps and lotions
Conjunctiva: Necrosis		>45 Gy Radioactive plaque therapy		Pain Dry, irritated eye Foreign-body sensation	Eye Exam Slit lamp Fluorescein stain	Steroids/antibiotic drops
Sclera: Thinning		>50 Gy		May be asymptomatic Grey, charred, blue sclera	Eye Exam Slit lamp exam	Antibiotic drops Avoid trauma Protective glasses

Table 3.9. Continued

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Cornea: Ulceration Keratinization		>45Gy		Pain Foreign-body sensation Decreased VA Photosensitivity	Eye Exam Slit lamp Fluorescein staining	Antibiotics Soft bandages Soft contact lens Surgery Ophthalmology
Lens: Cataract	Steroids (incidence varies with dose)	>6 Gy (single dose or >10 Gy fractionated)		Decreased visual acuity Opaque lens	Direct ophthalmoscopic exam Decreased red reflex Slit lamp Opaque lens	Prevention by shielding during treatment Surgical removal Educate regarding UV protection
Iris: Neovascularization		>50 Gy		May be asymptomatic New blood vessels in iris (rubeosis) Blood in anterior chamber	Eye Exam Slit lamp	Steroid drops
Secondary glaucoma				Eye pain, headache, nausea/vomiting, decreased peripheral vision, increased IOP	Measure ocular pressure	Beta blocker drops Atropine Diamox
Atrophy		>50 Gy		Decreased iris stroma at pupillary margin	Slip lamp/penlight exam	Photocoagulation
Retina: Infarction		>50 Gy		Blanched white cotton spots Decreased visual acuity Decreased visual field Blurred vision (central or peripheral)	Visual acuity Visual field	Steroids Photocoagulation Education regarding avoiding ASA and bleeding precautions
Hemorrhage Telangiectasia Neovascularization		>50 Gy >50 Gy >50 Gy				
Mascula edema		>50 Gy		Blister of fluid in the mascula		
Optic neuropathy		>50 Gy	Tumor resection	Pale optic disc Abnormal pupillary responses	Visual evaluation	Visual aids

Table 3.10. Evaluation of patients at risk for late effects: ovarian

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Ovarian failure	CPM, PCB, bus, BCNU, CCNU, Ifos	4–12 Gy Tolerance decreases with increasing age	Oophorectomy or oophoropexy	Delayed/arrested/absent pubertal development Changes in duration, frequency, and character of menses (cramping) Estrogen deficiency: Hot flashes Vaginal dryness Dyspareunia Low libido Infertility	Tanner stage, LH, FSH, estradiol at: 1) Age 12 yrs 2) Failure of pubertal development 3) Baseline when fully mature 4) PRN symptoms	Hormone replacement therapy Anticipatory guidance regarding symptoms of estrogen deficiency and early menopause Alternate strategies for parenting

Table 3.11. Evaluation of patients at risk for late effects: peripheral system effects

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Peripheral neuropathy	VP-16, VCR CDDP	60 Gy		Weakness Lack of coordination Tingling Numbness	Annual neurologic examination	Protecting affected area from excess heat or cold exposure Physical therapy Occupational therapy

Table 3.12. Evaluation of patients at risk for late effects: pulmonary

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Pulmonary fibrosis	Bleo, CCNU, BCNU, (CPM), (MTX), (Vinca alkaloids)	Pulmonary RT >10 Gy Risk increases with doses, larger volume irradiated, and younger age		Fatigue Cough Dyspnea on exertion Reduced exercise tolerance Orthopnea Cyanosis Finger clubbing Rales Cor pulmonale	CXR, O_2 saturation, PFT with DLCO, baseline then q 3–5 yrs prn	If symptomatic, refer to pulmonologist Prevention: Avoidance of smoking Avoidance of infections: Influenza vaccine Pneumovax After bleomycin: Avoid $Fi0_2$ >30% (e.g. during surgery)

Table 3.13. Evaluation of patients at risk for late effects: testicular

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Germ cell damage: Oligospermia/ azoospermia	CPM, HN_2 CCNU/BCNU PCB, Ifos	>1–6 Gy to the testes (direct or scatter)	Orchiectomy or surgical manipulation	Testicular atrophy (softer, smaller) Failure to impregnate	Tanner stage Inquire regarding previous sperm banking Assess testicular size and consistency. LH, FSH, testosterone: 1) For failure of pubertal development 2) Baseline when sexually mature 3) For failure to impregnate (repeat q 3 yr for possible recovery) Spermoto-analysis at maturity or for failure to impregnate (repeat q 3–5 years prn to assess recovery)	Instruct: Testicular self-examination Anticipatory guidance re: Infertility counseling: Alternate strategies for fathering
Leydig cell damage:	CPM	>24 Gy to the testes (direct or scattered from pelvis)	Orchiectomy or surgical manipulation	Testicular atrophy (softer, smaller)	LH and testosterone at:	Testosterone replacement
Testosterone deficiency	VP-16 Ifos, CCNU, BCNU, HN_2			Delayed/arrested/ absent pubertal development: Pubic and axillary hair (female hair pattern) Lack of penile and testicular enlargement, Voice change or Body odor and acne	Age 13 yrs Failure of pubertal development Baseline, if sexually mature Changes in libido or sexual performance	Anticipatory guidance regarding testosterone deficiency

Table 3.14. Evaluation of patients at risk for late effects: cardiac

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Cardiomyopathy (Ventricular dysfunction)	Anthracycline >300 mg/m^2 >200 mg/m^2 and RT to mediastinum High-dose CTX (BMT)	>30 Gy >20 Gy and Anthracyclines		Fatigue Cough Dyspnea on exertion Peripheral edema Hypertension Tachypnea/rales Tachycardia Cardiomegaly (S3/S4) Hepatomegaly	EKG, ECHO/RNA and CXR baselines, q 1–5 yr (depending on risk factors)	Diuretics Digoxin Afterload reducers Antiarrhythmics Cardiac transplant Education: risks of smoking, pregnancy, anesthesia, alcohol, drug use, Isometric exercise
Valvular damage (Mitral/tricuspid aortic)		>30 Gy		Weakness Cough Dyspnea on exertion New murmur Pulsating liver	ECHO and CXR (baseline), q 3–5 yr and prn symptoms	Penicillin prophylaxis for surgery/dental procedures
Pericardial damage		>30 Gy		Fatigue Dyspnea on exertion Chest pain Cyanosis Ascites Peripheral edema Hypotension Friction rub Muffled heart sounds Venous distention Pulsus paradoxicus	EKG (ST–T changes, decreased voltage), ECHO, CXR baseline, q 3–5 yr	Pericardial stripping
Coronary artery disease		>30 Gy		Chest pain on exertion (radiates to arm/neck) Dyspnea Diaphoresis Pallor Hypotension Arrhythmias	EKG q 3 yrs Stress test (consider dobutamine stress echocardiography) baseline, q 3–5 yr or prn symptoms	Diuretics Cardiac medications Low-sodium, low-fat diet Conditioning regimens

Table 3.14. Continued

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
Conduction abnormality	Anthracycline >300 mg/m^2 >200 mg/m^2 and RT to mediastinum	>30 Gy		Syncope Palpitations Arrhythmias	EKG Holter monitor after high cumulative anthracycline dose (>300 mg/m^2) or symptoms	

Central Nervous System Effects

Nina S. Kadan-Lottick · Joseph P. Neglia

Contents

4.1 Introduction

Treatment for childhood cancer can result in damaging effects on the central nervous system (CNS). The spectrum of potential toxicities includes paralysis, neuropathies, blindness, and seizures. Furthermore, survivors may experience decline in intellectual function, learning problems, behavior disorders, school failure, and impaired employability. Although these phenomena were originally described for children who underwent cranial radiation, subsequent studies have demonstrated that children treated only with chemotherapy are also at risk for neurological deficits. This chapter will review the pathophysiology, clinical presentation, risk factors, diagnosis, and management of late CNS morbidity resulting from the treatment of childhood cancer.

4.2 Pathophysiology

4.2.1 Pre- and Post-Natal Brain Development

Normal development of the central nervous system begins at conception and includes numerous overlapping processes, thought to be orchestrated by genetic and epigenetic events that are amenable to external influence [1, 2]. The two main periods of development can be divided into (1) the major histogenetic events of neurulation (i.e., the embryonic formation of the neural tube by closure of the neural plate), and (2) reorganization of the human cortex through dendritic and axonal growth, synapse production, neuronal and synaptic pruning, and changes in neurotransmitter sensitivity [2].

The processes of the latter reorganization period continue in the post-natal period into adulthood, and, thus, they may be vulnerable to toxic and metabolic insults from pediatric cancer and its therapy. For example, Bergmann glial cells of the Purkinje cell layer of the cerebellar cortex assist in the migration of granule cells even in adulthood [3]. During dendritic proliferation and synaptogenesis in the normal developing brain, an excessive number of synapses are formed that are later eliminated when redundant collateral axons are retracted. Dendritic arborization and synaptic remodeling starts during fetal development, but continues through infancy and early childhood [1, 4]. Myelination is another process that is not completed until later in life. The myelination cycle varies for each tract: the medial longitudinal fasciculus is from 24 weeks' gestation to 2 weeks postnatally, the corticospinal tract is from 38 weeks' gestation to 2 years of life, the corpus callosum is from 4 months postnatally to late adolescence, and the ipsilateral association bundle (between the anterior frontal and temporal lobes) is complete at 32 years of age [5].

The central nervous system also develops in other important ways during the post-natal period. The whole brain grows enormously in overall size with a four-fold increase in brain volume in the first decade of life [2]. This increase in volume is a function of the number, size, and density of neurons, glia, and dendritic cells. Pruning and normal elimination of neurons contributes to the usual loss of gray matter with age [6]. In contrast, white matter increases during childhood and adolescence. Sensory circuits established in utero may be modified in response to the postnatal environment. Because of the rapid rate of growth early in the post-natal period, infancy may be a period of development that is more vulnerable to damage from external factors such as disease, trauma, or metabolic disturbances. The same exposures occurring in an older child or adult usually results in less impairment in structure and function of the central nervous system [2, 7].

The ability of the brain to recover from post-natal insult is not well understood. Recent studies suggest that there is a potential for neural plasticity manifested by ongoing neurogenesis and synaptogenesis in several areas of the cortex in later childhood and adulthood [2]. The infant brain may recover more easily from some forms of brain injury than is possible later in life. This is supported by the observation that congenitally deaf children have a superior response if they receive sensory stimulation from cochlear implants before the age of 5 years [8]. Also, children with early visual deprivation will have less constriction of the visual fields if regular patching is started early [9].

4.2.2 Disease Considerations

The late toxicities manifested by the CNS are best considered as a combination of several factors acting in a unique host. Certainly the therapy applied to treat the primary disease can have late manifestations; however, the primary disease process will also impact on the late effects. Children with leukemia and brain tumors comprise over 50% of all children with newly- diagnosed cancer [10] and represent the majority of long-term survivors. These children, and children with other neoplasms originating in, or abutting, the CNS are at risk not only because of the primary site of disease, but also because of the need to administer CNS-directed therapy.

Although most children with leukemia do not present with CNS manifestations of their disease, a subset of children will. Hyperleukocytosis (characteristically white cell counts of over 100,000 per cubic millimeter) is associated with an increased risk of stroke even prior to the initiation of therapy. Aggressive management of hyperleukocytosis with hydration, exchange transfusion, or cytapheresis is emergently indicated to reduce this risk. Infants and children with T-cell leukemia are more likely to present with high white counts than children with standard risk ALL. Meningeal infiltration of leukemia, most often diagnosed by examination of the CSF, will occur in fewer than 5% of children with newly diagnosed ALL [11]. Although usually not symptomatic, CNS leukemia may lead to infiltration of normal structures and dysfunction of cranial nerves, which, in some cases, may be permanent.

Children with central nervous system tumors are uniquely at risk. While adults with CNS tumors will

frequently present with seizures (as a result of hemispheric tumors), children are more likely to present with symptoms of increased intracranial pressure, resulting from obstruction of the normal CSF flow. Tumors involving the fourth ventricle (most commonly, PNET/medulloblastoma) are most likely to obstruct CSF flow and lead to hydrocephalus, which can present with headache, morning vomiting, ataxia, and ultimately somnolence. The late effects of the hydrocephalus are not entirely clear. One investigation has shown that children with hydrocephalus severe enough to require a ventriculo-peritoneal shunt (VP shunt) have more severe declines in IQ than those that do not require the VP shunt [12]; however, the need for a shunt probably reflects of the size of the presenting tumor. Another complication unique to children with posterior fossa tumors is the entity of "cerebellar mutism." Mutism will typically be evident in the immediate posto-perative period. Although speech may be restored within a few weeks, in some instances it may take up to a year or more to recover [13]. Children are more frequently affected than adults, and, while speech will typically return, recent data have shown that speech may never be completely normal [14].

Tumors may also directly damage CNS function resulting in both short and long-term sequelae. Even among children with benign tumors of the CNS treated by surgery alone, only one-third can be expected to be essentially without long-term complications. A Nordic study of children with benign tumors of the CNS (predominately low grade astrocytomas) found only 31% of children to be completely without deficits on follow-up. Approximately 35% had moderate to severe sequelae, including ataxia, spastic paresis, vision loss, or epilepsy [15]. In another study of over 1600 long-term survivors of CNS tumors, children who received at least 50 Gy to the frontal brain regions had a moderately elevated risk for motor problems (RR 2.0; $P<0.05$). Seizure disorders were reported in 25% of patients, including 6.5% who had a late first occurrence. A radiation dose of 30 Gy or more to any cortical segment of the brain has been associated with a two-fold elevated risk for a late seizure disorder [16].

4.2.3 Radiation

The neurotoxic effects of cranial radiation therapy (CRT) have been well-documented and, for many individuals, can be extremely debilitating. CRT is associated with histological and radiographic abnormalities that have been correlated with clinical findings of impairment. Histological changes associated with CRT consist of subacute leukoencephalopathy, mineralizing microangiopathy, and cortical atrophy, most often becoming apparent several months to years after CRT [17–19]. Corresponding neuroimaging abnormalities after CRT include myelin degeneration, intracerebral calcifications, and ventricular dilatation, respectively [17, 19–21]. Illustrates some of these findings on magnetic resonance imaging. White matter is especially vulnerable to CRT exposure (see below) [22].

Ionizing radiation therapy produces biologically charged materials within the target tissue, which leads to DNA damage. While radiation therapy may lead to immediate cell death in some instances (as a result of the direct ionization of DNA), cell death is more commonly delayed until the cells attempt to move through mitosis. This loss of proliferative capacity eventually leads to tissue death within the irradiated field, ideally leading to death of the tumor target but sparing the normal tissue nearby. To achieve this effect it is helpful to think of the delivery of radiation therapy within a "therapeutic window"; that is, a range in which the therapy will cause death of the tumor cell, but not produce unacceptable damage to the normal tissue of adjacent structures. This therapeutic window varies from site to site within the body, and, while the CNS is able to withstand significant doses of ionizing radiation, the "window" of acceptable normal tissue damage may be quite small. Fractionation, the process of delivering radiation therapy through multiple small doses, enlarges the therapeutic window by allowing for repair of sublethal damage to normal tissue. While radiation therapy may result in cellular death through the direct interactions of ionized particles with cellular DNA, late tissue injury from radiation therapy may not be immediately evident. It may manifest in the years following radiation therapy, as a result of a vasculopathy

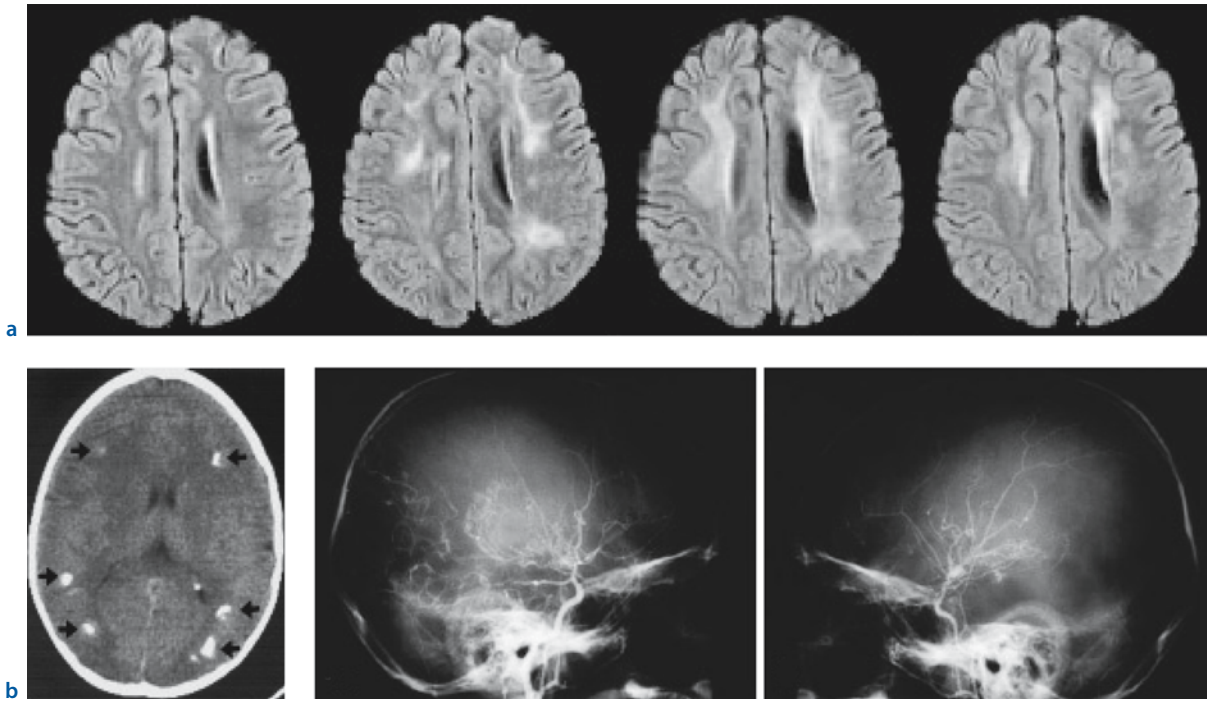


Figure 4.1 aє

a Progressive leukoncephalopathy by MRI Fluid Attenuated Inversion Recovery (FLAIR) in patient with ALL who received high-dose intravenous methotrexate at weeks 7, 18, 44, and 132 (reprinted with permission from Mulhern RK, Palmer SL. Curr Probl Cancer 2003; 27: 177–197)

b Subcortical calcifications on unenhanced computed tomographic (CT) scan in patient with ALL who received cranial irradiation and intrathecal methotrexate central nervous system prophylaxis (reprinted with permission from Iuvone L, Mariotti P, Colosimo C, et al. Cancer 2002; 95: 2562–70)

c Moyamoya disease on carotid angiogram in the basal ganglia of an 8 year old boy with brain stem glioma (reprinted with permission from Kitano S, Sakamoto H, Fujitani K, et al. Child's Nerv System 2000; 16: 251–255)

arising from radiation-induced damage to the endothelial cells.

The study of the pathophysiology of radiation injury to the CNS has focused on two major processes: vasculopathy and demyelination. Direct damage to the endothelial cells may initially be evident as increases in vascular permeability; scarring and wall thickening follow and ultimately lead to ischemia in the affected area. Demyelination occurs as a result of radiation damage to the precursor cell for new oligodendrocytes, known as the O-2A progenitor cell. Over time, the lack of replacement progenitor cells for the existing oligodendrocytes results in the demyelination characteristically associated with radiation injury. While these two processes (vasculopathy and demyelination) account for most of the changes seen following radiation, the exact process of radiation damage is likely to be much more complex, involving many of the other cells of the CNS [23].

Domains of neurobehavioral impairment after CRT include short term memory impairment, distractibility, fine motor coordination, visual–spatial ability, and somatosensory functioning [24–29]. These cognitive impairments have been associated

with a significantly reduced intelligence quotient and academic failure [25, 30]. The deficits, which often do not emerge until four to five years after diagnosis [31–33], are most severe in those diagnosed at an age younger than 6 years [25, 34], particularly among females [35, 36]. Children who received cranial radiation as part of their therapy for acute lymphoblastic leukemia are more likely to be referred to special education services and may achieve a lower final level of secondary education than their siblings [37]. There appears to be a dose–response relationship, with cranial radiation doses greater than 2400 cGy resulting in greater impairment [38]. It is not clear that a decrease to 1800 cGy is associated with less neurocognitive toxicity [32].

4.2.4 Intrathecal Chemotherapy

Chemotherapy exposures are associated with neurobehavioral consequences, although the effects may not be as devastating as those produced by CRT. Chemotherapeutic agents for the treatment of childhood ALL administered by the intrathecal route include methotrexate, cytarabine, and hydrocortisone, often in combination. Acute toxicity as a result of intrathecal methotrexate and intrathecal cytarabine can include chemical arachnoiditis, hallucinations, somnolence, seizures, and neurological symptoms [39, 40]. Several months to years after termination of intrathecal methotrexate therapy, patients may exhibit radiographic evidence of cortical atrophy, necrotizing leukoencephalopathy, subacute myeloencephalopathy, mineralizing angiopathy, and cerebellar sclerosis [29, 41].

Long-term neurobehavioral abnormalities have also been observed in children who received systemic and/or intrathecal methotrexate. In a study of patients treated at St. Jude Children's Research Hospital, Ochs et al. concluded that children who received intravenous methotrexate and intrathecal methotrexate had similar neurotoxicity to those who received 1800 cGy CRT and intrathecal methotrexate. Neurobehavioral deficits included decreases in full scale and verbal IQ, as well as in arithmetic achievement [27]. These conclusions were confirmed by Mulhern et al. in a longitudinal study which compared children who received 1800 cGy, 2400 cGy, and no CRT [31]. There was no statistically significant difference between these groups, but overall, 22%–30% of children experienced a clinically apparent deterioration in neurobehavioral function at follow-up (median 7.4 years). The deficits were most marked among females.

Raymond-Speden et al. compared ALL patients with chronic asthmatics. This study demonstrated that the detrimental effects of intrathecal chemotherapy are independent of the limitations of having a chronic disease (i.e., missed school, reduced energy levels, etc.) [42]. When comparing children with leukemia who received systemic and intrathecal CNS-directed therapy and children diagnosed with solid tumors who received systemic chemotherapy alone, the former group exhibited more severe problems on academic tests involving reading, spelling, and arithmetic, and these problems only became apparent 3 years post-diagnosis [43].

The effects of intrathecal cytarabine and hydrocortisone have not been studied extensively as single agents. However, there is biochemical and autoradiographic evidence for glucocorticoid binding sites in the spinal cord [44]. Given the toxic effects of systemically administered steroids (see below), the direct administration of a steroid formulation into the CSF may result in further neurotoxicity.

4.2.5 Systemic Chemotherapy

Systemic administration of methotrexate may enhance both the acute and late toxicities of other CNS-directed therapies. Among children with ALL treated on a non-radiation containing protocol, acute neurotoxic events occurred significantly more often in those children who received IV methotrexate (1,000 mg/m^2) in addition to IT methotrexate during consolidation therapy [45]. The presenting acute event consisted most often (in 80% of cases) of seizures. Other observed neurotoxicities included paresthesias, weakness, headaches, aphasia, ataxia, dysarthria, arachnoiditis, and choreoathetosis. CT and MRI findings among children with acute neurotoxicity were most commonly white matter changes characterized as hypo-dense areas, with or without

microangiopathic calcifications. Overall, approximately 10% of children in this trial who were treated with combined intermediate-dose systemic methotrexate and intrathecal methotrexate developed neurotoxicity. Ongoing follow-up of this group has continued to show both clinical and radiographic evidence of sequelae (P. Duffner 2003, personal communication). Systemic methotrexate is administered in many other settings in cancer therapy, often at substantial doses. When not combined with intrathecal therapy or cranial radiation, the systemic administration of high doses of methotrexate, as in the treatment of osteosarcoma, has not been consistently associated with CNS sequelae.

Systemic high dose cytarabine therapy has been associated with acute cerebellar syndrome, seizures, and encephalopathy [21]. Systemic and intrathecal cytarabine have also been associated with spinal cord necrosis [46].

Glucocorticoids may result in CNS toxicity, as evidenced by both animal experiments and clinical observation. Rat studies demonstrate that glucocorticoids disrupt the energy metabolism of neurons of the hippocampus, an important organ for memory processing, rendering them more vulnerable to toxic insults [47]. This finding is worrisome in the childhood cancer population because these patients are given steroids concurrently with other toxic agents [48]. Other experiments with rats have demonstrated the impairment of spatial learning in response to chronic corticosteroid treatment [49].

These laboratory findings correlate with clinical observations. Children with asthma on long-term steroid therapy at higher doses experience greater depression, anxiety, and verbal memory deficits [50]. Associated mood and behavior changes range from irritability to depression and psychosis [51]. Among healthy volunteers, administration of high dose steroids resulted in a spectrum of behavior changes as well as reduced cognitive function [52].

Steroid administration has been shown to be harmful to the developing brain in other pediatric populations. The administration of postnatal dexamethasone to pre-term infants results in impaired cerebral cortical gray matter growth [53]. Dexamethasone-treated neonates also have a significantly higher incidence of cerebral palsy and developmental delay than those who receive placebo [54]. The side effects of dexamethasone are more severe than those of another steroid preparation, methylprednisolone [55].

4.3 Clinical Presentations

Acute effects from CNS-directed therapy are relatively uncommon. Acute radiation changes to the CNS can result in significant edema at the irradiated site (often following single dose therapies such as "gamma knife" or "stereotactic radiosurgery") and may present with worsening of pre-existing symptoms (i.e. seizure, weakness, headaches). These symptoms, when they occur, are usually manageable with corticosteroid therapy [56]. Acute effects of chemotherapy on the CNS are also relatively uncommon. Ifosfamide has been associated with changes in mental status, cerebellar function, cranial nerve function, and cerebellar and motor system function, as well as with seizures [57]. The risk of this acute toxicity may be exacerbated by prior chemotherapy exposure, specifically exposure to cis-platinum [58]. Ara G, a new antimetabolite with selective efficacy against T-cell leukemia, is also associated with acute neurotoxicity. Somnolence and other acute CNS changes may be dose-limiting for this new agent [59]. It is too early to know the long-term effects.

Subacute effects of radiation therapy (those occurring within the first 6 months of exposure) are more common than acute effects. One of the most common of these, the somnolence syndrome, has been described as occurring in up to 50% of children who receive radiation as CNS prophylaxis for acute lymphoblastic leukemia. The syndrome presents with fatigue, somnolence, anorexia, and nausea typically occurring 4–8 weeks after the completion of radiation therapy [60]. In some instances, the syndrome may include fever and changes in EEG. While the condition is usually self-limited, treatment with steroids may ameliorate the symptoms. Typically occurring in the setting of cranial radiation for ALL or other CNS-directed whole brain radiation, the somnolence syndrome has also, on rare occasions, been reported

following the use of total body irradiation in the setting of bone marrow transplantation [61]. Similarly, L'Hermitte's syndrome may present following spinal irradiation with shock-like paresthesias of the extremities. While the etiology of these syndromes is unclear, the effects of radiation on the replicating oligodendrocytes have been implicated [62].

Subacute effects of chemotherapy may also occur. Intrathecal cytosine arabinoside and methotrexate have been associated with subacute spinal cord damage, sometimes irreversible [46]. L-asparaginase is clearly associated with the occurrence of thrombosis of the CNS, typically not occurring until the completion of several weeks of therapy [63]. The mechanism for this is related to the reduction of proteins associated with coagulation pathways by asparagine depletion, rather than to direct effects on neural tissue.

The learning difficulties experienced by children treated with combinations of radiation and chemotherapy for ALL or brain tumors are the most commonly noted clinical presentations of late CNS toxicity. While any child receiving CNS-directed therapy is at risk for late effects, the severity of the late effects associated with combined modality CNS-directed therapies sets this group of children apart. Often called "neurocognitive" or "neurobehavioral" late effects, these toxicities are characterized by subtle onsets and may not become evident for many years after the acute insult.

In an excellent recent review of neurocognitive late effects, Mulhern and Palmer described what they termed the "neurocognitive phenotype." This phenotype is characterized by limitations in the age-appropriate activities of daily living including school performance, independent living, and some domains of quality of life [64]. Global declines in IQ and performance, characteristic of many children who have received CNS-directed therapies, are secondary effects resulting from "core" changes in a child's ability to attend to and process new information. This difficulty, together with that of information acquisition, underlies the challenges these children face and explains why, without proactive investigation, the effects may not become evident for years. Longitudinal studies of children with medulloblastoma have demonstrated that it is not a loss of information, but rather the failure to acquire new information at a rate similar to their peers, that leads to this apparent diminution of function [65].

Difficulties in the acquisition of new information can result from the failure of many of the processes necessary for learning. Characterized as "domains" of function, declines among children treated with both radiation therapy and chemotherapy to the CNS have been well documented. Of these domains, "executive function," i.e., the ability to allocate attentional resources to planning and organization, may be one of the most impacted. Although often difficult to directly measure, children affected may spend significant time "working" to learn, but realize a relatively limited return from their efforts. The ability to sustain concentration on a specific task is critical to the acquisition of new knowledge and is frequently impacted in such children. When children with ALL treated with cranial radiation were compared to demographically matched controls, those treated with CRT showed deficits in IQ, working memory, and processing speed. Differences in IQ were mediated primarily by differences in working memory [66].

The larger issues of educational attainment among survivors of childhood cancer were recently addressed by the Childhood Cancer Survivor Study, a large retrospective study of children treated for cancer in the 1970s and early 1980s. An analysis of 12,430 survivors and 3,410 full siblings found that special education services were used in 23 % of survivors and 8 % of siblings. The greatest differences were observed among survivors who were diagnosed before age 6 years, most notably survivors of CNS tumors and leukemia. Survivors of leukemia and CNS tumors were also significantly less likely than siblings to finish high school [67].

Survivors of childhood cancer are at risk for other neurologic late effects of therapy. Packer et al. assessed self-reported neurosensory and neurologic dysfunctions among 1,607 patients diagnosed between 1970 and 1986 with a primary CNS tumor [16]. Seventeen percent of these patients reported neurosensory impairment. In comparison to siblings, patients were at elevated risk for hearing impairments, blindness in one or both eyes, cataracts, and double

vision. Radiation exposure greater than 50 Gy to the posterior fossa was associated with a higher likelihood of developing hearing impairment, probably due to irradiation of the cochlea and shunting procedures (refer to the chapter 8 by Landier et al.). Conformal radiation therapy may reduce such risks in future survivors. Packer et al. reported seizure disorders in 25% of patients, including 6.5% who had a late first occurrence. Exposure of any cortical segment of CNS to 30 Gy or more was associated with a two-fold elevated risk for a late seizure [16].

Other, more severe sequelae can occasionally follow CNS-directed therapies. Radiation necrosis of the CNS occurs in fewer than 5% of children treated. The risk of radiation necrosis is increased by larger fractions and larger total doses [68]. The onset of symptoms due to radiation necrosis may be delayed for years following the initial treatment of the child, and, in many instances, the symptoms may mimic those of recurrent tumors. Newer imaging modalities, including PET scanning and MR-spectroscopy, may help discriminate radiation necrosis from tumor recurrence, but biopsy may be needed to establish the diagnosis. Treatment options that exist, but may be of limited efficacy, include surgery, steroids, pentoxifylline, heparin, and, in some instances, hyperbaric oxygen [69]. Vascular events are also rare, but potentially devastating, late effects of radiation therapy. Typically, these involve small blood vessel disease, often leading to small strokes. On very rare occasions, large vessel stokes may also occur.

4.4 Moderators and Mediators of Central Nervous System Outcomes

Brouwers has proposed a model for describing the neurobehavioral late effects in survivors of childhood cancer [70]. According to this model, the neurobehavioral outcome following childhood cancer may be influenced by a number of factors, which can be subdivided into mediators and moderators. *Mediators* are factors that specify how or by which mechanisms an effect occurs and are largely comprised of the therapy exposures described above. *Moderators*

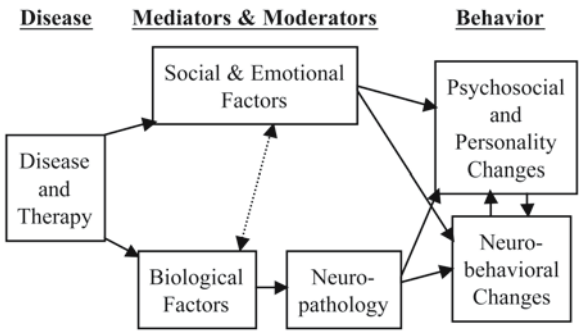


Figure 4.2
Model describing neurobehavioral late effects

are factors that affect the direction and/or strength of the relation between a mediator and an outcome variable but are not by themselves pathogenic [71]. The following moderators have been shown to affect neurobehavioral outcome following brain insult for various diseases in a number of studies: age at insult, time since insult, age at testing, gender, and socioeconomic/family factors.

Outcomes studies of children with cancer, as well as other conditions, have suggested that younger children are more vulnerable to the effects of insult on the brain [7, 33, 72–74]. This is reflected by a greater magnitude of deficits and a slower rate of development in these children than in children who experience an insult at a later age. The neurobehavioral outcome is related to the interaction between the time of the insult and the development of neurobehavioral functions in the immature brain. A number of theoretical considerations may explain the different profiles of neurocognitive functioning dependent on the age at insult [75–77]. The first concept is the dominance of the development of language functions and the earlier maturity of the left cerebral hemisphere. This process results in the representation of language functions primarily in the left hemisphere. The second concept is plasticity, which suggests that other parts of the brain will take over the functions of damaged parts. As already noted, plasticity decreases with increasing age. Finally, it

is assumed that cognitive functions that are not yet well established are more vulnerable to the effects of an insult.

The effect of cancer treatment on the brain and on neurobehavioral functioning is believed to be progressive. Deficits become more pronounced, both in terms of brain imaging abnormalities [78] and neurobehavioral functioning [33, 79], as the time after treatment increases.

Gender may moderate the neurobehavioral outcome following brain injury, but the direction and magnitude of the effect seems to be dependent on age, and on the type and location of the injury. The findings in different patient populations are conflicting. Among children who receive preventive cranial irradiation for ALL, females experience greater neurobehavioral deficits [80]. However, adult women generally have fewer language deficits following unilateral cerebrovascular events or a tumor [81]. Women may also be less vulnerable to seizure-associated brain damage [82]. In contrast, a meta-analysis of studies of traumatic brain injury concluded that the outcome was worse for women than for men with respect to 85% of the included measures [83]. Animal studies have also demonstrated gender differences in response to experimental lesions. Studies of experimental stroke have shown smaller infarcts, but greater degrees of inflammation, for female rats compared to male rats [84, 85]. Other animal studies have proposed a protective effect of estrogen and progesterone, which would favor females [86].

Some studies have suggested that environmental, sociodemographic, and family factors may moderate the neurobehavioral outcome following pediatric head injury and, thus, may affect the neurodevelopmental course of affected children. Environmental factors, such as family distress, family functioning, family resources, parental adjustment, and family interactions, have been investigated. Some studies have concluded that these variables identify children at increased risk for long-term neurobehavioral abnormalities following brain injury [87, 88].

4.5 Prevention and Intervention

4.5.1 Prevention: Primary and Secondary

The primary prevention of adverse CNS outcomes largely consists of seeking alternative therapies that are less toxic but do not compromise cure. Childhood cancer researchers have been successful in implementing this strategy in many instances. In response to the severity of long-term side effects observed after radiation therapy, intrathecal chemotherapy has replaced CRT for CNS leukemia prophylaxis for most types of ALL [43]. Children with ALL who have poor prognosis features or who have sustained a relapse still require CRT, but they receive lower doses than previously [89]. In young brain tumor patients, chemotherapy has been administered as neoadjuvant therapy to delay the administration of CRT for as long as possible [90]. Refinements in radiation oncology techniques, such as conformal radiation therapy and stereotactic radiotherapy, have further reduced long-term toxicity [11]. The Children's Oncology Group is currently investigating children with ALL who were randomized on previous clinical trials to determine (1) whether prednisone confers less neurobehavioral impairment than dexamethasone and, (2) whether intrathecal methotrexate alone results in less impairment than intrathecal methotrexate with cytarabine and hydrocortisone.

Although primary prevention of CNS late effects is often not possible, secondary prevention is an attainable goal. Caregivers should seek early detection of potential adverse outcomes with the goal of improving prognosis. First, health providers should monitor the patient at clinic visits with a history that includes questions, tailored to the age of the patient, about developmental milestones, school performance, peer relations, the need for special education services, and neurological abnormalities (e.g. weakness, seizures). More detailed questions should assess domains of neurocognitive functioning that tend to be impaired specifically in childhood cancer patients. Table 4.1 reviews the domains of function, as well as possible screening questions that could be included in a history.

Table 4.1. Domains of neurobehavioral function potentially affected in survivors of childhood cancer

Domain*	Definition	Screening questions: does the individual…
Intelligence	Basic reasoning ability	• "get" new concepts that are introduced? • have good problem-solving skills? • understand things in an age-appropriate way?
Processing Speed	Rate of mental processing	• take longer than most children to process information? • seem slow to respond?
Academic Achievement	School Performance	• acquire academic skills at a rate similar to that of peers? • have grades that are appropriate for the child's ability?
Attention/ Concentration/ Distractibility	Ability to focus on task for appropriate amount of time. Distractibility is the degree to which one is sidetracked by internal thoughts or external stimuli	• follow multi-step directions? • finish schoolwork and other potentially less interesting tasks without getting off-track?
Executive Function	Ability to plan, organize, and keep information in mind while processing and manipulating that information	• do well on tests that contain previously studied material that is now presented in a novel format? • organize the material to answer math word problems correctly? • successfully complete projects which require planning of multiple, sequential steps (e.g. book reports)?
Language	Ability to understand others and to express oneself	• readily understand what is said to him/her without excessive repetition and rephrasing? • explain what he/she is thinking in an understandable way?
Visuo-perceptual Function	Ability to make sense of what you see and to display spatial skills	• easily get from one place to another in the neighborhood or within the school (e.g. find the cafeteria or a friend's house)? • tie his/her shoes alone? • understand when something is shown to him/her, instead of requiring that an explanation be also verbally provided?
Fine Motor/ Speed/ Dexterity	Ability to make small, fine movements	• manipulate small objects without dropping them? • button his/her clothes independently? • know how to hold a pencil? • use scissors well?
Visuo-motor Integration	Ability to copy what you see using your fine motor skills.	• have legible handwriting? • copy shapes and letters well?
Memory	Ability to learn and store new information	• retain what he/she has learned?
Adaptive Function	Ability to display independent functioning in activities of daily living, social skills, and communication with others	• care for him/herself in an age-appropriate fashion, e.g. teeth-brushing, dressing, bathing, etc.? • play with other children in an age-appropriate fashion?

Table 4.1. Continued

Domain*	Definition	Screening questions: does the individual…
Emotional and Behavioral Function	State of your mood and regulation of your emotions and behavior	• seem to lose control of him/herself • have problems with depression or anxiety • display extreme emotions for the situation (e.g., rage, despair, etc.) or excessive mood swings

* It should be emphasized that there is the potential for overlap among these domains, and all should be considered within the developmental context of the child (i.e., are the child's abilities age-appropriate?).

This table was constructed with the expert input of Fiona Anderson, PhD. Assistant Professor, Division of Pediatric Clinical Neuroscience, University of Minnesota.

Table 4.2. Sample Neurobehavioral Battery to Assess Neurobehavioral Function in Children Previously Treated for Cancer

Domain of Function	Neurobehavioral Instrument
Intelligence	• Wechsler Intelligence Scale for Children – Fourth Edition (WISC IV)
Visuoconstructive/ Fine Motor Coordination	• Beery Developmental Test of Visual Motor Integration – Fifth Edition (VMI) • Grooved Pegboard
Executive Functioning	• FAS Word Fluency • Behavior Rating Inventory of Executive Function (BRIEF) completed by parent
Attention-Concentration	• Conners' Continuous Performance Test II (CPT II): • Conners' Parent Rating Scale - Revised: Short Form (CPRS-R:S)
Verbal and Non-Verbal Memory	• Children's Memory Scale (CMS)
Academic Achievement	• Wechsler Individual Achievement Test – Second Edition – Abbreviated (WIAT-II-A)
Social Adaptation and Behavior	• Child Behavior Checklist for Ages 6-18 (CBCL/6-18) completed by parent

* This battery is currently being used to assess children previously treated for acute lymphoblastic leukemia in a research protocol. It is displayed to give examples of the types of assessments that should be considered. Components of this battery should be modified according to the patient's individual needs.

Deficits in neurocognitive functioning often do not present until several years after treatment and can be subtle and/or sub-clinical. For these reasons, a pre-symptomatic neuropsychological assessment should be strongly considered. The components of a comprehensive neurobehavioral battery may vary based upon the individual preference of the neuropsychologist. A suggested battery compiled for research related to the treatment of children with leukemia is shown in Table 4.2. Modification according to the individual patient's clinical situation is advised. Patients may demonstrate abnormalities in more than one domain of function, given that the domains often overlap in terms of brain function. Another caveat the neuropsychologist should be aware of is the coexistence of physical impairments, which could affect testing on standardized tests. Examples include hearing loss after cis-platinum, blindness after retinoblastoma, and hemiplegia after a stroke.

The timing of the assessment depends on the individual patient, but may be particularly helpful at school re-entry to facilitate transition. For younger patients who are not yet in school, or for those who attended school during therapy, an evaluation at the end of therapy is recommended. Mulhern and Palmer have suggested that a surveillance plan of for-

mal neuropsychological testing be devised for each individual based on his or her treatment exposures and pre-morbid risk factors, even in asymptomatic patients [64]. For example, a child with ALL who did not receive CRT might receive a single neurocognitive evaluation at the completion of therapy and then several years after therapy. In contrast, an infant with a brain tumor should be evaluated every six months after diagnosis until school entry.

4.5.2 Interventions

The comprehensive neurobehavioral assessment provides valuable data that can be used for educational accommodations and remediation in areas of impairment. It is essential that test findings be communicated directly to teachers, who can use the information to enhance the child's learning. Examples of educational accommodation include placing the child in the front of the classroom, where there is less distraction; reducing the number of items on multiple choice tests; breaking assignments into several smaller steps; and allowing more time for the completion of examinations [91]. School education services can assist in the remediation of domains of impairment. Commonly needed services include speech/language therapy and occupational therapy. Sometimes communication with staff at the child's school is benefited by conferences with medical caregivers who can share how areas of neurobehavioral impairment are related to childhood cancer treatments. This is particularly helpful in children whose school failure is perceived by school officials to be disinterest, laziness, or bad behavior. Armstrong and colleagues are currently collecting data in an ongoing study to assess the implementation and effectiveness of individualized educational plans (IEPs) in children with cancer.

Other exciting intervention possibilities include cognitive rehabilitation and pharmacotherapy. Cognitive rehabilitation is an intervention "intended to restore lost cognitive functions or to teach the patient skills to compensate for cognitive losses that cannot be restored" [64]. Butler and colleagues have developed an outpatient rehabilitation program targeted at disorders of attention and associated processes [92]. This intervention was piloted in 21 childhood cancer survivors who displayed improvements in vigilance, attention, and arithmetic academic achievement compared with 10 survivors who did not receive the intervention.

Stimulant medications, such as methylphenidate hydrochloride (MPH), are mixed dopaminergic–noradrenergic agonists that are thought to improve the function of the fronto-striatal attentional network in the brain [91]. Children treated for cancer often exhibit symptoms similar to those who have attention-deficit hyperactivity disorder and may similarly respond to MPH. Thompson et al. demonstrated in a double-blind, placebo-controlled study of learning-impaired survivors of childhood cancer that MPH was associated with improvements in attention [93]. Mulhern et al. are currently completing a multi-institutional, NCI-funded trial of MPH in a randomized, double blind, 3-week home crossover study of children previously treated for cancer [64]. If there is evidence of objective improvement at the end of 3 weeks, MPH will be continued for 12 additional months. Preliminary analyses have demonstrated that most participants have had some response in the home crossover trial [92]. The long-term effect of MPH on attention and academic achievement will be of great interest.

4.6 Future Directions

As the field of pediatric oncology has advanced, the likelihood of the successful treatment of childhood cancer has progressively increased. Currently, it is estimated that well over 70 % of all children diagnosed with cancer in the United States will survive 5 years or more from the time of the original diagnosis. Moderating the enthusiasm over this success is the realization that "cure" is more than successful treatment or eradication of the disease. The ultimate goal of therapy is to return the patient to health and allow the most complete realization possible of his or her pre-morbid potential. The toxicities that modern cancer therapy can impose on the CNS may severely limit that potential for patients. It is important to investigate all possible strategies in order to under-

stand the pathogenesis of the risk factors. Research on host factors other than gender or age ranges from the molecular level to ecological; from genetic polymorphisms that impact on drug or radiation sensitivity to studies of the social environment of the child, before, during, and after cancer therapy. New treatment approaches, including therapies that eliminate radiation, must not be assumed to be non-toxic; late toxicities must be investigated with rigor. Finally, ongoing research for the recovery and rehabilitation of children who have experienced toxicity from CNS-directed therapies is crucial and could impact positively on thousands of lives. Despite the difficulties they may experience, children with cancer are growing up, entering our workforce and contributing to our society daily. Clearly, our commitment to them must extend beyond the conventional notion of "cure" to include the realization of their maximum potential.

Acknowledgements. We would like to thank Dr. Pim Brouwers, of Baylor University, Dr. Fiona Anderson, of the University of Minnesota, and Dr. Robert Butler, of the Oregon Health Sciences University, for their helpful and insightful discussions during the preparation of this manuscript.

References

1. Menkes JH (1990) Textbook of child neurology, 4th edn. Lea and Febiger, Philadelphia
2. Webb SJ, Monk CS, Nelson CA (2001) Mechanisms of postnatal neurobiological development: implications for human development. Dev Neuropsychol 19:147–171
3. Sarnat HB (1992) Cerebral dysgenesis: embryology and clinical expression. Oxford University Press, New York
4. Corriveau RA, Huh GS, Shatz CJ (1998) Regulation of class I MHC gene expression in the developing and mature CNS by neural activity. Neuron 21:505–520
5. Minkowski A, Council for International Organizations of Medical Sciences, France (1967) Dâelâegation gâenâerale áa la recherche scientifique et technique. Regional development of the brain in early life. Davis, Philadelphia
6. Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB (1996) Brain development, gender and IQ in children. A volumetric imaging study. Brain 119:1763–1774
7. Taylor HG, Alden J (1997) Age-related differences in outcomes following childhood brain insults: an introduction and overview. J Int Neuropsychol Soc 3:555–567
8. Robinson K (1998) Implications of developmental plasticity for the language acquisition of deaf children with cochlear implants. Int J Pediatr Otorhinolaryngol 46:71–80
9. Bowering ER, Maurer D, Lewis TL, Brent HP (1997) Constriction of the visual field of children after early visual deprivation. J Pediatr Ophthalmol Strabismus 34:347–356
10. Ries LA, Smith MA, Gurney JG, Linet M, Tamra T, et al. (1999) Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute SEER Program, NIH Publ no 9904649. National Cancer Institute, Bethesda MD
11. Pizzo PA, Poplack DG (2002) Principles and practice of pediatric oncology, 4th edn. Lippincott Williams and Wilkins, Philadelphia, p xv, 1692 pp
12. Packer RJ, Sposto R, Atkins TE, Sutton LN, Bruce DA, Siegel KR et al. (1987) Quality of life in children with primitive neuroectodermal tumors (medulloblastoma) of the posterior fossa. Pediatr Neurosci 13:169–175
13. Gelabert-Gonzalez M, Fernandez-Villa J (2001) Mutism after posterior fossa surgery. Review of the literature. Clin Neurol Neurosurg 103:111–114
14. Steinbok P, Cochrane DD, Perrin R, Price A (2003) Mutism after posterior fossa tumour resection in children: incomplete recovery on long-term follow-up. Pediatr Neurosurg 39:179–183
15. Sonderkaer S, Schmiegelow M, Carstensen H, Nielsen LB, Muller J, Schmiegelow K (2003) Long-term neurological outcome of childhood brain tumors treated by surgery only. J Clin Oncol 21:1347–1351
16. Packer RJ, Gurney JG, Punyko JA, Donaldson SS, Inskip PD, Stovall M et al. (2003) Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. J Clin Oncol 21: 3255–3261
17. Brouwers P, Riccardi R, Fedio P, Poplack DG (1985) Long-term neuropsychologic sequelae of childhood leukemia: correlation with CT brain scan abnormalities. J Pediatr 106: 723–728
18. Crosley CJ, Rorke LB, Evans A, Nigro M (1978) Central nervous system lesions in childhood leukemia. Neurology 28: 678–685
19. Price R (1983) Therapy related central nervous system diseases in children with acute lymphocytic leukemia. In: Mastrangelo R, Poplack D, Riccardi R (eds) Central nervous system leukemia. Nijhoff, Amsterdam
20. Price RA, Birdwell DA (1978) The central nervous system in childhood leukemia. III. Mineralizing microangiopathy and dystrophic calcification. Cancer 42:717–728

21. Peylan-Ramu N, Poplack DG, Pizzo PA, Adornato BT, di Chiro G (1978) Abnormal CT scans of the brain in asymptomatic children with acute lymphocytic leukemia after prophylactic treatment of the central nervous system with radiation and intrathecal chemotherapy. N Engl J Med 298:815–818
22. Schultheiss TE, Kun LE, Ang KK, Stephens LC (1995) Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 31:1093–1112
23. Tofilon PJ, Fike JR (2000) The radioresponse of the central nervous system: a dynamic process. Radiat Res 153:357–370
24. Meadows AT, Gordon J, Massari DJ, Littman P, Fergusson J, Moss K (1981) Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. Lancet 2:1015–1018
25. Cousens P, Waters B, Said J, Stevens M (1988) Cognitive effects of cranial irradiation in leukaemia: a survey and meta-analysis. J Child Psychol Psychiatry 29:839–852
26. Rogers J, Britton PG, Morris RG, Kernahan J, Craft A (1992) Memory after treatment for acute lymphoblastic leukemia. Arch Dis Child 67:266–268
27. Ochs J, Mulhern R, Fairclough D, Parvey L, Whitaker J, Ch'ien L, et al. (1991) Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate: a prospective study. J Clin Oncol 9:145–151
28. Brown RT, Madan-Swain A (1993) Cognitive, neuropsychological, and academic sequelae in children with leukemia. J Learn Disabil 26:74–90
29. Stehbens JA, Kaleita TA, Noll RB, MacLean WEJ, O'Brien RT, Waskerwitz MJ et al. (1991) CNS prophylaxis of childhood leukemia: what are the long-term neurological, neuropsychological, and behavioral effects? Neuropsychol Rev 2:147–177
30. Radcliffe J, Bunin GR, Sutton LN, Goldwein JW, Phillips PC (1994) Cognitive deficits in long-term survivors of childhood medulloblastoma and other noncortical tumors: age-dependent effects of whole brain radiation. Int J Dev Neurosci 12:327–334
31. Mulhern RK, Fairclough D, Ochs J (1991) A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. J Clin Oncol 9:1348–1356
32. Rubenstein CL, Varni JW, Katz ER (1990) Cognitive functioning in long-term survivors of childhood leukemia: a prospective analysis. J Dev Behav Pediatr 11:301–305
33. Jankovic M, Brouwers P, Valsecchi MG, van Veldhuizen A, Huisman J, Kamphuis R et al. (1994) Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukaemia. ISPACC. International Study Group on Psychosocial Aspects of Childhood Cancer. Lancet 344:224–227
34. Robison LL, Nesbit MEJ, Sather HN, Meadows AT, Ortega JA, Hammond GD (1984) Factors associated with IQ scores in long-term survivors of childhood acute lymphoblastic leukemia. Am J Pediatr Hematol Oncol 6:115–121
35. Waber DP, Urion DK, Tarbell NJ, Niemeyer C, Gelber R, Sallan SE (1990) Late effects of central nervous system treatment of acute lymphoblastic leukemia in childhood are sex-dependent. Dev Med Child Neurol 32:238–248
36. Bleyer WA, Fallavollita J, Robison L, Balsom W, Meadows A, Heyn R et al. (1990) Influence of age, sex, and concurrent intrathecal methotrexate therapy on intellectual function after cranial irradiation during childhood: a report from the Children's Cancer Study Group. Pediatr Hematol Oncol 7:329–338
37. Kingma A, Rammeloo LA, van der Does-van den Berg A, Rekers-Mombarg L, Postma A (2000) Academic career after treatment for acute lymphoblastic leukaemia. Arch Dis Child 82:353–357
38. Fuss M, Poljanc K, Hug EB (2000) Full Scale IQ (FSIQ) changes in children treated with whole brain and partial brain irradiation. A review and analysis. Strahlenther Onkol 176:573–581
39. Moleski M (2000) Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. Arch Clin Neuropsychol 15:603–630
40. Ruggiero A, Conter V, Milani M, Biagi E, Lazzareschi I, Sparano P et al. (2001) Intrathecal chemotherapy with antineoplastic agents in children. Paediatr Drugs 3:237–246
41. Prassopoulos P, Cavouras D, Golfinopoulos S, Evlogias N, Theodoropoulos V, Panagiotou J (1996) Quantitative assessment of cerebral atrophy during and after treatment in children with acute lymphoblastic leukemia. Invest Radiol 31:749–754
42. Raymond-Speden E, Tripp G, Lawrence B, Holdaway D (2000) Intellectual, neuropsychological, and academic functioning in long-term survivors of leukemia. J Pediatr Psychol 25:59–68
43. Brown RT, Sawyer MB, Antoniou G, Toogood I, Rice M, Thompson N et al. (1996) A 3-year follow-up of the intellectual and academic functioning of children receiving central nervous system prophylactic chemotherapy for leukemia. J Dev Behav Pediatr 17:392–398
44. Orti E, Tornello S, de Nicola AF (1985) Dynamic aspects of glucocorticoid receptors in the spinal cord of the rat. J Neurochem 45:1699–1707
45. Mahoney DH Jr, Shuster JJ, Nitschke R, Lauer SJ, Steuber CP, Winick N et al. (1998) Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy – a Pediatric Oncology Group study. J Clin Oncol 16:1712–1722
46. Watterson J, Toogood I, Nieder M, Morse M, Frierdich S, Lee Y, et al. (1994) Excessive spinal cord toxicity from intensive central nervous system-directed therapies. Cancer 74: 3034–3041

47. Sapolsky RM (1993) Potential behavioral modification of glucocorticoid damage to the hippocampus. Behav Brain Res 57:175–182
48. Waber DP, Carpentieri SC, Klar N, Silverman LB, Schwenn M, Hurwitz CA et al. (2000) Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone. J Pediatr Hematol Oncol 22:206–213
49. Bodnoff SR, Humphreys AG, Lehman JC, Diamond DM, Rose GM, Meaney MJ (1995) Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. J Neurosci 15:61–69
50. Bender BG, Lerner JA, Poland JE (1991) Association between corticosteroids and psychologic change in hospitalized asthmatic children. Ann Allergy 66:414–419
51. Drigan R, Spirito A, Gelber RD (1992) Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. Med Pediatr Oncol 20:13–21
52. Wolkowitz OM (1994) Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. Psychoneuroendocrinology 19:233–255
53. Murphy BP, Inder TE, Huppi PS, Warfield S, Zientara GP, Kikinis R et al. (2001) Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. Pediatrics 107:217–221
54. Shinwell ES, Karplus M, Reich D, Weintraub Z, Blazer S, Bader D et al. (2000) Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. Arch Dis Child Fetal Neonatal Ed 83:F177–F181
55. Andre P, Thebaud B, Odievre MH, Razafimahefa H, Zupan V, Dehan M et al. (2000) Methylprednisolone, an alternative to dexamethasone in very premature infants at risk of chronic lung disease. Intensive Care Med 26:1496–1500
56. Alexander E 3rd, Loeffler JS (1998) Radiosurgery for primary malignant brain tumors. Semin Surg Oncol 14:43–52
57. Pratt CB, Green AA, Horowitz ME, Meyer WH, Etcubanas E, Douglass E et al. (1986) Central nervous system toxicity following the treatment of pediatric patients with ifosfamide/mesna. J Clin Oncol 4:1253–1261
58. Pratt CB, Goren MP, Meyer WH, Singh B, Dodge RK (1990) Ifosfamide neurotoxicity is related to previous cisplatin treatment for pediatric solid tumors. J Clin Oncol 8:1399–1401
59. Kurtzberg J, Keating M, Moore J et al. (1996) 2-amino-9-B-D-arabinosyl-6-methoxy-9H-guanine (GW506U; compound 506U) is highly active in patients with T-cell malignancies; results of a phase I trial in pediatric and adult patients with refractory hematological malignancies (abstract). Blood 88:699a
60. Freeman JE, Johnston PG, Voke JM (1973) Somnolence after prophylactic cranial irradiation in children with acute lymphoblastic leukaemia. Br Med J 4:523–525
61. Miyahara M, Azuma E, Hirayama M, Kobayashi M, Hori H, Komada Y et al. (2000) Somnolence syndrome in a child following 1200-cGy total body irradiation in an unrelated bone marrow transplantation. Pediatr Hematol Oncol 17:489–495
62. Van der Kogel A (1991) Central nervous system radiation injury in small animal models. In: Gutin P, Leibel S, Sheline G (eds) Radiation injury to the nervous system. Raven, New York, pp 91–112
63. Priest JR, Ramsay NK, Latchaw RE, Lockman LA, Hasegawa DK, Coates TD et al. (1980) Thrombotic and hemorrhagic strokes complicating early therapy for childhood acute lymphoblastic leukemia. Cancer 46:1548–1554
64. Mulhern RK, Palmer SL (2003) Neurocognitive late effects in pediatric cancer. Curr Probl Cancer 27:177–197
65. Palmer SL, Goloubeva O, Reddick WE, Glass JO, Gajjar A, Kun L et al. (2001) Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. J Clin Oncol 19:2302–2308
66. Schatz J, Kramer JH, Ablin A, Matthay KK (2000) Processing speed, working memory, and IQ: a developmental model of cognitive deficits following cranial radiation therapy. Neuropsychology 14:189–200
67. Mitby PA, Robison LL, Whitton JA, Zevon MA, Gibbs IC, Tersak JM et al. (2003) Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 97:1115–1126
68. Rottenberg DA, Chernik NL, Deck MD, Ellis F, Posner JB (1977) Cerebral necrosis following radiotherapy of extracranial neoplasms. Ann Neurol 1:339–357
69. New P (2001) Radiation injury to the nervous system. Curr Opin Neurol 14:725–734
70. Brouwers P (1987) Neuropsychological abilities of long-term survivors of childhood leukemia. In: Aaronson N, Bechman J (eds) The quality of life of cancer patients. Raven, New York, pp 153–166
71. Baron RM, Kenny DA (1986) The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 51:1173–1182
72. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE (1998) Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol 16: 1723–1728
73. Hack M, Breslau N, Aram D, Weissman B, Klein N, Borawski-Clark E (1992) The effect of very low birth weight and social risk on neurocognitive abilities at school age. J Dev Behav Pediatr 13:412–420
74. Kaleita TA (2002) Central nervous system-directed therapy in the treatment of childhood acute lymphoblastic leukemia and studies of neurobehavioral outcome: Children's Cancer Group trials. Curr Oncol Rep 4:131–141

75. Bates E (1999) Language and the infant brain. J Commun Disord 32:195–205
76. Stiles J (2000) Neural plasticity and cognitive development. Dev Neuropsychol 18:237–272
77. Vicari S, Albertoni A, Chilosi AM, Cipriani P, Cioni G, Bates E (2000) Plasticity and reorganization during language development in children with early brain injury. Cortex 36:31–46
78. Riccardi R, Brouwers P, Di Chiro G, Poplack DG (1985) Abnormal computed tomography brain scans in children with acute lymphoblastic leukemia: serial long-term follow-up. J Clin Oncol 3:12–18
79. Jannoun L (1983) Are cognitive and educational development affected by age at which prophylactic therapy is given in acute lymphoblastic leukaemia? Arch Dis Child 58:953–958
80. Waber DP, Tarbell NJ, Fairclough D, Atmore K, Castro R, Isquith P et al. (1995) Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. J Clin Oncol 13:2490–2496
81. McGlone J (1977) Sex differences in the cerebral organization of verbal functions in patients with unilateral brain lesions. Brain 100:775–793
82. Briellmann RS, Berkovic SF, Jackson GD (2000) Men may be more vulnerable to seizure-associated brain damage. Neurology 55:1479–1485
83. Farace E, Alves WM (2000) Do women fare worse: a meta-analysis of gender differences in traumatic brain injury outcome. J Neurosurg 93:539–545
84. Alkayed NJ, Harukuni I, Kimes AS, London ED, Traystman RJ, Hurn PD (1998) Gender-linked brain injury in experimental stroke. Stroke 29:159–165; discussion 166
85. Brady MT, McGrath N, Brouwers P, Gelber R, Fowler MG, Yogev R et al. (1996) Randomized study of the tolerance and efficacy of high- versus low-dose zidovudine in human immunodeficiency virus-infected children with mild to moderate symptoms (AIDS Clinical Trials Group 128). Pediatric AIDS Clinical Trials Group. J Infect Dis 173:1097–1106
86. Roof RL, Hall ED (2000) Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma 17:367–388
87. Yeates KO, Taylor HG, Drotar D, Wade SL, Klein S, Stancin T et al. (1997) Preinjury family environment as a determinant of recovery from traumatic brain injuries in school-age children. J Int Neuropsychol Soc 3:617–630
88. Wade S, Drotar D, Taylor HG, Stancin T (1995) Assessing the effects of traumatic brain injury on family functioning: conceptual and methodological issues. J Pediatr Psychol 20:737–752
89. Nesbit ME, Jr., Sather HN, Robison LL, Ortega J, Littman PS, D'Angio GJ et al. (1981) Presymptomatic central nervous system therapy in previously untreated childhood acute lymphoblastic leukaemia: comparison of 1800 rad and 2400 rad. A report for Children's Cancer Study Group. Lancet 1:461–466
90. Duffner PK, Horowitz ME, Krischer JP, Friedman HS, Burger PC, Cohen ME et al. (1993) Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med 328:1725–1731
91. Butler RW, Mulhern RK (2004) Neurocognitive interventions for children and adolescents surviving cancer. J Pediatr Psychol (in press)
92. Butler RW, Copeland DR (2002) Attentional processes and their remediation in children treated for cancer: a literature review and the development of a therapeutic approach. J Int Neuropsychol Soc 8:115–124
93. Thompson SJ, Leigh L, Christensen R, Xiong X, Kun LE, Heideman RL et al. (2001) Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. J Clin Oncol 19:1802–1808

Neuroendocrine Complications of Cancer Therapy

Wing Leung · Susan R. Rose · Thomas E. Merchant

Contents

Table 5.1. Anterior pituitary hormones and major hypothalamic regulatory factors

Pituitary hormone	Hypothalamic factor	Effect
Growth hormone	Growth hormone-releasing hormone	+
	Somatostatin	–
Prolactin	Dopamine	–
Luteinizing hormone	Gonadotropin-releasing hormone	+
Follicle-stimulating hormone	Gonadotropin-releasing hormone	+
Thyroid-stimulating hormone	Thyrotropin-releasing hormone	+
	Somatostatin	–
Adrenocorticotropin	Corticotropin-releasing hormone	+
	Vasopressin	+

Effects on the hypothalamus are either stimulatory (+) or inhibitory (–)

5.1 Pathophysiology

5.1.1 Normal HypothalamicPituitary Axis

The hypothalamic–pituitary axis (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 functions. The hypothalamus has extensive neural communications with other brain regions and regulates brain functions, including temperature, appetite, thirst, sexual behavior, and fear. The hypothalamus also contains two types of neurosecretory cells (Fig. 5.1): (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 5.1.

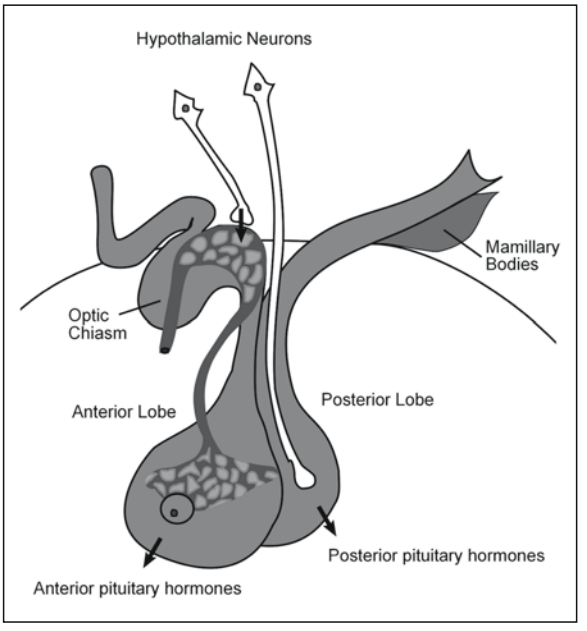


Figure 5.1
Diagrammatic representation of the hypothalamic–pituitary axis

5.1.1.1 Growth Hormone

Growth hormone (GH) is a 191-amino acid polypeptide synthesized and secreted by the somatotrophs in the anterior pituitary gland in response to the hypothalamus 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 [45]. When somatostatin concentrations decrease, the tonic concentration of GHRH causes the release of GH into the systemic circulation. Factors such as neuropeptide Y, leptin, galanin, and ghrelin may also regulate GH secretion. In healthy children and adults, GH secretion is pulsatile, particularly during sleep, with two to six pulses per night [50]. In adolescents, additional pulses occur during the day, and the pulses have higher peaks than those seen in children and adults (Fig. 5.2a).

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) [71]. 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.

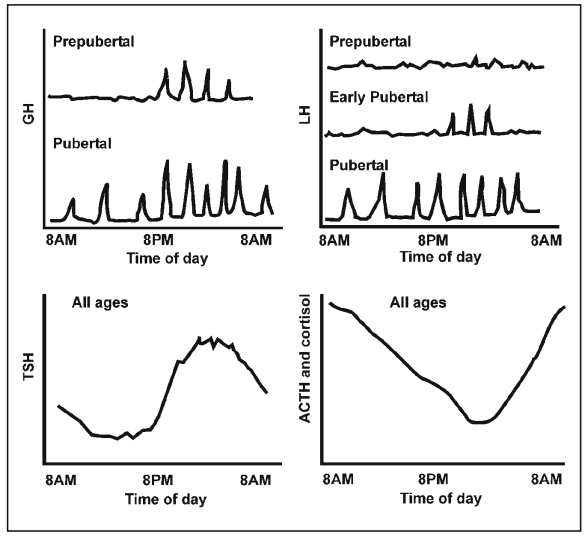


Figure 5.2 a, b

a Changes with pubertal status in the normal daily pattern of growth hormone (GH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and adrenocorticotropin (ACTH) and cortisol secretion. **b** Normal changes in LH and FSH levels from infancy to adolescence

5.1.1.2 Gonadotropins

Luteinizing hormone (LH) and follicle stimulating hormone (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 (Fig. 5.2a). The hypothalamic stimulus is actively inhibited between 6 months of age and the onset of puberty (Fig. 5.2b). This inhibition can be disturbed by tumor mass, cranial surgery, or irradiation, thereby resulting in precocious puberty in children. In men, LH stimulates testosterone production in the Leydig cells of the testes; normal spermatogenesis requires both LH and FSH. In women, FSH stimulates the production of estrogen and LH stimulates the production of progesterone in the ovary. 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 (see section 5.2.2 for information on the normal development of the gonads).

5.1.1.3 Thyroid-Stimulating Hormone

Thyrotropin, also known as thyroid-stimulating hormone (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, the TSH concentration is low in the afternoon, rises dramatically (*surges*) after 1900 hours, and reaches its highest concentrations between 2200 and 0400 hours (Fig. 5.2a) [51]. Thus, 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 [48]. Altered TSH glycosylation, resulting in altered bioactivity, is seen in mixed hypothyroidism (central hypothyroidism with mild TSH elevation [5–15 mU/l]) [23, 49].

TSH stimulates the thyroid gland to produce thyroxine (T4) and triiodothyronine (T3). T4 and T3 circulate in the blood stream bound to thyroxine-binding globulin and albumin; only small amounts are free or unbound. Free T4 undergoes intracellular deiodination to form free T3, which interacts with the DNA in a cell's nucleus to influence cellular mRNA and protein synthesis. Free T4 also provides negative feedback to the hypothalamus and pituitary to modulate the secretion of TRH and TSH.

5.1.1.4 Adrenocorticotropin

Adrenocorticotropin (ACTH) is a 39-amino acid peptide hormone processed in the corticotrophs from a large precursor molecule, pro-opiomelanocortin. In healthy individuals, hypothalamic corticotrophin-releasing hormone and vasopressin are released in two or three synchronous pulses per hour synergistically and stimulate the secretion of ACTH from the pituitary [9]. ACTH secretion is pulsatile and varies throughout the day; it peaks before the person awakens in the morning (Fig. 5.2a), increases with stress, and is inhibited by glucocorticoids. Because cortisol secretion is regulated by ACTH, cortisol secretion has characteristics similar to the secretion of ACTH. In addition to the negative feedback of glucocorticoids, ACTH inhibits its own secretion (short loop feedback).

5.1.1.5 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. Hypothalamic control of PRL secretion (primarily through dopamine release) is different from that of the other pituitary hormones in that the hypothalamus inhibits, rather than stimulates, secretion of PRL. Thus, elevated PRL levels can be a useful marker of hypothalamic disorders that leave the pituitary intact.

5.1.2 Injury of the HypothalamicPituitary Axis in Patients with Cancer

The hypothalamic–pituitary axis (HPA) is vulnerable to damage by certain tumors, surgical trauma, irradiation, and chemotherapy [11, 60]. A summary of common risk factors for HPA disorders that develop after cancer treatment is presented in Table 5.2. Patients with tumors in the area of the HPA (e.g. craniopharyngioma or hypothalamic/chiasmatic tumor) are at particular risk for neuroendocrinopathy [15, 33]. Many HPA injuries are attributable to damage caused by radiation therapy (see section 5.1.1.3). However, the incidence of pre-RT neuroendocrinopathies in pediatric patients with brain tumors is high. For example, out of 68 pediatric patients in one study [32], 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 %) revealed abnormalities in GH, 19 (43 %) in TSH and 10 (22 %) in ACTH. Six patients (13 %) had aberrations in

Table 5.2. Risk factors, diagnostic studies, and treatment options

Disorder	Highest risk	Diagnostic studies	Treatment options
GH deficiency	≥ 18 Gy CRT Pre-transplant CRT TBI Young age Tumor near HPA Hydrocephalus	IGF-1, IGFBP-3 GH stimulation tests	Recombinant GH GHRH GnRH agonist (if pubertal maturity too advanced for height)
Gonadotropin deficiency	≥ 30 Gy CRT Tumor near HPA	LH, FSH, estradiol, or testosterone (4 to 8 AM) Bone age GnRH stimulation test	Estrogen / progestin (women) Testosterone (men)
Precocious puberty	18–24 Gy CRT Female Young age Tumor near HPA	LH, FSH, estradiol or testosterone (4 to 8 AM) Bone age radiograph Pelvic ultrasound (female) +/– GnRH stimulation test +/– GH stimulation test	GnRH agonist
TSH deficiency	≥ 30 Gy CRT TBI Tumor near HPA Hydrocephalus	Free T4, TSH (8 AM) Nocturnal TSH surge TRH stimulation test	L-thyroxine
ACTH deficiency	≥ 30 Gy CRT Tumor near HPA Hydrocephalus	Cortisol (8 AM) Adrenal stimulation test	Hydrocortisone
Hyper-prolactinemia	≥ 50 Gy CRT Tumor near HPA	Prolactin	Dopamine agonists
Diabetes insipidus	Histiocytosis Germinomas Tumor or tumor-related cysts near HPA	Simultaneous serum and urine osmolarity after 8–12 hours without fluid intake	Desmopressin
Osteopenia	Low GH, TSH, or LH/FSH High prolactin	DEXA or quantitative CT	Calcium + vitamin D +/– bisphosphonates
Hypothalamic obesity	Young age (<6 years) ≥ 50 Gy (hypothalamus) Tumor near HPA	Fasting insulin and glucose Oral glucose tolerance test with insulin levels	Diet and exercise Ritalin or Dexedrine Metformin (monitor for hypoglycemia) Octreotide

GH, growth hormone; CRT, cranial radiation therapy; TBI, total body irradiation; HPA, hypothalamic–pituitary axis; IGF-1, insulin-like growth factor 1; IGFBP3, IGF binding protein 3; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; T4, thyroxine; TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone; ACTH, adrenocorticotrophin

gonadotropin. In addition to these dysfunctions, patients who receive chemotherapy alone (with no history of RT or CNS tumor) may be at risk for neuroendocrinopathy. Of the 31 patients evaluated in one study for altered growth and development, 48% had GH deficiency, 52% had central hypothyroidism, and 32% had pubertal abnormalities [57].

GH deficiency is commonly believed to be the first hypothalamic–pituitary deficiency to emerge after injury to the HPA, followed by deficiencies of gonadotropin, ACTH and TSH [60, 65]; however, these deficiencies can occur in any order [11, 21, 35, 54, 67]. 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 [54]. The next most common alteration is in pubertal timing (precocious, rapid, delayed, or absent). ACTH deficiency, although 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. Hypothalamic injury resulting from tumor, surgery, or irradiation can result in unrelenting weight gain, termed "hypothalamic obesity."

5.1.3 Contribution of Radiation to HypothalamicPituitary Axis Injury

Radiation therapy (RT) is a significant contributor to neuroendocrine complications commonly observed after treatment for CNS tumors, CNS preventative therapy for ALL and following total body irradiation. Similar complications are observed when the HPA is incidentally irradiated in the treatment of nasopharyngeal cancer, retinoblastoma, Hodgkin's disease with involvement of Waldeyer's ring or pediatric sarcomas of the head and neck (e.g. parameningeal and orbital rhabdomyosarcoma) (Fig. 5.3). The incidence of neuroendocrine sequelae after RT and also the time to onset are difficult to predict. This is largely due to other contributors to HPA dysfunction, which may coincide temporally with the administration of RT. A notable example is hydrocephalus, which can cause a 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 [22]. 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 tumor diagnosis to one 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 (Fig. 5.4). 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. Moreover, it demonstrated the importance of managing hydrocephalus, which commonly occurs in children with posterior fossa tumors.

Clinical data describing the 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 using single-dose or fractionated TBI (8–14 Gy), cranial irradiation for ALL (18 Gy and 24 Gy) and tumors of the sellar or parasellar region, in which the HPA was uniformly included in the volume of the prescribed dose (>50 Gy) (Fig. 5.5). For other diseases, the HPA may have been located within the irradiated volume for part or all of the treatment, or it may have been located in the gradient of dose (dose fall off), with the result that the HPA experienced only a fraction of the daily dose administered (Fig. 5.6). These circumstances make it difficult to assign a dose to the HPA or to determine the risk for late effects. The difficulties become apparent 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 can be calculated and reported more accurately. When correlated with ob-

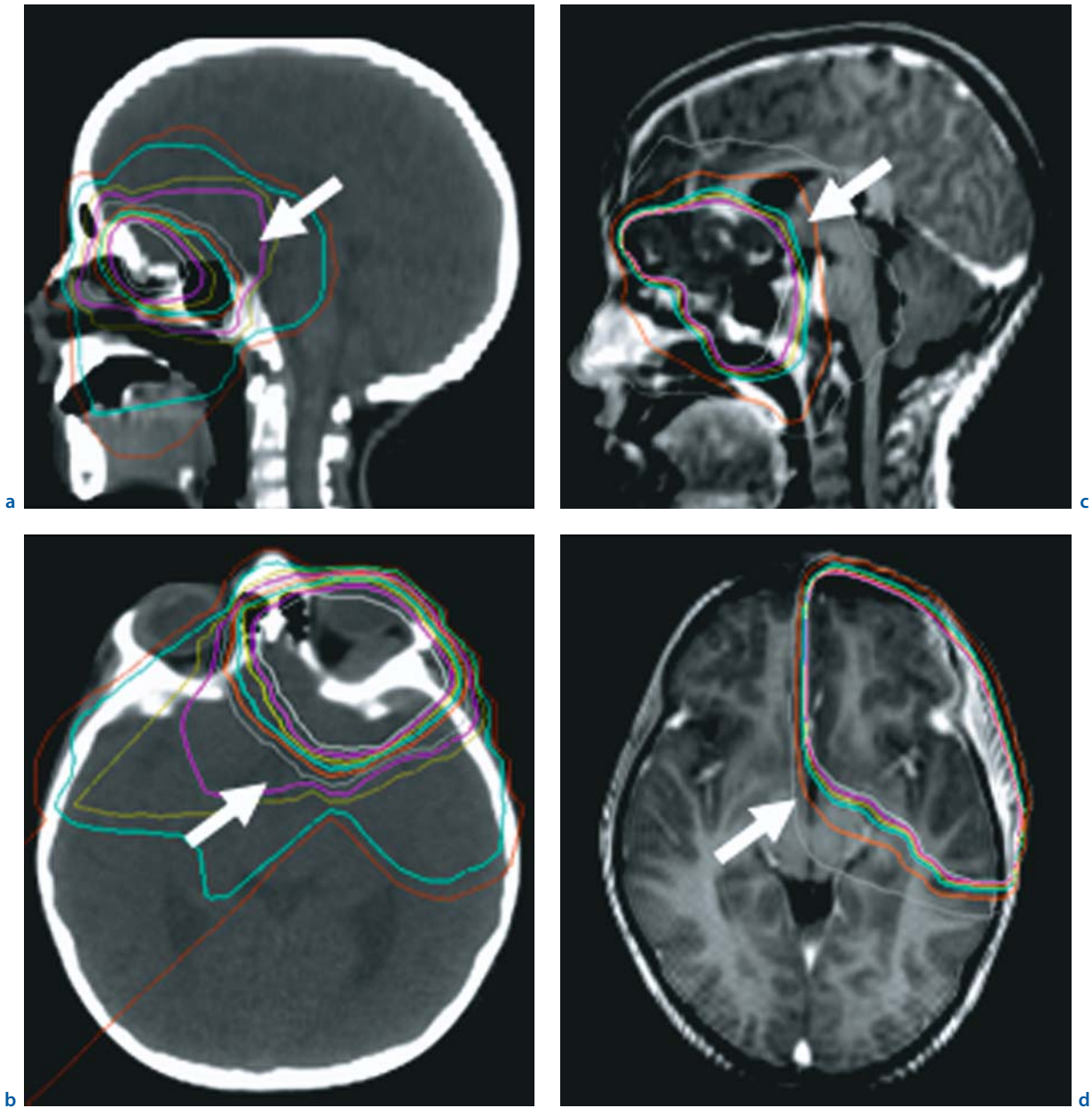
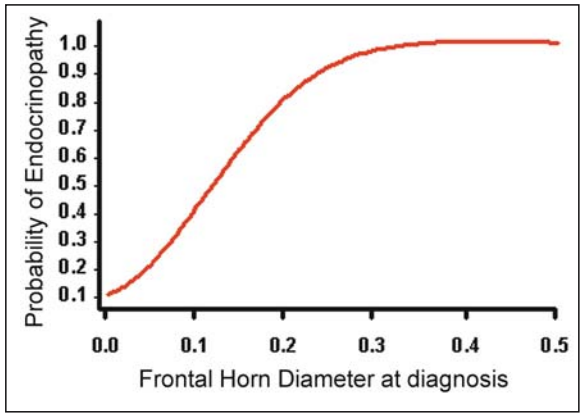
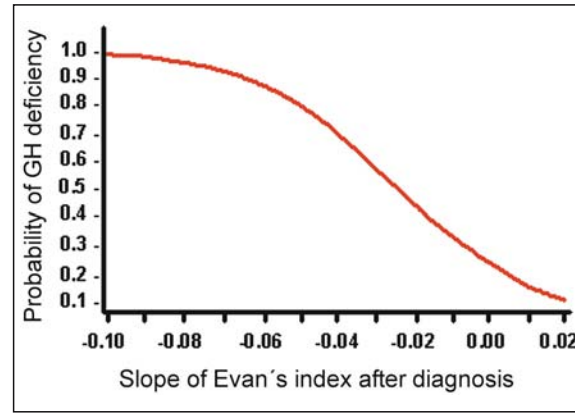


Figure 5.3 ad

Radiation dosimetry taken from the treatment of children with orbital (**a**, **b**) and infratemporal fossa (**c**, **d**) rhabdomyosarcoma. The images illustrate cases in which the HPA is incidentally irradiated and may receive all or a portion of the prescription dose (*arrow* indicates location of hypothalamus)



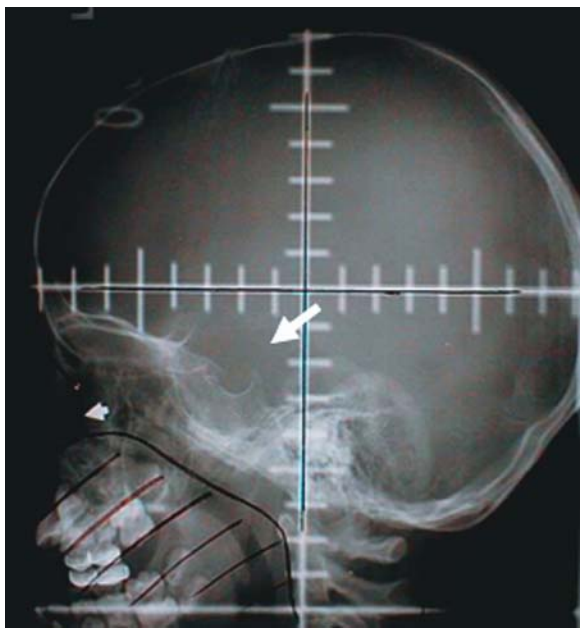
a



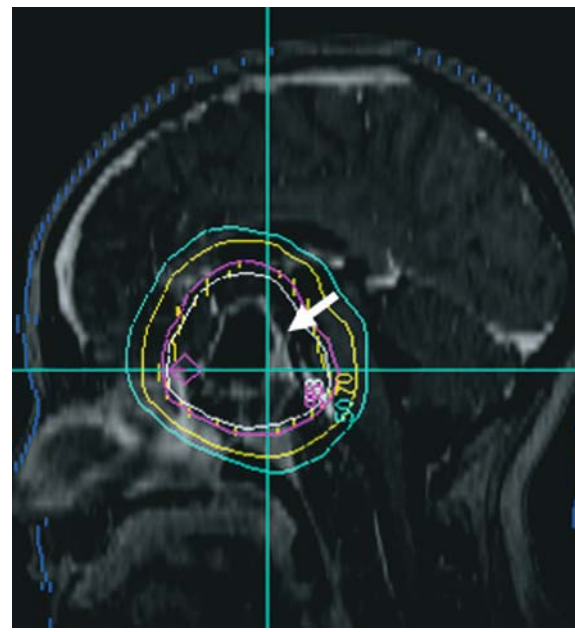
b

Figure 5.4 a, b

The effect of hydrocephalus on pre-irradiation endocrinopathy in children with infratentorial ependymoma. **a** Probability of pre-irradiation endocrine deficiency based on frontal horn diameter measured at diagnosis. **b** Probability of pre-irradiation growth hormone (GH) deficiency based on change (slope) in the Evan's index after diagnosis. The Evan's index is the ratio of the distance between the most lateral extent of the frontal horns of the lateral ventricles and the width of the parietal brain at the same level



a



b

Figure 5.5 a, b

Homogeneous irradiation of the HPA, including: **a** a traditional treatment portal used for cranial irradiation in ALL, and **b** dosimetry from focal treatment of craniopharyngioma (*arrow* indicates location of hypothalamus)

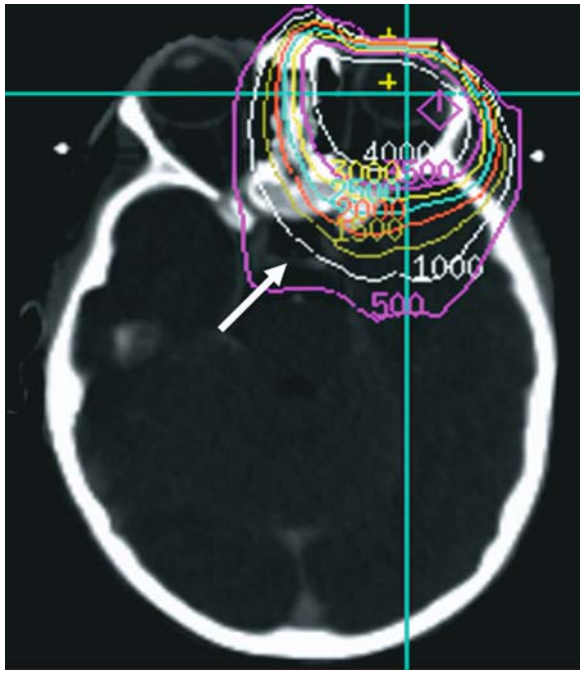
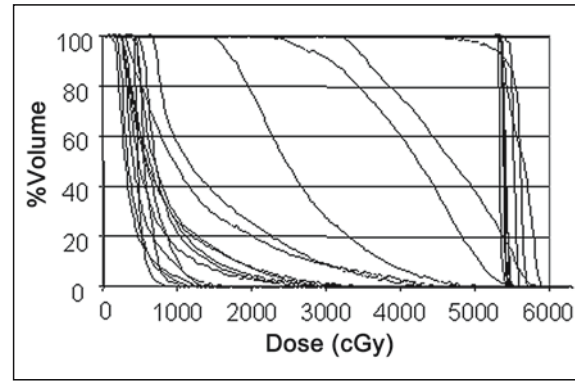
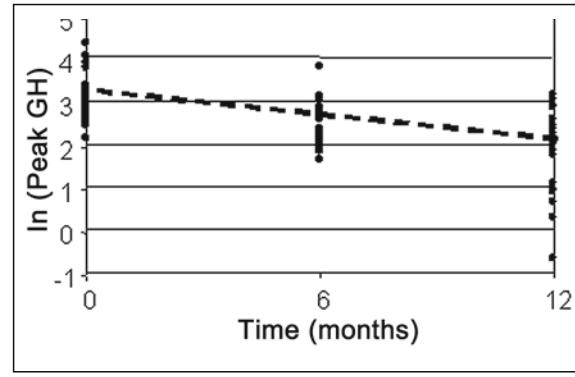


Figure 5.6

Dosimetry for a typical patient treated with conventional radiation therapy (40 Gy). This example illustrates that the HPA receives only a portion of the total dose given to the primary tumor (*arrow* indicates location of pituitary)



a



b

Figure 5.7 a, b

HPA dose–volume data from patients treated with conformal radiation therapy. **a** Dose–volume curves represent the percent–volume of the hypothalamus receiving a specific dose. **b** Correlation with change in peak GH (ATT/L-dopa) measured before, 6 and 12 months after radiation therapy results in an estimating equation that can be used to predict GH deficiency up to 12 months after irradiation, based on the volume (V) received dose over specified intervals. ln [peak GH] $= 3.072 - (0.00058 \times V_{0–2,000\ cGy} + 0.00106 \times V_{2,000–4,000\ cGy} + 0.00156 \times V_{4,000–6,000\ cGy}) \times$ time

jective measures of endocrine effects, this information is becoming increasing valuable in predicting the incidence of specific endocrine effects. Already this type of data has been modeled to predict peak GH secretion after radiation therapy [34]. In the future, it may also be used to optimize RT for children (Fig. 5.7).

In pediatric radiation oncology, reducing the side effects of treatment is an important goal. This can be achieved primarily by limiting CNS irradiation 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 it has been eliminated from a significant proportion of children with low-grade glioma, who may be cured with surgery. For the remainder of children with brain tumors (this constitutes most children), CNS irradiation will remain a mainstay of the treatment. 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 radiation therapy. Increased awareness of the importance of the hypothalamus as the effector organ in radiation-related neuro-

endocrine sequelae and the use of 3-dimensional imaging in planning the treatment of tumors may lead to a reduction in late effects. Reducing the risk of complications can also be achieved by delaying the administration of radiation therapy [29, 60, 66], by reducing the total dose, and by reducing the volume irradiated. 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 [31, 36]. 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 radiation therapy, but it should not be used as a reason to avoid curative therapy. Careful follow-up and evaluation will lead to early intervention and provide the means to mitigate the consequences of irradiation.

5.2 Clinical Manifestations

5.2.1 GH Deficiency

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 after total body irradiation (≥12 Gy). Hypothalamic function is affected more than pituitary function [60]. In most patients with GH deficiency, 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 [34]. A large fraction size of radiation administered over a short period of time is more likely to cause GH deficiency 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 GH deficiency and a significant slowing of growth within 2 years after irradiation [6]. At doses of cranial irradiation higher than 30 Gy (e.g. for suprasellar or posterior fossa tumor), the risk for GH deficiency may be more than 80% by 10 years after RT [59]. Cranial irradiation doses greater than 24 Gy result in GH deficiency in as many as two thirds of patients who receive this treatment [60, 62]. In many younger children, GH deficiency results from lower doses (>18 Gy). Doses of only 12–14 Gy, when used for total body irradiation, combined with chemotherapy and bone marrow transplantation, also pose a significant risk for GH deficiency [24, 26, 62].

The growth rate is typically slow in children who are undergoing treatment for cancer and usually improves (or catches up) after completion of cancer therapy (Fig. 5.8). 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 (Fig. 5.9). Causes of slow growth other than GH deficiency 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, GH deficiency is usually asymptomatic [71], but may be associated with easy fatigability, decreased muscle with increased fat mass, and increased risk for cardiovascular disease [12, 16].

5.2.2 LH or FSH Deficiency

High doses of cranial radiation (≥30 Gy) are more likely to cause hypothalamic GnRH deficiency and, as a result, gonadotropin deficiency. In some patients, high doses of cranial radiation leads to the precocious onset of puberty, due to the damage of GABA secretory neurons, andlater progresses to gonadotropin deficiency due to the loss of GnRH secretory cells. Lower doses of cranial radiation (18–24 Gy) are more likely to cause damage only to the neurons secreting gamma-aminobutyric-acid (leading to disinhibition and premature activation of GnRH neurons) and, therefore, to a rapid tempo in puberty or

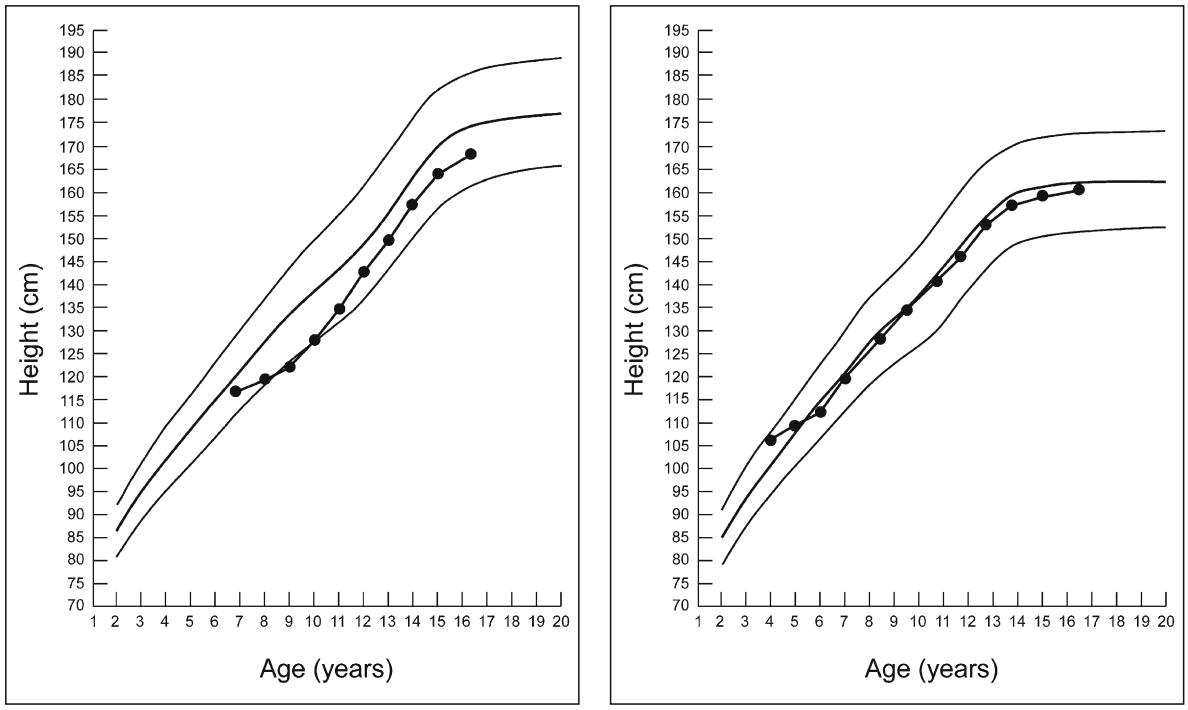
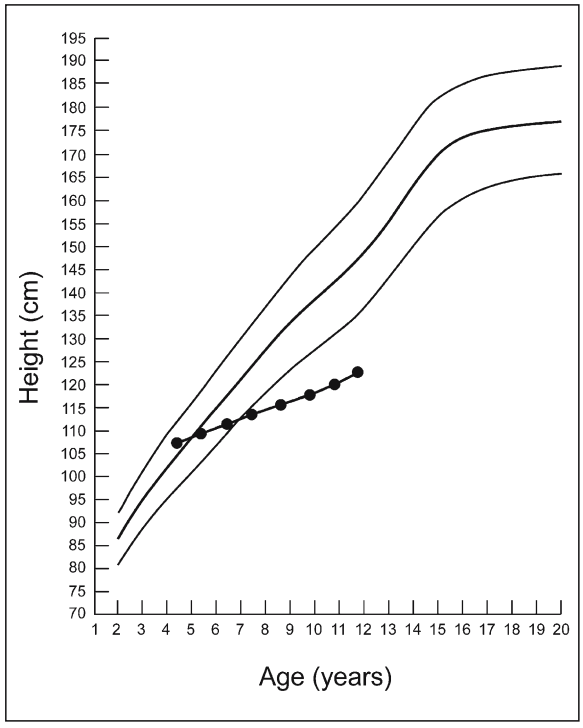


Figure 5.8 a, b

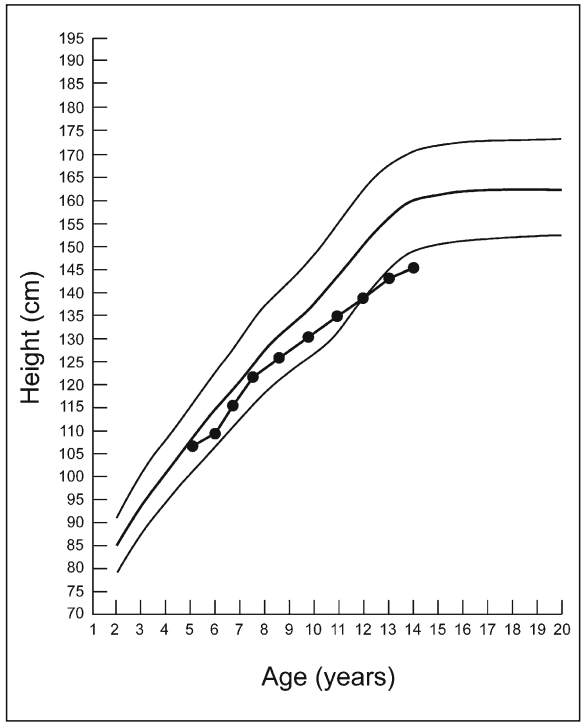
a Complete catch-up growth in a boy after cancer therapy. **b** Growth in a girl after cancer therapy, without catch-up growth. Normal percentiles (5th, 50th, and 95th, as shown) are obtained from the National Center for Chronic Disease Prevention and Health Promotion [38]

precocious puberty [39, 40, 58]. In girls, the first signs of puberty are a 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, followed by a 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 [69]. 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 the average age they experience menarche is 12.8 years; the average age when boys experience testicular growth is 11 years.

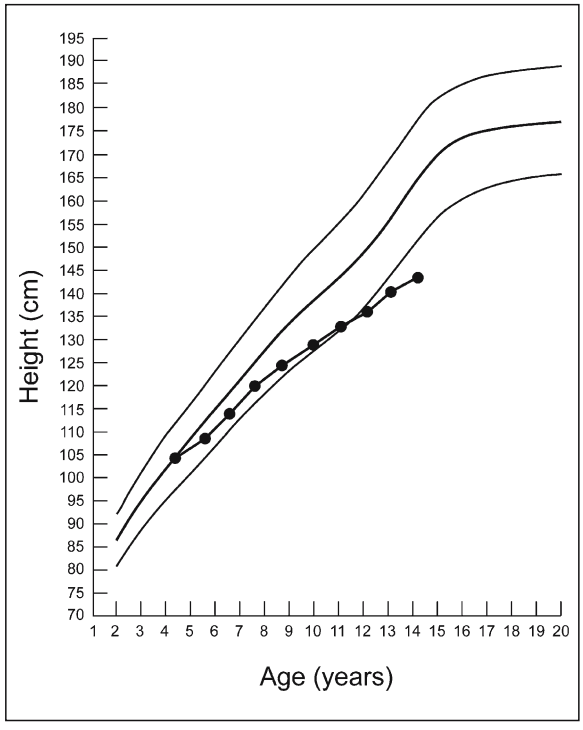
Patients with gonadotropin deficiency may have a delayed, interrupted, or absent puberty. The staging of puberty is usually performed using the criteria of Tanner [69]. In survivors of childhood cancer, we initiate evaluation for delayed puberty in girls who show no onset of breast development by 12 years of age or no menarche by 14 years of age; we initiate evaluation for delayed puberty in boys who show no sign of testicular growth by 13 years of age. Boys treated with agents that can cause infertility may have in normal pubertal hormones but reduced testicular volume, due to damage to the seminiferous tubules and reduced sperm production.


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

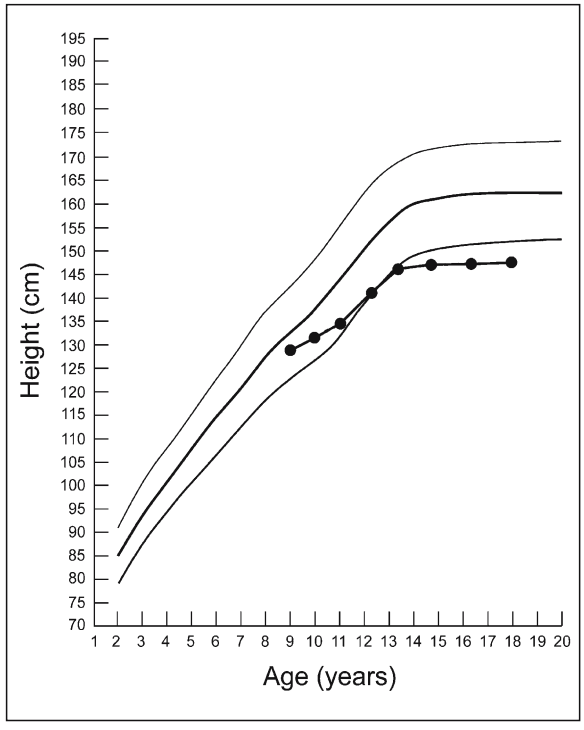
a


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

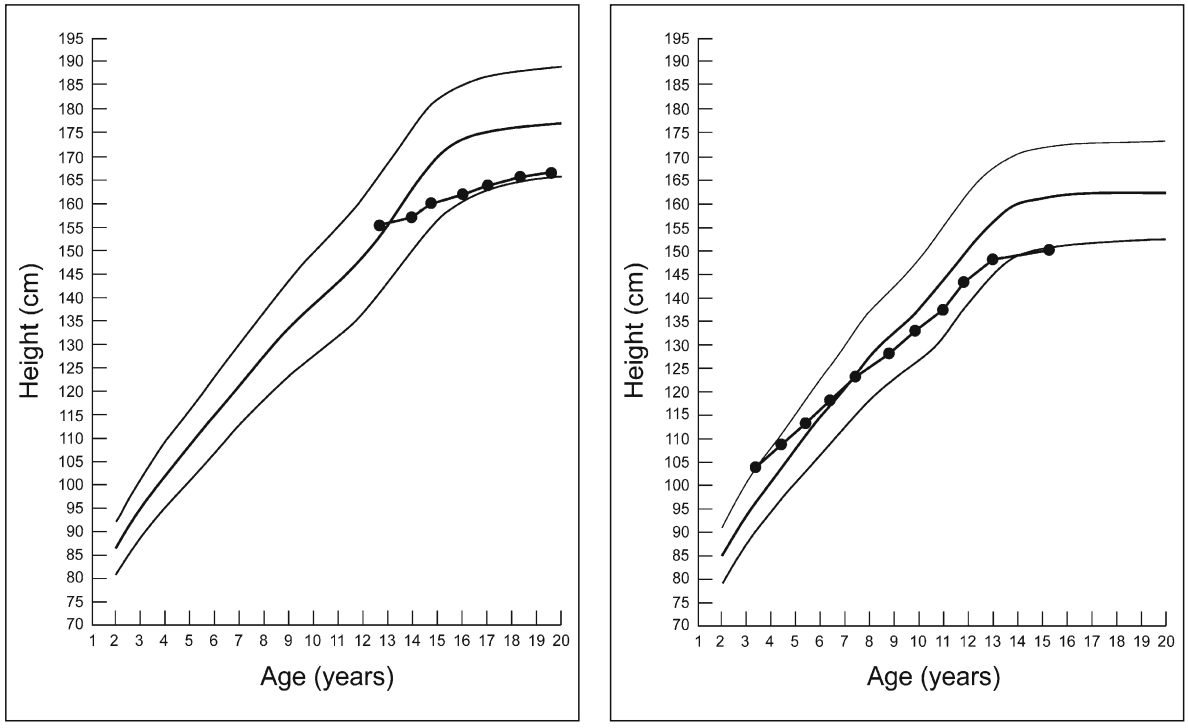
b


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

c


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

d



e f

◀ **Figure 5.9 af**

a Persistent growth failure in a boy after cancer therapy. **b** Later growth failure in a girl after recovery of normal growth. **c** Subtle persistent growth failure in a boy. **d** Growth in a girl with missed GH deficiency. **e** Growth in a boy with missed late onset GH deficiency. **f** Growth in a girl with central hypothyroidism

5.2.3 Precocious or Rapid Tempo Puberty

Precocious puberty is defined as the onset of secondary sexual development characteristics before age 8 years in girls and before age 9 years in boys [4]. Despite controversy that puberty prior to these ages may occur in normal children [18], younger occurrence than age 8 or 9 may be the only clue to the presence of pathology and should not be ignored [37]. 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, elevated intracranial pressure, cranial surgery, or low dose cranial irradiation (18–24 Gy) [7, 40]. Female sex and younger age at the time of cancer treatment are risk factors. In some children who have received cranial irradiation, puberty may start at a normal age but advance rapidly. Thus, tempo of progression as well as timing of onset must be monitored. Rapid puberty is also caused by a loss of inhibition of hypothalamic GnRH secretion. The outcome of early onset and/or rapid tempo of puberty is short adult height. This is due to early bony maturation, which causes children to lose 1 to 3 years of height growth (Fig. 5.10).

5.2.4 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 an under functioning of the thyroid gland itself. Primary hypothyroidism is the most common form of hypothyroidism in the general population. It may occur in cancer survivors due to a family history of hypothyroidism as well as to cancer therapy. The thyroid gland can be injured through irradiation or autoimmune activity, leaving the central axis 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 [44]. Using sensitive testing of TRH and nocturnal TSH surge, Rose et al. [54] showed that central hypothyroidism, defined by a blunted TSH surge, low or delayed TSH peak, or delayed TSH decline after TRH administration, is more common than previously suspected. Central hypothyroidism has been 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 [48, 49].

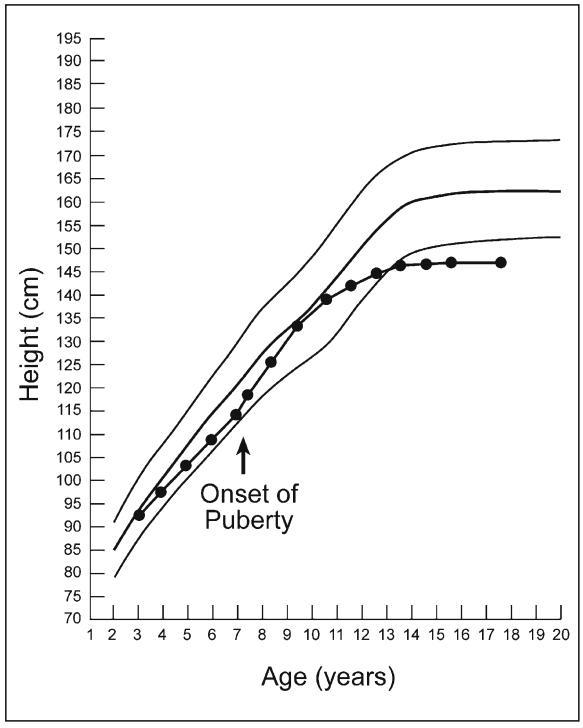
In cancer survivors, mixed hypothyroidism reflects separate injuries to the thyroid gland and the hypothalamus (e.g. radiation injury to both structures). TSH values are elevated and, in addition, the secretory dynamics of TSH are abnormal, with a blunted or absent TSH surge or a delayed peak response (i.e. >45 minutes) to TRH [53, 54]. This contrasts with primary hypothyroidism in which the TSH surge and the timing of the response to TRH are normal. In a study of 208 childhood cancer survivors referred for evaluation for possible hypothyroidism or hypopituitarism, mixed hypothyroidism was present in 15 (7 %) [54]. 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 [54]. 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, one year after receiving cranial irradiation for nasopharyngeal carcinoma, 90 % of the patients in one study had a delayed TSH peak response to TRH, which is suggestive of central hypothyroidism [21]. Five years later, 64 % of this cohort had GH deficiency, 31 % had gonadotropin deficiency, and 27 % had ACTH deficiency. In another investigation, 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 [65]. In another cohort of patients with central hypothyroidism, 34 % had dysregulation of TSH secretion before the development of GH deficiency [54].

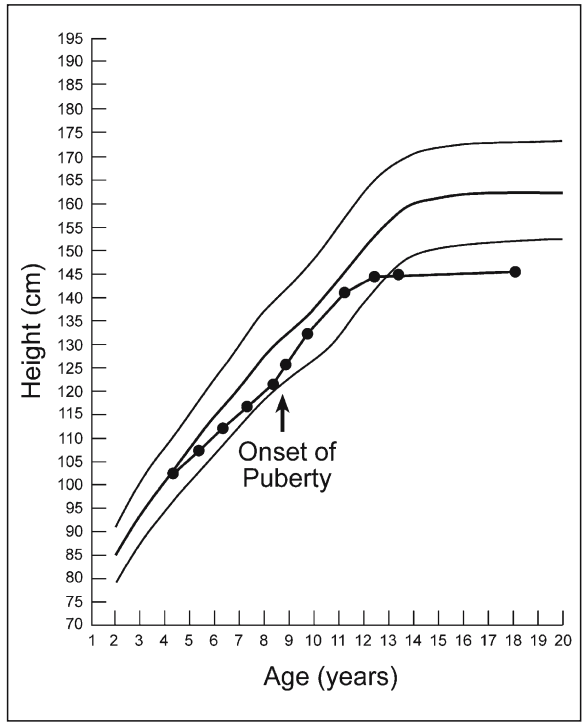
Central hypothyroidism is difficult to diagnose because of its subtle clinical and laboratory presentation. It is particularly difficult to recognize in patients whose growth is complete, because slowed growth rate can no longer be used as a sign. Symptoms of central hypothyroidism (e.g. asthenia, edema, drowsiness, adynamia, skin dryness) may have a gradual onset and go unrecognized until thyroid replacement therapy is initiated and the patient feels better [14]. In addition to causing delayed puberty and slow growth (Fig. 5.9 f), hypothyroidism may cause fatigue, dry skin, constipation, increased sleep requirement, and cold intolerance.

Figure 5.10 ad ▶

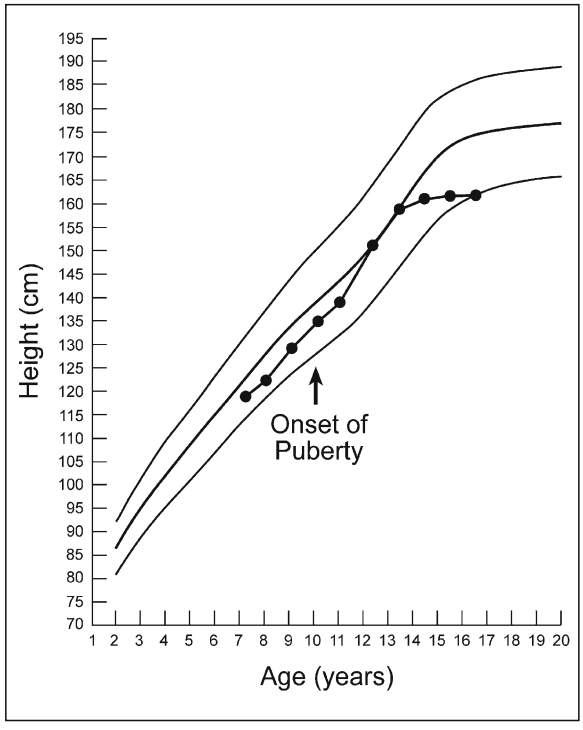
a Growth in a girl with precocious puberty. **b** Growth in a girl with rapid/early puberty. **c** Growth in a boy with rapid/early puberty. **d** Growth in a girl with GH deficiency hidden by precocious puberty (no growth spurt)


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)
Onset of Puberty

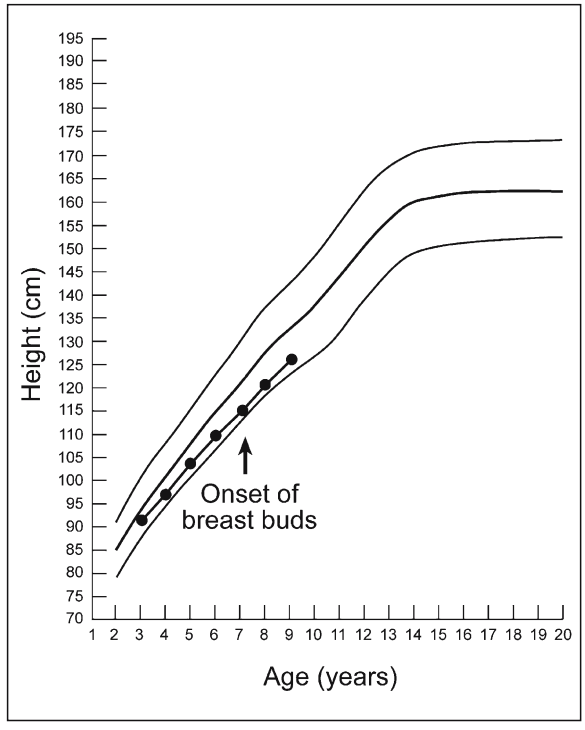
a


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)
Onset of Puberty

b


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)
Onset of Puberty

c


Height (cm)
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)
Onset of breast buds

d

5.2.5 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 [11, 56]. Although uncommon, ACTH deficiency can occur in patients who have received intracranial radiation that did not exceed 24 Gy. It has been reported to occur in fewer than 3 % of patients after chemotherapy alone [56, 57].

The symptoms of central adrenal insufficiency can be subtle. They 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.

5.2.6 Hyperprolactinemia

Hyperprolactinemia has been described in patients who have received doses of radiation to the hypothalamus greater than 50 Gy, as well as in patients who have undergone 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 can result. Primary hypothyroidism may lead to hyperprolactinemia as a result of hyperplasia of thyrotrophs and lactotrophs, probably due to TRH hypersecretion. The PRL response to TRH is usually exaggerated in these patients.

5.2.7 Diabetes Insipidus

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, diabetes insipidus may not be recognized until affected patients 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.

5.2.8 Osteopenia

Osteopenia may result from HPA abnormality (GH deficiency, hypothyroidism, hypogonadism or hyperprolactinemia) in association with the 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 >1.645 SD below the mean of normal population). Risk factors for bone mineral decrements included male gender, Caucasian race and cranial irradiation. BMD was inversely correlated with the cumulative dose of cranial irradiation or antimetabolites [20].

5.2.9 Hypothalamic Obesity

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 [27]. 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 [28]. 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 the presence of endocrinopathy (deficiency of GH, sex hormones, ACTH or vasopressin) [27, 29]. No effects were noted on body mass index from V-P shunting, steroid use (<6 months) or chemotherapy. Thus, any form of hypothalamic damage, whether due to tumor, surgery or RT, is a regional-specific primary risk factor for the development of obesity.

5.3 Detection and Screening

5.3.1 Signs and Symptoms Prompting Immediate Evaluation

Survivors of childhood cancer with any of the following 10 symptoms should be referred for a neuroendocrinopathy evaluation:

(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 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.

5.3.2 Surveillance of Asymptomatic Patients

Asymptomatic patients who are at risk for neuroendocrinopathy (Table 5.2) 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
- Review of organ systems (Table 5.3)
- Measurement of the serum concentrations of free T4 and TSH

5.3.3 GH Deficiency

GH deficiency should be considered in children who have a slow growth rate and a medical history that indicates they are at risk for GH deficiency [17, 72]. 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. A combination of previous cranial or total body irradiation, slow growth rate, abnormal weight gain, no intercurrent illness, delayed bone maturation, and low plasma levels of IGF-I and IGFBP3 (i.e. concentrations lower than 1 SD from the mean for the child's age group) are highly suggestive of GH deficiency. The diagnosis should be confirmed by GH stimulation testing [52]. Evaluation of the nocturnal profile of GH secretion is rarely necessary to make the diagnosis, but, after cranial irradiation, the study may be abnormal in symptomatic children who have normal stimulated GH results [2].

Recognition of GH deficiency 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 GH deficiency in adults requires evidence of other hypothalamic–pituitary hormone deficiencies and a low peak response to GH stimulation tests [1].

5.3.4 LH or FSH Deficiency

During the range of ages that puberty is normally expected to occur, breast development, pubic hair growth and distribution, and and vaginal estrogenization should be monitored every 6 months in girls

Table 5.3. Review of systems

The child currently has these problems (circle each one that the child has):	
Activity:	overactive, unable to exercise, poor stamina, frequently tired
Sleep:	daytime sleepiness, difficulty falling asleep, waking after falling asleep
Appetite:	loss of appetite, excessive appetite, weight gain, weight loss increased thirst, decreased thirst, difficulty swallowing
Mood:	rapid changes in mood, dizziness, depression, hard to get started doing task
Neurology:	headaches, vision change, seizures change in ability to smell, change in taste of foods balance difficulty, weakness, poor coordination, muscles too tight, spasticity disruptive behavior, unable to finish tasks poor attention, poor concentration, can't remember things
Skin/hair:	hair loss, excess hair, dry skin, oily skin, cold intolerance, heat intolerance
Heart:	rapid heart beat, irregular heart beat, slow heart beat, edema in feet
Abdomen:	Nausea, vomiting, diarrhea, constipation, abdominal pain
Urinary:	frequent urination, bed wetting, night awaking to urinate
Puberty/breast:	breast growth, age of first breast buds _____ soreness under nipples, fluid from nipples age of first pubic hair _____, age of first deodorant use _____ age of first period _____, menses irregular interrupted puberty, rapid tempo of puberty
Sexual function:	loss of libido, impotence, decreased nocturnal emissions

at risk of having LH or FSH deficiencies. 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 genital maturation because of RT- or chemotherapy-induced damage to the seminiferous tubules.

Measurement of bone age, serum LH, FSH and sex steroid (testosterone or estradiol) should be performed in children with a delayed or interrupted progression of puberty. Evaluation by an endocrinologist is warranted in the absence of the progression of puberty by 1 year after the completion of cancer therapy in girls >13 years of age, and 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. As an alternative to the GnRH stimulation test, a serum sample for LH, FSH and testosterone or estradiol may be used. The samples should be drawn between 4 and 8 AM, shortly after nighttime pulses of LH have been occurring (Fig. 5.2a).

5.3.5 Precocious Puberty

Precocious puberty is diagnosed if the onset of secondary sexual development occurs before age eight in girls or nine in boys. A radiograph of the left hand and wrist shows bone age that is advanced compared with chronological age; however, bone age may be consistent with chronological age, or even delayed, in a child who has concurrent GH deficiency or hypothyroidism and who has not undergone a growth spurt. (Fig. 5.10 d). Because concurrent GH deficiency may not be discovered until after successful treatment of precocious puberty (Fig. 5.10 d), we routinely perform provocative GH testing in patients with precocious puberty who have a history of cancer.

5.3.6 TSH Deficiency

We suggest that routine annual measurements of TSH and free T4 be taken in all patients who have received cranial irradiation. This is because the symptoms of central hypothyroidism are often subtle, and TSH secretory dysregulation after irradiation may precede other endocrine disorders [21, 54]. The diagnosis of hypothyroidism may be delayed in as many as one third of all childhood cancer patients if TSH secretion is not tested until GH deficiency becomes apparent. Such a delay may be acceptable in a minimally symptomatic adult. In children, however, the potential functional implications of hypothyroidism and lost growth opportunity are not acceptable [46]. Early diagnosis of mild hypothyroidism permits early intervention, which improves the ability to affect growth velocity and quality of life.

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, some patients with central hypothyroidism may have free T4 concentrations in the lowest third of the normal range [46, 47, 54]. The first laboratory evidence of central hypothyroidism may be a small decline in free T4. If further testing confirms hypothyroidism, treatment should be initiated even though free T4 is still within the normal range. This is because the free T4 level is likely to be below the individual's optimal set-point. In our own investigation, both the TRH test and the TSH surge test were performed for patients whose free T4 was in the lowest third of the normal range and whose 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 are optimal in order to identify all cases [54]. Unfortunately, however, TRH, is no longer available in the United States as a test agent.

5.3.7 ACTH Deficiency

For patients at risk for ACTH deficiency (e.g. those who received ≥30 Gy irradiation to HPA), surveillance should include an annual measurement of plasma cortisol concentration at 0800 hours. If the cortisol level is below 18 µg/dl (497 nmol/l) at 0800 hours, then further evaluation is needed and should be directed by an endocrinologist. The optimal evaluation for ACTH deficiency is controversial [55]. Measurement of the basal plasma ACTH concentration usually can distinguish primary adrenal disease from central adrenal insufficiency, provided 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 as 4000 pg/ml (880 pmol/l) or even higher. 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 to 80 pg/ml (4.5–18 pmol/l).

The approach is somewhat different in patients who present in hypotensive crisis. These patients may have adrenal insufficiency or one of several other possible disorders. Furthermore, adrenal insufficiency, if present, may be 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. 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 [10, 61].

An attempt to simplify the evaluation of the hypothalamic–pituitary-adrenal axis led to the development of the one-hour ACTH test (or high-dose ACTH test), which consists of the administration of ACTH (250 µg/m^2) by intravenous infusion during a one-minute time frame [55]. Serum cortisol is measured an hour 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 one-hour serum cortisol concentration of more than 20 µg/dl (552 nmol/l) [64]. 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. In this test, a more physiologic dose of ACTH (1 µg/m^2) is administered by intravenous infusion over a period of one minute, and blood for a serum cortisol assay is drawn 20 minutes 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 [64]. Further evaluation can include a second low-dose ACTH test or metyrapone administration two months to a year later.

The low-dose and high-dose ACTH stimulation tests have supplanted insulin-induced hypoglycemia 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.

5.3.8 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 (section 5.2.6) 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.

5.3.9 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 rule out other causes of polyuria.

5.3.10 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 density. Identification requires performance of either a dual-energy x-ray absorptiometry (DEXA), which offers precise estimates of bone mineral area 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. T-score may be calculated in reference to normal young adults (age of peak bone mass is between 20–35 years) and Z-score in reference to age-matched normal individuals of the same gender. Results of DEXA must be adjusted for patient height and age.

5.3.11 Hypothalamic Obesity

Clinical symptoms are the basis for diagnosing hypothalamic obesity. These include rapid weight gain (Fig. 5.11a), voracious appetite, and aggressive food

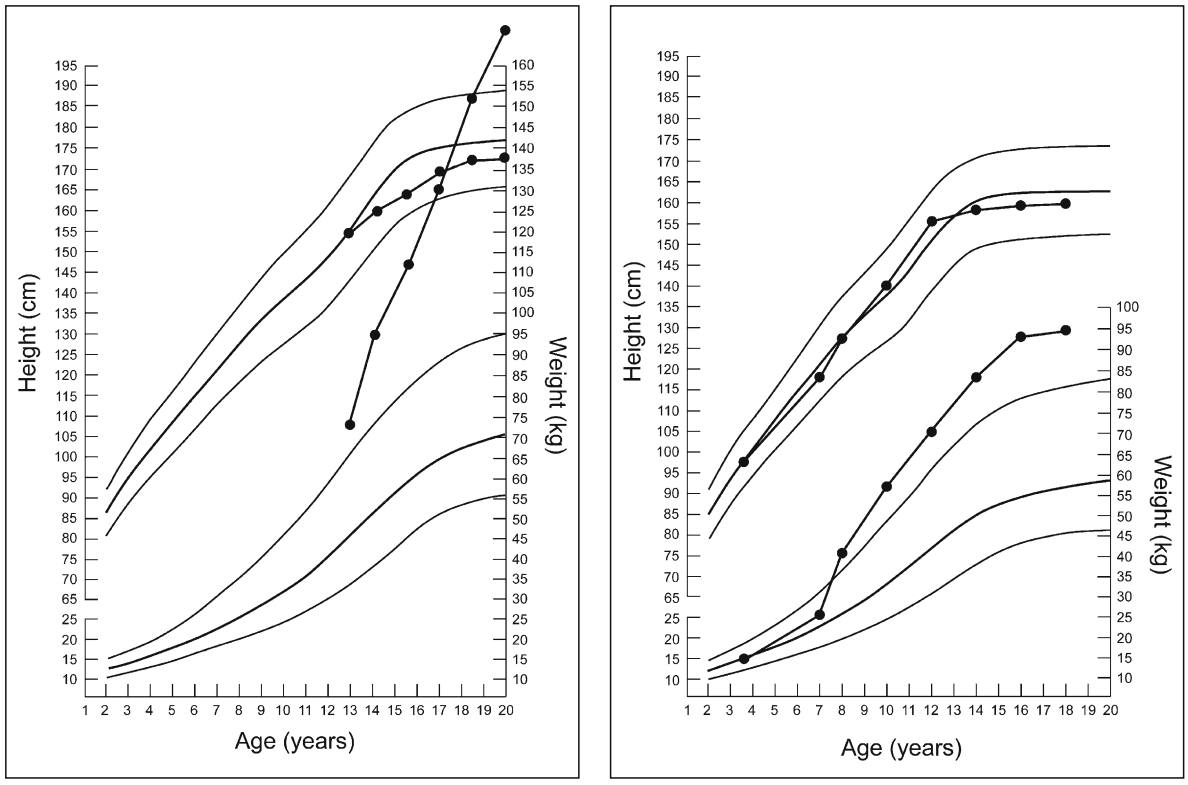


Figure 5.11 a, b

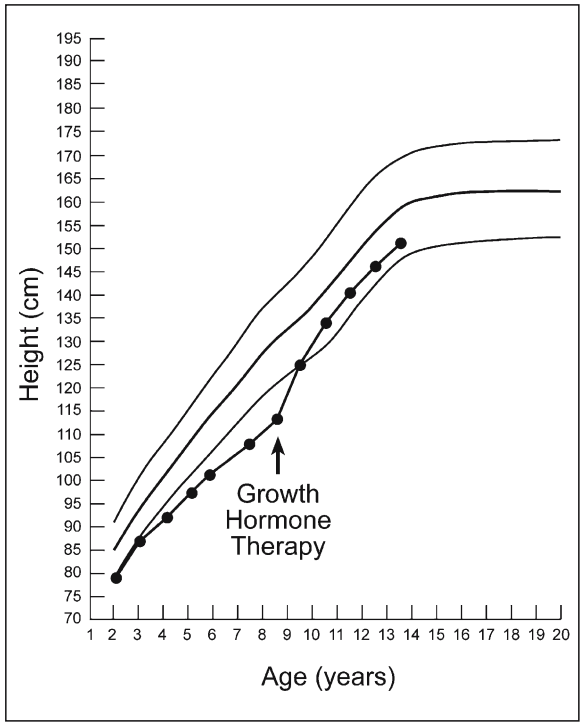
a Hypothalamic Obesity and GH deficiency in a boy. **b** Exogenous obesity in a girl

seeking. Patients may have rapid weight gain for other reasons (Fig. 5.11b): exogenous steroid use, inactivity, overfeeding, excessive thirst and drinking of sugared drinks. Obesity in adults is defined as having a body mass index (BMI) 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 a high post-prandial insulin level, as well as early and rapid insulin excursions to OGTT. However, these results may be seen in any person who becomes obese.

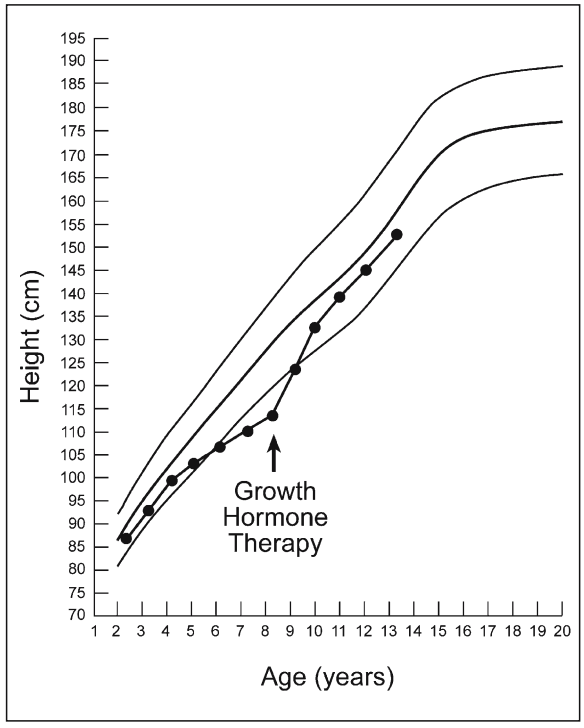
5.4 Management of Established Problems

5.4.1 GH Deficiency

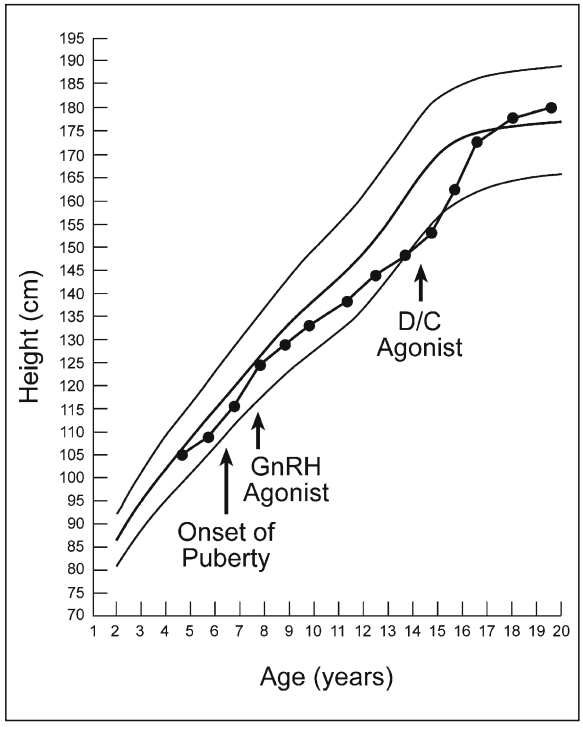
Standard therapy for GH deficiency is synthetic recombinant human GH (Fig. 5.12a, b). Any patient identified with GH deficiency should be evaluated for possible ACTH deficiency and for central hypothyroidism. If ACTH is deficient, adequate cortisol therapy should be started before GH or thyroid therapy. Patients with GH deficiency who have partial or total ACTH deficiency and are receiving suboptimal hydrocortisone replacement may be at risk for


Height (cm)
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
Growth
Hormone
Therapy
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

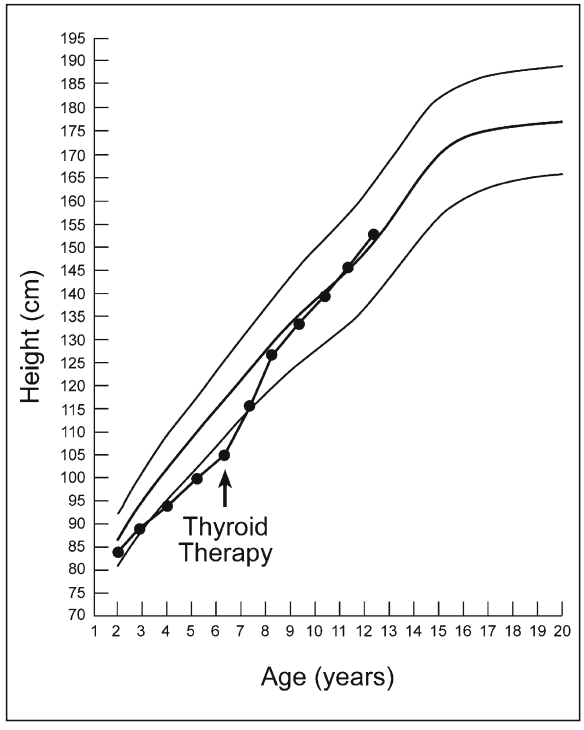
a


Height (cm)
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
Growth
Hormone
Therapy
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

b


Height (cm)
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
D/C
Agonist
GnRH
Agonist
Onset of
Puberty
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

c


Height (cm)
195
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
Thyroid
Therapy
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)

d

◀ Figure 5.12 ad

a Response to GH therapy in a girl with GH deficiency. **b** Response to GH therapy in a boy with GH deficiency. **c** Response to GnRH agonist in a boy with precocious puberty. **d** Response to thyroid hormone in a boy with central hypothyroidism

developing cortisol deficiency when GH therapy is initiated. This is because of the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1, the enzyme that converts cortisone to cortisol [70].

The usual dose of GH in children is 0.15 to 0.3 mg/kg per week divided into daily doses and administered subcutaneously in the evening. Lower doses are used in adults [71]. Each dose produces a pharmacologic level of GH for approximately 12 hours. 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 adult height SD score of leukemia survivors with GH deficiency usually approaches the height SD score at the time of diagnosis [26]. The growth response may be poorer in patients who have received total body or spinal irradiation, or in patients with a disease such as neuroblastoma [19, 42].

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 nighttime 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 two years earlier were treated with twice-daily subcutaneous injections of GHRH for one year and then with daily GH injections for one year [41]. Both GHRH and GH increased height velocity from baseline: GHRH increased height velocity from 3.3 cm/y to 6.0 cm/y, and GH increased it from 3.3cm/y to 7.5 cm/y. GHRH as therapy has been taken off the market recently in the USA.

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). Usually, the 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 [17]. After the first two 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 endocrinopathies (thyroid, gonadotropins, ACTH) should be performed at least annually. Even with GH therapy, some childhood cancer survivors do not grow as well as expected, a finding that suggests that other factors, such as thyroid hormone deficiency, are present.

GH treatment in children is usually safe [72]. Adverse effects are rare and occur soon after therapy is initiated. They include pancreatitis, benign intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis and carpal tunnel syndrome [3]. Pseudotumor cerebri and carpal tunnel syndrome are probably caused by sodium and water retention. Increases in the growth and pigmentation of nevi also have been reported [5]. GH therapy does not increase the risk of brain tumor or leukemia recurrence [26, 43, 68]. In the Childhood Cancer Survivor Study [63], GH therapy did not appear to increase the risk of secondary leukemia or solid malignancy in patients who did not received RT. Because all of the evaluable patients who developed a second neoplasm in this study had received RT, the synergistic effects of GH and irradiation on the development of the second malignancy could not be discerned [63]. The absolute number of excess solid tumors attributable to GH (including many benign meningiomas), if any, will probably be very small (<4/1000 person years at 15 years after diagnosis).

5.4.2 LH or FSH Deficiency

The use of estrogen or testosterone therapy should not be initiated without careful attention to the pediatric survivor's growth pattern. Replacement of pu-

bertal 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 an 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) or ethinyl estradiol (5 mcg daily, one quarter of a 20-mcg tablet daily) [47]. Menstrual spotting can be treated with medroxyprogesterone, 10 mg per day, for 10 days, followed by the resumption of low-dose estrogen. Boys can be treated with 45 or 50 mg/m^2 testosterone enanthate injected intramuscularly once each month. After the achievement of a height acceptable to the patient, both boys and girls may 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). Boys who have attained their adult height can be treated with testosterone (200 mg injected intramuscularly every 2 weeks) or with androgen by patch or a 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 400 IU of vitamin D per day to improve bone mineralization.

5.4.3 Precocious Puberty

GnRH analogs are the most effective treatments for precocious puberty, rapid tempo puberty or normally-timed puberty that is inappropriate for height. GnRH analogs 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 analogs to delay pubertal progression optimizes adult height potential by permitting the child to grow taller without experiencing a rapid change in bone maturation [8] (Fig. 5.12 c).

Treatment with GnRH analogs should be prescribed and monitored by a pediatric endocrinologist [73]. GnRH analogs can be administered as a daily subcutaneous injection or every four weeks in a sustained or depot preparation. GnRH analog therapy is usually continued until patients attain the third percentile for adult height: 152 cm (60 inches) in girls and 162 cm (64 inches) in boys.

5.4.4 Hypothyroidism

The standard treatment for TSH deficiency or primary hypothyroidism is levothyroxine replacement therapy (Fig. 5.12 d). Thyroid hormone replacement can precipitate clinical decompensation in patients with unrecognized adrenal insufficiency, because levothyroxine treatment may improve the metabolic clearance of cortisol. Thus, it is necessary to evaluate patients for adrenal insufficiency and, if this condition is present, treat it with hydrocortisone before initiating thyroid hormone therapy. In patients who also have ACTH deficiency, we usually initiate cortisol replacement three days before beginning thyroid hormone therapy.

The typical thyroid hormone replacement dose for infants under three years of age and for healthy children and adolescents with TSH less than 30 mU/l is levothyroxine 3 mcg/kg orally every morning. Children over three years of age who have TSH greater than 30 mU/l, or about whom there are concerns regarding medical stability, can begin levothyroxine at a low-dose (0.75mcg/kg by mouth every morning)

and increase it by 0.75 mcg/kg per day each month to permit a gradual physiologic and psychological adjustment to the new metabolic state. Thyroid hormone concentrations should be measured after four weeks of therapy, due to the fact that 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 a 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 [14]. 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).

5.4.5 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 mineralocorticoid 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 because it has a greater potential to suppress growth than does hydrocortisone.

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, or the newer anticonvulsants, rifampin, mitotane, and aminoglutethimide, which accelerate hepatic steroid metabolism [13]. Patients with GH 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). 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, and who are unable to retain oral medication or 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 six hours) during management of the critical illness [64]. At stress doses, hydrocortisone provides some mineralocorticoid 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 issues:

- 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 a syringe at all times. The syringes can be obtained either as 250 mg/2 ml vials or 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 10 times the daily hydrocortisone dose. Thus, typical doses for children would be 50–125 mg (0.4 to 1.0 ml of a 250 mg/2 ml solution). Unused syringes should be replaced every year or sooner if the solution inside becomes cloudy or discolored.

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 of the following circumstances:

- The patient has a major injury with substantial blood loss, 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 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).

5.4.6 Hyperprolactinemia

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

5.4.7 Diabetes Insipidus

The drug of choice for hormone replacement is desmopressin acetate or DDAVP®, which can be given by subcutaneous injection, 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 standard 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 hours (Fig. 5.13). The process of starting desmopressin therapy may require close monitoring of the volume of fluid taken in and urine output. Several weeks of dose adjustment may be required before achieving a stable dose (Fig. 5.13). In patients with partial diabetes insipidus, chlorpropamide may be used to enhance the effect of the limited antidiuretic hormone that remains.

5.4.8 Osteopenia

Osteopenia after cancer therapy may be prevented by maintaining optimal calcium (1500 mg daily) and vitamin D (400 units daily) in the diet. Nutritional supplements may be needed in cases of osteopenia that is unresponsive to behavioral and dietary management. In addition, early diagnosis and replacement of hormone deficiencies will benefit bone min-

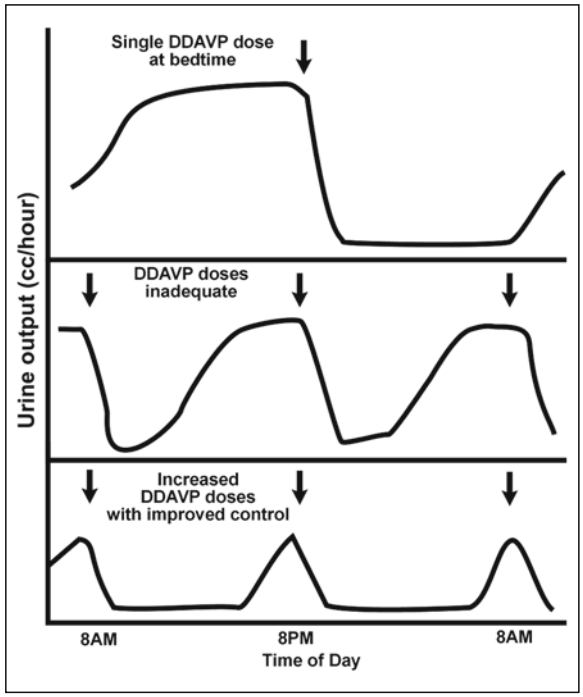


Figure 5.13

Urine output with inadequate DDAVP treatment (*top and middle panels*) and improved control of urine output with adjusted DDAVP dosing (*bottom panel*)

eralization. In the event of fractures, bisphosphonates may be beneficial.

5.4.9 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, several drug therapies have been used pragmatically or in research efforts. These include Dexedrine, Ritalin, metformin, and octreotide. Dexedrine and Ritalin are taken orally and act as stimulants with the side effect of appetite suppression (in this situation, beneficial). 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 should resolve the problem. If the obesity is hypothalamic and the hyperinsulinism is the cause of the increased appetite, metformin use may lead to hypoglycemia and no reduction in appetite. Octreotide is a somatostatin analog that binds to the somatostatin receptor. It not only decreases insulin secretion from pancreatic β-cells, it also decreases growth hormone 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 an improved sense of well being [28, 29]. Octreotide is taken as 2–3 injections daily. Side effects may include gallstones. Patients treated with octreotide may also require therapy with growth hormone and thyroid hormone.

References

1. Biller BM, Samuels MH, Zagar A, Cook DM, Arafah BM, Bonert V, Stavrou S, Kleinberg DL, Chipman JJ, Hartman ML (2002) Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab 87:2067–2079
2. Blatt J, Bercu BB, Gillin JC, Mendelson WB, Poplack DG (1984) Reduced pulsatile growth hormone secretion in children after therapy for acute lymphoblastic leukemia. J Pediatr 104:182–186
3. Blethen SL, Allen DB, Graves D, August G, Moshang T, Rosenfeld R (1996) Safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study Experience. J Clin Endocrinol Metab 81:1704–1710
4. Boepple PA, Crowley WF Jr (1996) Precocious puberty. In: Adashi EY, Rock JA, Rosenwaks Z (eds) Reproductive endocrinology, surgery, and technology, vol 1. Lippincott-Raven, Philadelphia, p 989
5. Bourguignon JP, Pierard GE, Ernould C, Heinrichs C, Craen M, Rochioccioli P, Arrese JE, Franchimont C (1993) Effects of human growth hormone therapy on melanocytic naevi. Lancet 341:1505–1506
6. Brauner R, Malandry F, Rappaport R, Zucker JM, Kalifa C, Pierre-Kahn A, Bataini P, Dufier JL (1990) Growth and endocrine disorders in optic glioma. Eur J Pediatr 149: 825–828

7. Burstein S (1994) Growth disorders after cranial radiation in childhood. J Clin Endocrinol Metab 78:1280–1281
8. Cassorla F, Mericq V, Eggers M, Avila A, Garcia C, Fuentes A, Rose SR, Cutler GB Jr (1997) Effects of luteinizing hormone-releasing hormone analog-induced pubertal delay in growth hormone (GH)-deficient children treated with GH: preliminary results. J Clin Endocrinol Metab 82:3989–3992
9. Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332:1351–1362
10. Clayton RN (1996) Short Synacthen test versus insulin stress test for assessment of the hypothalamo-pituitary-adrenal axis: controversy revisited. Clin Endocrinol (Oxf) 44:147–149
11. Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, Rubin P (1993) Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 328:87–94
12. Cummings DE, Merriam GR (2003) Growth hormone therapy in adults. Annu Rev Med 54:513–33
13. Elias AN, Gwinup G (1980) Effects of some clinically encountered drugs on steroid synthesis and degradation. Metabolism 29:582–592
14. Ferretti E, Persani L, Jaffrain-Rea ML, Giambona S, Tamburrano G, Beck-Peccoz P (1999) Evaluation of the adequacy of levothyroxine replacement in patients with central hypothyroidism. J Clin Endocrinol Metab 84:924–929
15. Fouladi M, Wallace D, Langston JW, Mulhern R, Rose SR, Gajjar A, Sanford RA, Merchant TE, Jenkins JJ, Kun LE, Heideman RL (2003) Survival and functional outcome of children with hypothalamic/chiasmatic tumors. Cancer 97:1084–1092
16. Gilchrist FJ, Murray RD, Shalet SM (2002) The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. Clin Endocrinol (Oxf) 57:363–370
17. Growth Hormone Research Society (2000) Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 85:3990–3993
18. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM (1997) Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 99:505–512
19. Hovi L, Saarinen-Pihkala UM, Vettenranta K, Lipsanen M, Tapanainen P (1999). Growth in children with poor-risk neuroblastoma after regimens with or without total body irradiation in preparation for autologous bone marrow transplantation. Bone Marrow Transplant 24:1131–1136
20. Kaste SC, Jones-Wallace D, Rose SR, Boyett JM, Lustig RH, Rivera GK, Pui CH, Hudson MM (2001) Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia 15:728–734
21. Lam KS, Tse VK, Wang C, Yeung RT, Ho JH (1991) Effects of cranial irradiation on hypothalamic-pituitary function – a 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med 78:165–176
22. Lee HM, Zhu J, Wheeler GC, Helton KJ, Merchant TE (2002) The influence of hydrocephalus on pre-irradiation IQ and endocrine function in children with infratentorial ependymoma. 44th annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), New Orleans, LA, 6–10 Oct 2002. Int J Radiat Oncology Biol Phys 54:150
23. Lee KO, Persani L, Tan M, Sundram FX, Beck-Peccoz P (1995) Thyrotropin with decreased biological activity, a delayed consequence of cranial irradiation for nasopharyngeal carcinoma. J Endocrinol Invest 18:800–805
24. Leung W, Hudson MM, Strickland DK, Phipps S, Srivastava DK, Ribeiro RC, Rubnitz JE, Sandlund JT, Kun LE, Bowman LC, Razzouk BI, Mathew P, Shearer P, Evans WE, Pui CH (2000) Late effects of treatment in survivors of childhood acute myeloid leukemia. J Clin Oncol 18:3273–3279
25. Leung W, Hudson M, Zhu Y, Rivera GK, Ribeiro RC, Sandlund JT, Bowman LC, Evans WE, Kun L, Pui CH (2000) Late effects in survivors of infant leukemia. Leukemia 14:1185–1190
26. Leung W, Rose SR, Zhou Y, Hancock ML, Burstein S, Schriock EA, Lustig R, Danish RK, Evans WE, Hudson MM, Pui CH (2002) Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 20:2959–2964
27. Lustig RH (2001) The neuroendocrinology of childhood obesity. Pediatr Clin North Am 48:909–930
28. Lustig RH, Rose SR, Burghen GA, Velasquez-Mieyer P, Broome DC, Smith K, Li H, Hudson MM, Heideman RL, Kun LE (1999) Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. J Pediatr 135:162–168
29. Lustig RH, Post SR, Srivannaboon K, Rose SR, Danish RK, Burghen GA, Xiong X, Wu S, Merchant TE (2003) Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 88:611–616
30. Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, Rai SN, Lensing SY, Wu S, Xiong X (2003) Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab 88:2586–2592
31. Merchant TE, Pritchard DL, Vargo JA, Sontag MR (2001) Radiation therapy for the treatment of childhood medulloblastoma: the rationale for current techniques, strategies, and dose-volume considerations. Electro Med 69:69–71

32. Merchant TE, Williams T, Smith JM, Rose SR, Danish RK, Burghen GA, Kun LE, Lustig RH (2002) Pre-irradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. Int J Radiat Oncol Biol Phys 54:45–50
33. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, Lustig RH, Kun LE (2002) Craniopharyngioma: the St Jude Children's Research Hospital experience 1984–2001. Int J Radiat Oncol Biol Phys 53: 533–542
34. Merchant TE, Goloubeva O, Pritchard DL, Gaber MW, Xiong X, Danish RK, Lustig RH (2002) Radiation dose-volume effects on growth hormone secretion. Int J Radiat Oncol Biol Phys 52:1264–1270
35. Merchant TE, Zhu Y, Thompson SJ, Sontag MR, Heideman RL, Kun LE (2002) Preliminary results from a phase II trial of conformal radiation therapy for pediatric patients with localized low-grade astrocytoma and ependymoma. Int J Radiat Oncol Biol Phys 52:325–332
36. Merchant TE, Krasin MJ, Kun LE, Xiong X, Mulhern RK, Khan RB, Danish RK, Boop FA, Sanford RA (2003) Results from a phase II trial of conformal radiation therapy for pediatric patients with localized ependymoma and quantification of radiation-related CNS effects. Proc ASCO 22:789, abstract #3206
37. Midyett LK, Moore WV, Jacobson JD (2003) Are pubertal changes in girls before age 8 benign? Pediatrics 111:47–51
38. National Center for Chronic Disease Prevention and Health Promotion (2000), www.cdc.gov/growtheharts
39. Oberfield SE, Soranno D, Nirenberg A, Heller G, Allen JC, David R, Levine LS, Sklar CA (1996) Age at onset of puberty following high-dose central nervous system radiation therapy. Arch Pediatr Adolesc Med 150:589–592
40. Ogilvy-Stuart AL, Clayton PE, Shalet SM (1994) Cranial irradiation and early puberty. J Clin Endocrinol Metab 78: 1282–1286
41. Ogilvy-Stuart AL, Stirling HF, Kelnar CJ, Savage MO, Dunger DB, Buckler JM, Shalet SM (1997) Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone. Clin Endocrinol (Oxf) 46:571–578
42. Olshan JS, Willi SM, Gruccio D, Moshang T Jr (1993) Growth hormone function and treatment following bone marrow transplant for neuroblastoma. Bone Marrow Transplant 12:381–385
43. Packer RJ, Boyett JM, Janss AJ, Stavrou T, Kun L, Wisoff J, Russo C, Geyer R, Phillips P, Kieran M, Greenberg M, Goldman S, Hyder D, Heideman R, Jones-Wallace D, August GP, Smith SH, Moshang T (2001) Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. J Clin Oncol 19:480–487
44. Pitukcheewanont P, Rose SR (1997) Nocturnal TSH surge: a sensitive diagnostic test for central hypothyroidism in children. Endocrinologist 7:226–232
45. Rose SR (1994) Neuroendocrine basis for insufficient growth hormone and its assessment. In: Savage MO, Bourguignon JP, Grossman AB (eds) Frontiers paediatric neuroendocrinology. Blackwell Scientific, Oxford, p. 149
46. Rose SR (1995) Isolated central hypothyroidism in short stature. Pediatr Res 38:967–973
47. Rose SR (1996) Induction of puberty in female hypogonadism. Endocrinologist 6:439
48. Rose SR (2000) Disorders of thyrotropin synthesis, secretion, and function. Curr Opin Pediatr 12:375–381
49. Rose SR (2001) Cranial irradiation and central hypothyroidism. Trends Endocrinol Metab 12:97–104
50. Rose SR, Municchi G (1999) Six-hour and four-hour nocturnal sampling for growth hormone. J Pediatr Endocrinol Metab 12:167–173
51. Rose SR, Nisula BC (1989) Circadian variation of thyrotropin in childhood. J Clin Endocrinol Metab 68:1086–1090
52. Rose SR, Ross JL, Uriarte M, Barnes KM, Cassorla FG, Cutler GB Jr (1988) The advantage of measuring stimulated as compared with spontaneous growth hormone levels in the diagnosis of growth hormone deficiency. N Engl J Med 319:201–207
53. Rose SR, Manasco PK, Pearce S, Nisula BC (1990) Hypothyroidism and deficiency of the nocturnal thyrotropin surge in children with hypothalamic-pituitary disorders. J Clin Endocrinol Metab 70:1750–1755
54. Rose SR, Lustig RH, Pitukcheewanont P, Broome DC, Burghen CA, Li H, Hudson MM, Kun L, Heideman RL. A (1999) Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab 84:4472
55. Rose SR, Lustig RH, Burstein S, Pitukcheewanont P, Broome DC, Burghen GA(1999) Diagnosis of ACTH deficiency. Comparison of overnight metyrapone test to either low-dose or high-dose ACTH test. Horm Res 52:73–79
56. Rose SR, Danish RK, Schreiber RE, Kearney NS, Hudson MM (2002) ACTH deficiency in childhood cancer survivors. Pediatr Res 51:116A #671
57. Rose SR, Schreiber RE, Kearney NS, Lustig RH, Danish RK, Burhhan GA, Hudson MM (2004) Hypothalamic dysfunction after chemotherapy. J Pediatr Endocrinol Metab 17:55–66
58. Roth C, Lakomek M, Schmidberger H, Jarry H (2001) Cranial irradiation induces premature activation of the gonadotropin-releasing-hormone. Klin Paediatr 213:239–243
59. Shalet SM, Beardwell CG, Pearson D, Jones PH (1976) The effect of varying doses of cerebral irradiation on growth hormone production in childhood. Clin Endocrinol (Oxf) 5:287
60. Shalet SM (1993) Radiation and pituitary dysfunction. N Engl J Med 328:131–133

61. Shankar RR, Jakacki RI, Haider A, Lee MW, Pescovitz OH (1997) Testing the hypothalamic-pituitary-adrenal axis in survivors of childhood brain and skull-based tumors. J Clin Endocrinol Metab 82:1995–1998
62. Sklar CA (1997) Growth and neuroendocrine dysfunction following therapy for childhood cancer. Pediatr Clin North Am 44:489–503
63. Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, Yasui Y, Robison LL (2002) Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 87:3136–3141
64. Soule SG, Fahie-Wilson M, Tomlinson S (1996) Failure of the short ACTH test to unequivocally diagnose long-standing symptomatic secondary hypoadrenalism. Clin Endocrinol (Oxf) 44:137–140
65. Spoudeas HA (1996) Hypothalamic dysregulation after cranio-spinal irradiation for childhood cerebellar tumors. 10th Int Cong Endocrinol, San Francisco, CA,165, #P1–123 (abstract)
66. Spoudeas HA (2002) Growth and endocrine function after chemotherapy and radiotherapy in childhood. Eur J Cancer 38:1748–1759
67. Spoudeas HA, Charmandari E, Brook CG (2003) Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posterior fossa tumors. Med Pediatr Oncol 40:224–229
68. Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, Ryder WD, Brada M, Hayward RD, Brook CG, Hindmarsh PC, Shalet SM (2000) Growth hormone treatment of children with brain tumors and risk of tumor recurrence. J Clin Endocrinol Metab 85:4444–4449
69. Tanner JM, Davies PS (1985) Clinical longitudinal standards for height and height velocity in North American children. J Pediatr 107:317–329
70. Toogood AA, Taylor NF, Shalet SM, Monson JP (2000) Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients. J Clin Endocrinol Metab 85:1727–1730
71. Vance ML, Mauras N (1999) Growth hormone therapy in adults and children. N Engl J Med 341:1206–1216
72. Wilson T, Rose SR, Rogol A, Cohen P and the Drug and Therapeutic Committee of the Lawson Wilkins Pediatric Endocrine Society (2003) Update of guidelines for the use of growth hormone in children. J Pediatr 143:415–421
73. Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, Cutler GB Jr (2003) Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. N Engl J Med 348:908–917

Ocular Complications Due to Cancer Treatment

Michael Ober · Camille A. Servodidio · David Abramson

Contents

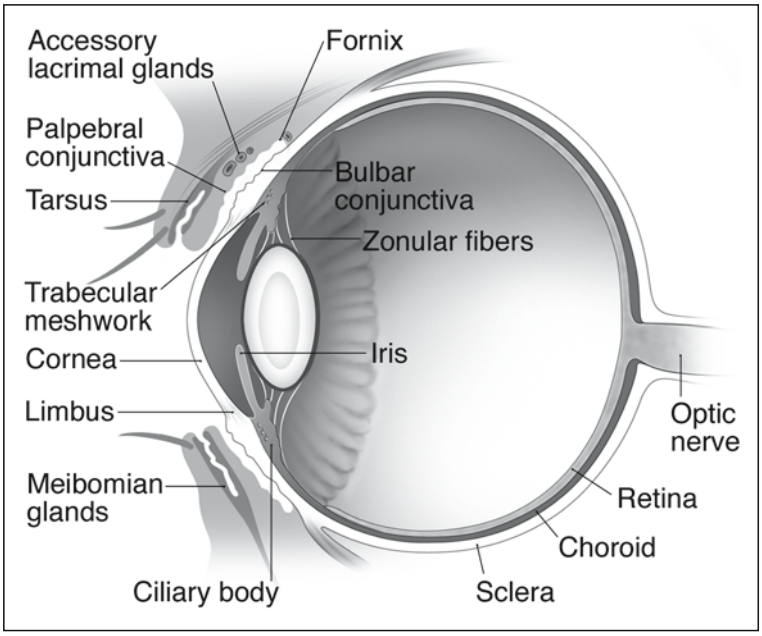


Figure 6.1
Cross-sectional anatomy of the eye

6.1 Introduction

The eye is composed of many tissues that vary greatly in their sensitivity to cytotoxic therapy. This chapter highlights the ocular complications of cancer treatment and discusses the relevant anatomy and medical management. Each section discusses the basic anatomy and physiology of a specific area of the eye (Fig. 6.1), common radiation and chemotherapeutic complications and therapeutic management.

6.2 Eyelids, Periorbital Skin and Tear Film

6.2.1 Anatomy and Physiology

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 tear film covers the anterior surface of the conjunctiva and cornea. It serves the vital role of supplying the cornea with moisture, nutrients, enzymes, immunoglobulins and protein signals, as well as allowing 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 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 dependant on each of these individual layers, and a deficiency in any layer will adversely affect the entire ocular surface.

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 nasal-lacrimal duct.

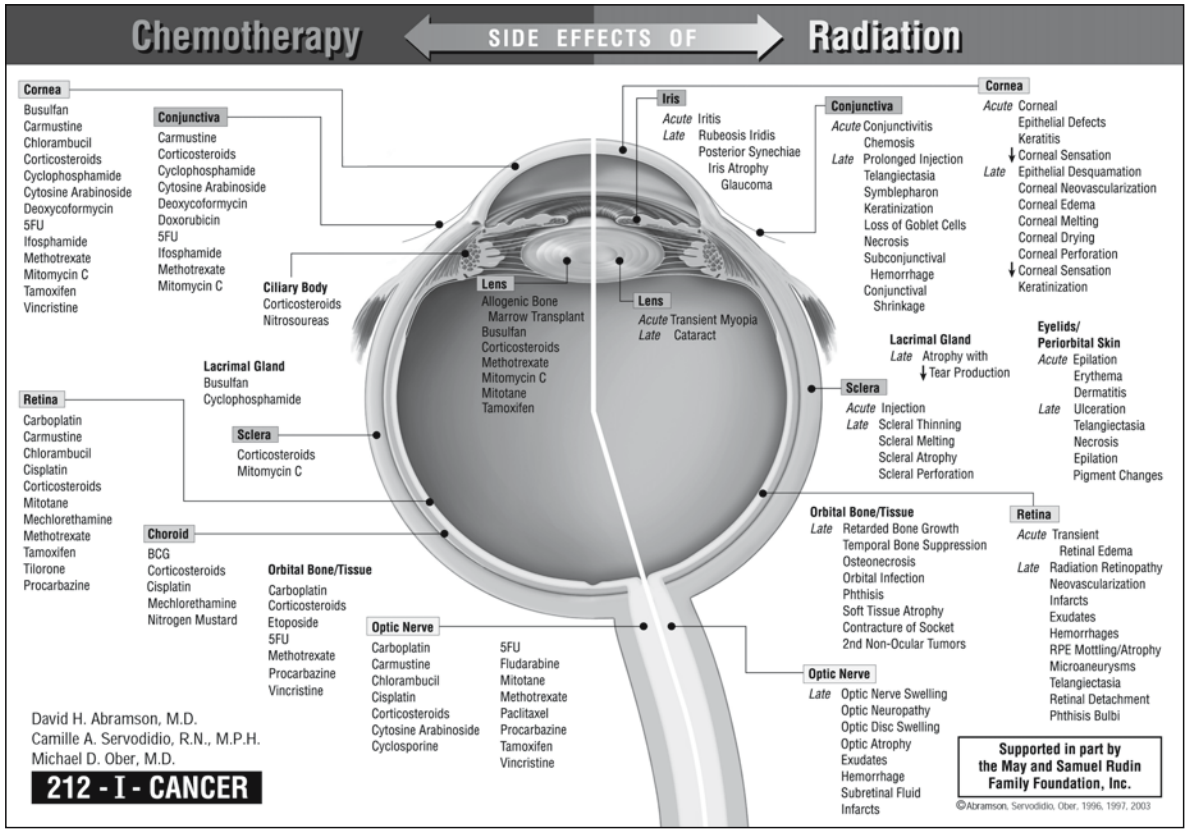


Figure 6.2

Side effects of chemotherapy and radiation of the eye

6.2.2 Acute Radiation Effects

Madarosis, or loss of eyelashes, and erythema are the first side effects of radiation therapy (RT) involving the eye. Usually, eyelashes will grow back; however, permanent loss does occur. Erythema can occur within days of treatment (generally after doses of at least 20–30 Gy) and usually persists for a few days. Dermatitis is the most common acute side effect of RT. Dry dermatitis of irradiated skin can occur with doses greater than 20 Gy and often leads to desquamation. Moist dermatitis, with exposure of the dermis and associated serum leakage, can occur after the fourth week of RT following doses of 40 Gy or more, fractionated over a 4-week period. Blisters and edema may precede moist dermatitis. Symptoms include redness, peeling, burning, itching and pain [1] (Fig. 6.2).

6.2.3 Chronic Radiation Effects

The late effects of RT to the eyelids following doses from 30–60 Gy include madarosis, telangiectasia (dilated, tortuous blood vessels; Fig. 6.3), hyperpigmentation, depigmentation, ectropion, hyperkeratosis, atrophy, necrosis, ulceration and punctual occlusion. Although rarely seen today, lid deformities, such as ectropion (out-turning of eyelid margin), entropion

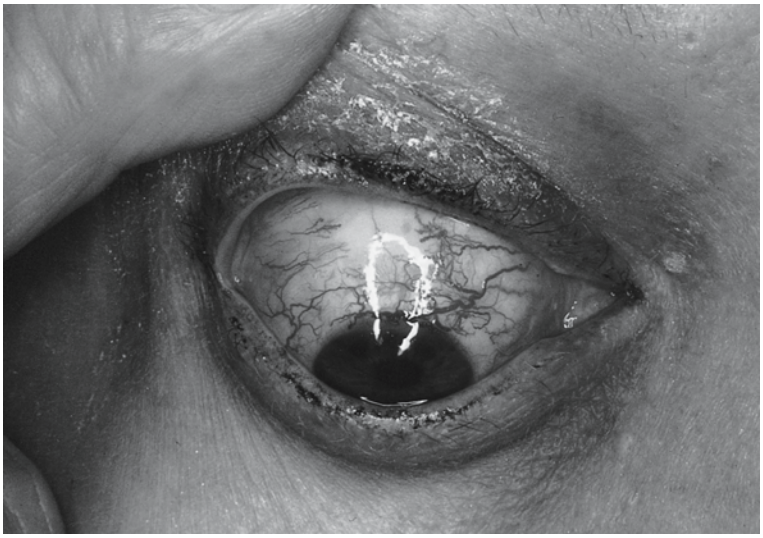


Figure 6.3
Telangiectasia of the conjunctival blood vessels

(in-turning of eyelid margin) and atrophy or contracture, are seen when the tarsus has been included in the radiation field. The time of onset ranges from 2 months to greater than 5 years after treatment. Destruction or occlusion of the puncta may occur when the medial portions of the eyelid are irradiated, which leads to impaired tear drainage. Lid necrosis, exacerbated by excess sun exposure in areas previously irradiated, may develop months to years after treatment [2, 3].

6.2.4 Chemotherapy

Many chemotherapeutic agents, such as cyclophosphamide, ifosfamide and methotrexate, 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 [4]. Patients treated with alkyl sulfonates, including busulfan and nitrosourea, have also reported developing dry eyes [5]. Both 5-fluorouracil [6] and docetaxel [7] have been associated with stenosis of the punctum and tear (canalicular) drainage system. In addition, some patients receiving 5-fluorouracil develop excessive lacrimation along with cicatricial eyelid malpositioning. Intravenous doxorubicin has also been associated with excessive lacrimation. Paleness of the periorbital skin has been reported following mithramycin infusion, while drooping of the upper eyelid, known as ptosis, has been reported following long-term corticosteroid use [8].

6.2.5 Medical and Nursing Management

The management for eyelid complications due to cancer treatment consists mainly of skin care, including the use of ultraviolet protection, meticulous hygiene with mild soaps, the use of skin lubricants, avoiding skin sensitizing drugs (i.e. tetracyclines) and occasionally corticosteroid and/or antibiotic creams. Ptosis, tear drainage or eyelid position may require minor surgical manipulation by an ophthalmologist and should be referred in clinically significant cases [9]. The mainstay of dry eye therapy consists of tear replacement with artificial tears drops and ointment. Patients with symptoms or at risk should be encouraged to use liberal amounts of artificial tears. Unpreserved artificial tears are preferred, especially when they are used more than four times per day, due to the fact that the preservatives them-

selves can be irritating to the cornea, conjunctiva and eyelids. Further aids include punctal occlusion, warm compresses to eyelids and, in advanced cases, cyclosporine drops. Patients with continued symptomatic or refractory dry eyes should be referred to an eye care professional without delay, as the consequences of hesitating could be permanent vision loss.

6.3 Conjunctiva

6.3.1 Anatomy and Physiology

The conjunctiva is a thin, transparent mucous membrane that lines both the posterior aspect of the eyelids (palpebral 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. Besides acting as a physical barrier, the conjunctiva aids in host defenses by hosting immune cells as well as colonizing bacteria.

6.3.2 Acute Radiation Effects

Conjunctival inflammation (conjunctivitis), which manifests as vascular injection with clear or mucoid discharge tends to occur 1–3 weeks after the start of radiation treatment. Edema of the conjunctiva, known as chemosis, may occur simultaneously or in isolation and usually lasts for a few days. Affected conjunctiva may also ulcerate leading to an increased risk of infection. The duration of these signs may be prolonged when RT doses over 30 Gy are used [1, 2, 10].

6.3.3 Chronic Radiation Effects

Late effects of RT to the conjunctiva include prolonged injection, telangiectasis, symblepharon (adhesions between the bulbar and palpebral conjunctiva) and subconjunctival hemorrhage, shortening of the fornices, loss of goblet cells, keratinization and necrosis. Exposure to 30–50 Gy results in prolonged conjunctival injection, which develops in 1–2 years, followed by telangiectatic vessels 3–6 years later. These fragile vessels tend to rupture with minor trauma, resulting in subconjunctival hemorrhage.

Chronic ulceration of the conjunctiva can be seen following treatment with 60 Gy. This leads to symblepharon formation, resulting in shortening of the fornices, trichiasis (turning of lashes onto the ocular surface) and eyelid malpositioning. Goblet cell loss occurs at relatively low doses, resulting in tear film instability and dry eye symptoms, while doses over 50 Gy may result in keratinization of the conjunctiva. These keratin plaques constantly irritate adjacent cornea, occasionally causing scarring and visual loss. Necrosis may occur after radioactive plaque therapy for retinoblastoma patients, where doses to the conjunctiva between 90–300 Gy are used [1–3, 10].

6.3.4 Chemotherapy

Conjunctivitis is a commonly reported symptom following induction therapy with many medications, including cyclophosphamide, ifosfamide, nitrosoureas, cytosine arabinoside, doxorubicin, methotrexate, deoxycoformycin and mitomycin. 5-fluorouracil is also associated with conjunctivitis and eye irritation. This usually occurs concurrently with the initiation of therapy and resolves within two weeks of treatment cessation. The immunosuppressive effects of corticosteroids are believed to facilitate opportunistic infections throughout the eye, including bacterial, viral and fungal conjunctivitis [11].

6.3.5 Medical and Nursing Management

Antibiotic eye drops, sometimes in combination with corticosteroids, are used for prolonged conjunctivitis and for conjunctival ulceration. Artificial teardrops

often aid chronic conjunctival irritation by providing the lubrication necessary to replace lost tear volume and dilute toxic chemotherapeutic metabolites excreted into the tear film. Vitamin A ophthalmic ointment (tretinoin 0.01% or 0.1%) may reverse squamous metaplasia and loss of vascularization from scar formation [12]. Patients with infectious conjunctivitis should be instructed to wash their hands frequently and take great care in interactions with others to prevent the spread of communicable diseases. In addition, sunglasses for protection from the sun and wind may be helpful in reducing symptoms. Severe conjunctival reactions, such as symblepharon and forniceal shortening, may require ophthalmologic manipulations such as symblepharon lysis on a repeated basis; or, alternatively, mucous membrane grafting with forniceal reconstruction may be necessary. Ophthalmologic referral is therefore indicated.

6.4 Cornea

6.4.1 Anatomy and Physiology

The cornea is the transparent, avascular anterior portion of the eye that refracts and transmits light to the inner structures of the eye. 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 directly to the loss of corneal transparency and often its integrity. The cornea is an avascular 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 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 maintaining clear vision. Endothelial cells can migrate to fill an area with damage, but they do not regenerate; therefore, all loss of endothelial cells is permanent. Inflammation of the cornea, known as keratitis, also increases the corneal thickness and blurs vision.

6.4.2 Acute Radiation Effects

The corneal epithelium is adversely affected after RT doses of 10–20 Gy. Early effects include epithelial defects, keratitis and decreased corneal sensation. When the tear film production or integrity is reduced, the epithelial cells become fragile and loosely adherent to themselves and the underlying stromal bed, resulting in epithelial defects. Patients with this problem will complain of ocular discomfort, foreign body sensation, excess reflex tearing and blurry vision. Acute keratitis is often self-limited following exposure to 30 Gy, but, following treatment with up to 50Gy, it may persist for months, along with conjunctivitis . Decreased corneal sensation may result from nerve damage and be exacerbated by impaired reflex tearing, which, in turn, diminishes the blink rate and delays complaints from the patient [1, 10].

6.4.3 Chronic Radiation Effects

Late RT effects on the cornea include chronic epithelial defects, neovascularization, keratinization, edema, ulceration and perforation. Epithelial defects may persist for months when radiation causes damage to corneal epithelial stem cells, accessory tear glands, goblet cells and/or corneal nerves. The cornea responds to these non-healing areas with neovascularization and keratinization, both of which temporarily or permanently decrease visual acuity. Abnormal blood vessels and chronic inflammation may lead to lipid deposition within the corneal stroma, further worsening vision. Damage to lacrimal glands, goblet cells and corneal sensation impairs host defenses by limiting the cornea's contact with tears and

their accompanying nourishment, lubrication, immunoglobulins and enzymes. Colonization and invasion of the corneal surface by bacteria may accelerate ulceration and perforation [1, 3, 10, 13].

6.4.4 Chemotherapy

Patients develop keratitis following treatment with many chemotherapeutic agents, including chlorambucil, cyclophosphamide, methotrexate, nitrosoureas, 5-fluorouracil and deoxycoformycin [4]. Punctate corneal opacities and keratitis will occur acutely with cytosine arabinoside therapy, usually resolving approximately four weeks after completion. Both vincristine and vinblastine have been associated with corneal hypoesthesia [14]. Patients undergoing long-term tamoxifen treatment may acquire whirl-like corneal inclusions known as verticillata [15]. In addition, the immunosuppressive effects of corticosteroids are believed to facilitate opportunistic infections throughout the eye, resulting in bacterial, viral and fungal keratitis, as well as in corneal ulcers.

6.4.5 Medical and Nursing Management

Artificial tears and ointment are important in maintaining a healthy cornea following insults from cancer treatment. Patients using these solutions more than four times daily should consider unpreserved formulations. Antibiotic drops are recommended for epithelial defects. Corticosteroid (dexamethasone) eye drops are often given prophylactically with antimetabolite treatment, especially cytosine arabinoside, to reduce corneal and conjunctival irritation. Steroid drops may also be used with specific types of sterile infiltrates for keratitis. Corneal infections and ulcerations are treated with administration of antibiotic eye drops as frequently as every 15 minutes. Bandage contact lenses, along with antibiotic drops, may be used for non-healing epithelial defects. Emergency surgical intervention may be required when corneal perforation is pending or apparent, or when permanent central corneal scarring becomes evident. Patients should be instructed to avoid factors that may contribute to eye irritation or dryness, such as fans, wind, smoke or low-humidity situations.

6.5 Lens

6.5.1 Anatomy and Physiology

The lens is the second clear, avascular refracting surface of the eye. It lies posterior to the iris and is suspended circumferentially by a ligament known as the zonule. This encapsulated structure is devoid of nerves and vasculature and thus depends on the aqueous and vitreous humor for nutrients. Throughout life, the mitotically active cells located within the anterior periphery of the lens migrate inward toward the denser nucleus in the center. The cells of the lens are never shed; rather, they are incorporated into the nucleus. Thus, injured cells leave permanent, visible defects. For this reason, the crystalline lens is particularly susceptible to the formation of a cataract after cancer treatment. A cataract simply refers to the loss of optical clarity within the lens, a condition that can vary widely in severity.

6.5.2 Acute Radiation Effects

On rare occasion, transient myopia may occur in the weeks following RT as a result of increased water content within the lens.

6.5.3 Chronic Radiation Effects

The posterior subcapsular cataract is the characteristic late complication of RT (Fig. 6.4). The lens is the most radiosensitive structure within the eye because of its perpetual mitotic activity and inability to remove injured cells or disperse heat efficiently. The report on cataracts following radiation therapy in 1957 by Merriam and Focht yielded results that remain clinically relevant today. They found the threshold for cataract development to be a single exposure to 200 rads, fractionated doses of 400 rads over 3 weeks to 3 months, or a total dose of 550 rads divided over more than 3 months. Furthermore, they reported that patients receiving a single treatment of 200 rads, fractionated doses of >1000 rads over 3 weeks to 3 months, or 1100 rads over greater than 3 months, developed cataracts 100% of the time [16]. The lens in children less than one year

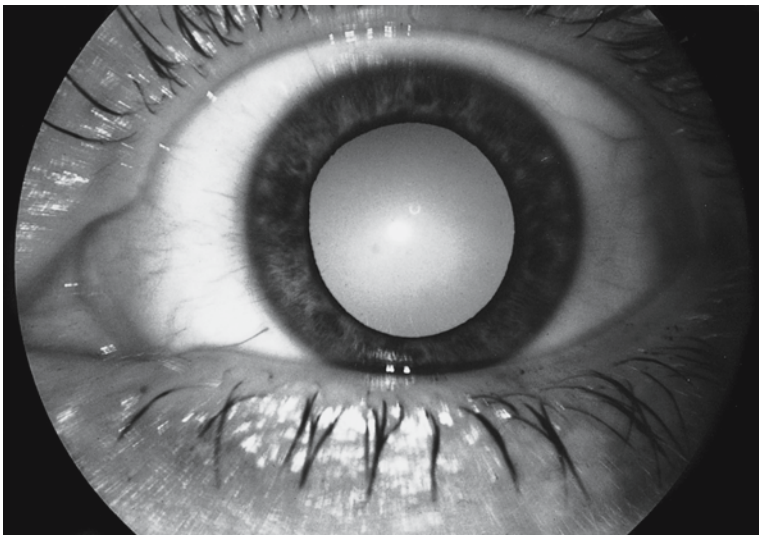


Figure 6.4
Radiation-induced cataract

of age is more sensitive to radiation, as compared to the adult lens, presumably due to higher mitotic activity [10].

6.5.4 Chemotherapy

The cataract is the most frequently reported side effect associated with corticosteroid use. The incidence of steroid-induced cataracts ranges from 15–52%, depending on dose and duration [17]. Although variable, the approximate threshold for cataract formation is 10 mg prednisone daily for one year [18]. It should be noted that steroid-induced cataracts have been reported following treatment with systemic, inhaled, topical and skin formulations. Some patients treated with busulfan [19] also acquire cataracts, as do those receiving topical mitomycin C. Patients taking tamoxifen have been found to have a higher proportion of a specific class of cataract (posterior subcapsular) following years of treatment, which also may be indicative of lenticular toxicity [4, 20].

6.5.5 Medical and Nursing Management

At the present time, there are no known medical treatments for the reversal of cataracts. Prevention of cataracts is best accomplished by fractionation of the RT dose, lens shielding during treatment and limiting exposure to toxic medications. Once a clinically significant cataract develops, surgical extractions and observation become the only options. Cataract extraction is elective in the vast majority of situations and depends upon the patient's and family's desires.

Visual pathways in the brain develop only during a finite period of time. When the central nervous system is presented with altered visual stimuli during this critical period, such as through an opaque lens, the potential visual acuity is reduced. When this phenomenon occurs, it is termed amblyopia. The vital time begins before or at birth and is believed to end between age 7 and 13. Once development is complete, alterations in the visual system no longer change the potential vision. When identified early in its course, amblyopia is potentially reversible. Visually impairing complications in children must therefore be recognized early.

6.6 Uvea: Iris, Ciliary Body and Choroid

6.6.1 Anatomy and Physiology

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 back-up 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.

6.6.2 Acute Radiation Effects

Uveitis is an early effect of RT. It is caused by an increase of vascular permeability, which leads to a leakage of protein and inflammatory cells [2]. Iritis (inflammation of the iris) is dose-related and can occur after a fractionated dose of greater than 60 Gy over 5–6 weeks.

6.6.3 Chronic Radiation Effects

Iris neovascularization, posterior synechiae (adhesions between the iris and the lens) and iris atrophy are the major long-term complications of RT. Iris neovascularization, also known as rubeosis iritis, occurs several months to years following RT with fractionated doses of 70–80 Gy over 6–8 weeks. The abnormal vessels that result from this condition can grow into the trabecular meshwork, thereby causing intractable glaucoma. Rubeosis iritis is believed to be caused by retinal ischemia, resulting in the liberation of vascular growth factors throughout the eye. Posterior synechiae can also cause glaucoma by preventing fluid produced behind the iris from reaching the trabecular meshwork located anterior to the iris. Iris atrophy has been reported three years after high doses of beta-irradiation with 170–250 Gy [2, 3].

6.6.4 Chemotherapy

Corticosteroid treatment is known to cause an elevation in intraocular pressure with the associated development of glaucoma. Several factors may influence a patient's susceptibility to steroid-induced glaucoma, including older age, genetic predisposition to glaucoma and length and increased dose of treatment [21–23]. Generally, therapy for at least two weeks is required for increased intraocular pressure to manifest. Although the increased pressure induced by corticosteroids usually resolves with cessation of the therapy, irreversible glaucoma has also been demonstrated [24]. In addition, corticosteroids have been implicated in facilitating infective uveitis.

Severe uveal reactions have been reported following intracarotid treatment with chemotherapeutic agents, including one case, with intracarotid cisplatin infusion, of serous retinal detachment [25]. In addition, one report found that 25% of patients treated with intracarotid mechlorethamine, a nitrogen mustard compound, developed an ipsilateral necrotizing uveitis [26].

6.6.5 Medical and Nursing Management

The medical management of non-infectious uveitis includes steroid ophthalmic drops and dilation drops (often Cyclogyl) to reduce inflammation, paralyze the ciliary body for pain control and pull the iris away from the lens. Beta-blocker, alpha-agonist, carbonic anhydrase inhibitors and prostaglandin analog eye

drops all aid in lowering intraocular pressure. Photocoagulation of the iris (peripheral iridotomy) is occasionally needed to restore aqueous flow from production by the ciliary body to drainage in the trabecular meshwork. Severe, unresponsive glaucoma may require surgical intervention to create an alternative pathway for aqueous drainage.

6.7 Sclera

6.7.1 Anatomy and Physiology

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.

6.7.2 Acute Radiation Effects

The sclera may become inflamed 2–4 weeks after the initiation of RT. This condition is transient and usually resolves on its own.

6.7.3 Chronic Radiation Effects

The sclera is able to tolerate doses of RT up to 900 Gy from an iodine or cobalt plaque when administered over a period of four days to one week. Thinning, melting or atrophy of the sclera can occur several years after fractioned RT doses of 20–30 Gy. These scleral conditions are uncommon after RT for childhood tumors treated with external beam radiation, unless extremely high doses are used. Scleral perforation may also occur, although it is rare [2].

6.7.4 Chemotherapy

There are no reported scleral complications when chemotherapy agents are used systemically; however, mitomycin C, which is used topically as adjunct treatment for ocular surface tumors, may lead to scleral ulceration, scleritis and scleral calcification [4].

6.7.5 Medical and Nursing Management

Scleritis may benefit from systemic corticosteroid therapy. More severe reactions, such as scleral melting and ulceration, require close observation, treatment with antibiotic drops and surgical repair with scleral grafting. Eye protection and the importance of avoiding trauma should be emphasized to patients.

6.8 Optic Nerve and Retina

6.8.1 Anatomy and Physiology

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. The blood–retina barrier, which is analogous to the blood–brain barrier, protects the retina. It is very sensitive to changes in vascular permeability that can lead to swelling of the retinal layers (i.e. macular edema).

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.

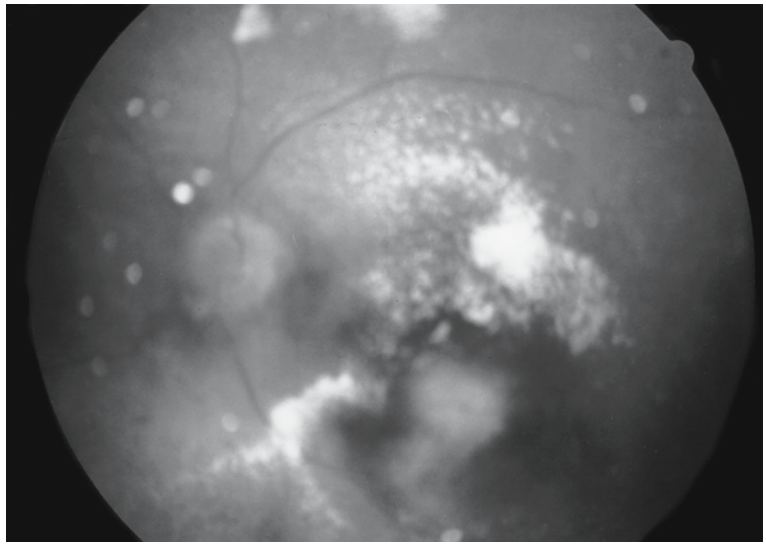
6.8.2 Acute Radiation Effects

RT, either with 20–35 Gy fractionated over 2–4 weeks or in doses in excess of 50 Gy, has been reported to produce a transient retinal edema [1, 2].

6.8.3 Chronic Radiation Effects

Radiation retinopathy (Fig. 6.5) is a well-documented consequence of radiation treatment. It is characterized by specific examination findings, including microaneurysms, hard exudates, cotton-wool spots, optic disc swelling, vascular occlusion, hemorrhages and neovascularization. These changes are clinically indistinguishable from retinal changes due to diabetes. Radiation retinopathy can develop as soon as 3 weeks, and as late as 15 years, following RT, although, typically, it occurs between 1 and 3 years.

Figure 6.5
Radiation retinopathy



Although as little as 15 Gy of external beam radiation has led to signs of retinopathy, 30–60 Gy are usually required. In the authors' experience, fewer than 5 % of children treated with external beam radiation for retinoblastoma develop radiation retinopathy. 50 Gy is regarded as the threshold for the development of retinopathy following radioactive plaque exposure. Either a history of diabetes mellitus or concurrent treatment with chemotherapy is believed to increase susceptibility to radiation retinopathy [3, 27].

6.8.4 Chemotherapy

The optic nerve and retina are common sites for chemotherapeutic complications. Retinal hemorrhages, cotton wool spots and optic disc edema have all been reported following systemic nitrosoureas [28], while intracarotid infusion has been implicated in optic neuritis and atrophy [29]. In some patients treated systemically, cisplatin has produced optic neuritis, papilledema and retinal toxicity that manifests as color blindness [30]. Intracarotid infusion can lead to visual loss from severe retinal and/or optic nerve ischemia, pigmentary retinopathy or exudative retinal detachment [31]. Carboplatin has led to visual loss due to retinopathy and optic neuropathy [32]. Intrathecal methotrexate has been reported to cause optic nerve atrophy, optic neuropathy, retinal pigment changes and retinal edema [33]. Patients treated with Tamoxifen for a period greater than nine months are susceptible to a crystalline retinopathy and visual impairment, although the visual impairment is generally reversible with cessation of treatment. In addition, bilateral optic neuritis with retinal hemorrhages has been reported within three weeks of Tamoxifen initiation [34].

Corticosteroids have been implicated in the development of pseudotumor cerebri and its associated optic nerve swelling. In addition, the immunosuppressive effects of corticosteroids have been linked to retinal infections. Plant alkaloids vincristine and vinblastine may lead to visual loss and double vision secondary to optic neuropathy, optic atrophy and cranial nerve palsies [35, 36]. Acute optic neuropathy, along with cranial nerve palsy, may also follow 5-fluorouracil treatment [4]. In addition, visual loss in the form of optic nerve damage has been attributed to fludarabine, cyclosporine, paclitaxel, nitrogen mustards and intrathecal cytosine arabinoside [37–40].

6.8.5 Medical and Nursing Management

Retinal hemorrhages and cotton wool spots as part of radiation retinopathy will resolve without treatment; however, they are clear indications of retinal damage and are cause for ophthalmologic referral. Retinal edema manifests as blurred vision when it affects the macula. It is diagnosed by careful slit lamp biomicroscopy with the aid of fluorescein angiography. Current treatment options include laser photocoagulation and corticosteroids. Neovascularization (both iris and retinal) is a manifestation of chronic retinal ischemia and is also treated with laser photocoagulation. Because diabetes mellitus and hypertension can mimic and/or potentiate radiation retinopathy, strict control of blood sugar and blood pressure should be emphasized.

The treatment of optic disc edema and optic neuropathy is controversial. While the use of systemic corticosteroids and pressure-lowering medications may be effective, observation is also a viable option.

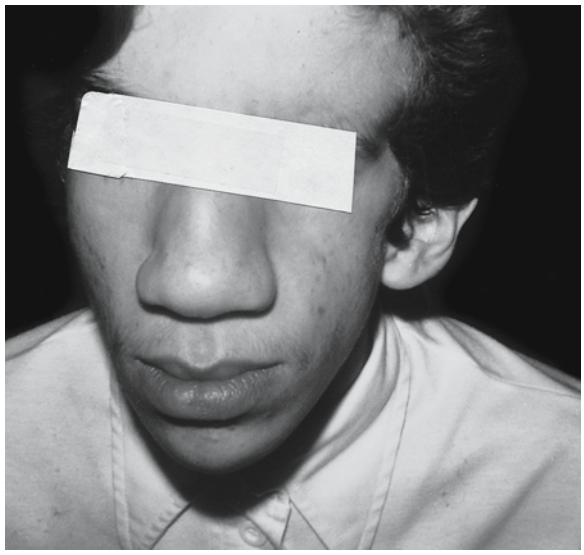


Figure 6.6
Orbital bone suppression

6.9 Orbital Bones and Tissue

6.9.1 Anatomy and Physiology

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.

6.9.2 Acute Radiation Effects

There are no known acute radiation effects to the orbital bones.

6.9.3 Chronic Radiation Effects

Suppression of bony growth remains the most common orbital complication of chronic RT. The result is especially noticeable in patients treated at a young age for retinoblastoma or rhabdomyosarcoma. A hollowing of the temporal bone, stunted vertical growth of the orbit and saddle nose (flattening and shortening of the bridge of the nose) are typical features which occur years after a dose of 40–70 Gy to the orbit, fractionated over a 3- to 7-week time period [2] (Fig. 6.6). The bony effects of radiation are reduced when treatment is delayed until 6 months or, even better, one year of age [3]. Furthermore, advanced radiation techniques allow greater precision in tissue localization, thus sparing anterior segments of the eye and uninvolved bone.

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 [41]. Osteonecrosis rarely results after very high doses of radiotherapy, but may be associated with concurrent orbital infections. Most devastatingly, second, non-

ocular cancers may also develop in the radiation field, especially in retinoblastoma patients who are predisposed to tumor formation [42].

6.9.4 Chemotherapy

Intracarotid carboplatin concurrent with intravenous etoposide may produce severe visual loss secondary to severe orbital inflammation and optic nerve ischemia [43].

Both 5-fluorouracil and methotrexate therapy have also led to clinically significant periorbital edema. Corticosteroids have been shown to cause a protrusion of the globe known as exophthalmos [44]. Paralysis of the eye muscles (ophthalmoplegia) has been reported with cyclosporine [45] and vincristine, due to cranial nerve palsy [14].

6.9.5 Medical and Nursing Management

There is no medical treatment to reverse the retardation of bone growth. Osteonecrosis may require surgical debridement and antibiotics. Anophthalmic socket syndrome is very difficult to treat and sometimes requires orbital reconstruction surgery. Anophthalmic sockets with ocular prosthesis require regular care and cleaning with gentle soaps. The orbit itself must be examined by a medical professional periodically for the development of second malignancies. Finally, counseling should be available to patients regarding the disfiguring effects of radiation on bone growth.

6.10 Conclusion

The present and future outlook for the treatment of children with primary ophthalmic tumors and other tumors involving the eye and its bony structures is encouraging. Cancers that were once uniformly fatal are today viewed as treatable. Newer techniques in radiotherapy, which provide the ability to conserve vision and spare non-involved bone, together with advancements in chemotherapy and surgery, offer not only a longer lifespan, but also, improved quality of life.

References

1. Haik BH, Jereb B, Abramson DH et al. (1983) Ophthalmic radiotherapy. In: Iliff NT (ed) Complications in ophthalmic surgery. Churchill Livingstone, New York, pp 4449–4485
2. Brady LW, Shields J, Augusburger JJ et al (1989) Complications from radiation therapy to the eye. Front Radiat Ther Oncol 23:238–250
3. Ober MD, Beaverson K, Abramson DH Ocular complications. In: Wallace H, Green D (eds) Late effects of childhood cancer. Arnold, London
4. Al-Tweigeri T, Nabholtz JM, Mackey JR (1996) Ocular toxicity and cancer chemotherapy. A review. Cancer 78:1359–1373
5. Sidi Y, Douer D, Pinkhas J (1977) Sicca syndrome in a patient with toxic reaction to busulfan. JAMA 238:1951
6. Straus DJ, Mausolf FA, Ellerby RA (1977) Cicatricial ectropian secondary to 5-fluorouracil therapy. Med Pediatr Oncol 3:15–19
7. Esmaeli B, Valero V, Ahmadi A et al (2001) Canalicular stenosis secondary to docetaxel (taxotere). A newly recognized side effect. Ophthalmology 108:994–995
8. Miller D, Pecxon JD (1965) Corticosteroid and functions in the anterior segment of the eye. Am J Ophthalmol 59:31
9. Seiff SR, Shorr N, Adams T (1985) Surgical treatment of punctual-canalicular fibrosis from 5-fluorouracil therapy. Cancer 56:2148–2149
10. Donnenfeld ED, Ingraham HJ, Abramson DH (1993) Effects of ionizing radiation on the conjunctiva, cornea, and lens. In: Alberti WE, Sagerman RH (eds) Medical radiology. Radiotherapy of intraocular and orbital tumors. Springer, Berlin Heidelberg New York, pp 261–270
11. Palmer ML, Hyndiuk RA (2000) Toxicology of corticosteroids and other antiinflammatory agents. In: Albert DM, Jakobiec FA (eds) Principals and practice of ophthalmology, 2nd edn. Saunders, Philadelphia, PA, pp 399–416
12. Tseng SC (1986) Topical treatment for severe dry-eye disorders. J Am Acad Dermatol 15:860–866
13. Blondi FC (1958) The late effects of x-radiation on the cornea. Trans Am Ophthalmol Soc 56:413–450
14. Albert DM, Wong VG, Henderson ES (1967) Ocular complications of vincristine therapy. Arch Ophthalmol 78:709–713
15. Kaiser-Kupfer MI, Lippman ME (1978) Tamoxifen retinopathy. Cancer Treat Rep 62:315–320
16. Merriam GR, Focht EF (1957) A clinical study of radiation cataracts and the relationship to dose. Am J Roentgenol 77:759–785
17. Braver DA, Richards RD Good TA (1967) Posterior subcapsular cataracts in steroid treated children. Arch Ophthalmol 77:161
18. Loredo A, Rodriguez RS, Murillo L (1972) Cataracts after short-term corticosteroid treatment. N Engl J Med 286:160

19. Podos SM, Canellos GP (1969) Lens changes in chronic granulocytic leukemia. Possible relationship to chemotherapy. Am J Ophthalmol 68:500–504
20. Gorin MB, Day R, Costantino JP (1998) Long-term tamoxifen citrate use and potential ocular toxicity. Am J Ophthalmol 125:493–501
21. Armaly MF (1966) The heritable nature of dexamethasone-induced ocular hypertension. Arch Ophthalmol 75:32–35
22. Armaly MF (1963) Effect of corticosteroids on intraocular pressure and fluid dynamics. I. Effect of dexamethasone in the normal eye. Arch Ophthalmol 70:482–490
23. Armaly MF (1963) Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. Arch Ophthalmol 70:492–499
24. Spaeth GL, Rodriques MM, Weinreb S (1977) Steroid induced glaucoma. A: Persistent elevation of intraocular pressure. B: Histopathological aspects. Trans Am Ophthalmol Soc 75:353–381
25. Margo CE, Murtagh FR (1993) Ocular and orbital toxicity after intra-carotid cisplatin therapy. Am J Ophthalmol 116: 508–509
26. Anderson B, Anderson B (1960) Necrotizing uveitis incident to perfusion of intracranial malignancies with nitrogen mustard and related compounds. Trans Am Ophthalmol Soc 58:95–104
27. Brown GC, Shields JA, Sanborn G et al (1982) Radiation retinopathy. Ophthalmology 89:1494–1501
28. Shingleton BJ, Bienfang DC, Albert DM et al (1982) Ocular toxicity associated with high-dose carmustine. Arch Ophthalmol 100:1766–1772
29. Miller DF, Bay JW, Lederman RJ (1985) Ocular and orbital toxicity following intra-carotid injection of BCNU and cisplatin for malignant gliomas. Ophthalmology 92:402–406
30. Ostrow S, Hohn D, Wiernik PH et al (1978) Ophthalmologic toxicity after cis-dichlorodiamine platinum (II) therapy. Cancer Treat Rep 62:1591–1593
31. Margo CE, Murtagh FR (1993) Ocular and orbital toxicity after intra-carotid cisplatin therapy. Am J Ophthalmol 116: 508–509
32. Rankin EM, Pitts JE (1993) Ophthalmic toxicity during carboplatin therapy. Ann Oncol 4:337–338
33. Millay, RH, Klein ML, Shults WT (1986) Maculopathy associated with combination chemotherapy and osmotic opening of the blood brain barrier. Am J Ophthalmol 102: 626–632
34. Ashford AR, Donev I, Tlwarl RP (1988) Reversible ocular toxicity related to tamoxifen therapy. Cancer 61:33–35
35. Albert DM, Wong VG, Henderson ES (1967) Ocular complications of vincristine therapy. Arch Ophthalmol 78:709–713
36. Shurin SB, Rekate HL, Annable W (1982) Optic atrophy induced by vincristine. Pediatrics 70:288–291
37. Porges Y, Blumen S, Fireman Z et al (1998) Cyclosporine-induced optic neuropathy, ophthalmoplegia, and nystagmus in a patient with Crohn's disease. Am J Ophthalmol 126: 607–609
38. Chun JH, Leyland-Jones BR, Caryk SM et al (1986) Central nervous system toxicity of fludarabine phosphate. Cancer Treat Rep 70:1225–1228
39. Capri G, Munzone E, Tarenzi E et al (1994) Optic nerve disturbances: a new form of paclitaxel neurotoxicity. J Natl Cancer Inst 86:1099–1101
40. Margileth DA, Poplack DG, Pizzo PA (1977) Blindness during remission in two patients with acute lymphoblastic leukemia. A possible complication of multimodality therapy. Cancer 39:58–61
41. Abramson DH (1988) The diagnosis of retinoblastoma. Bull NY Acad Med 64:283–317
42. Abramson DH, Frank CM (1998) Second non-ocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. Ophthalmology. 105: 573–579; discussion 579–5780
43. Lauer AK, Wobig JL, Shults WT et al (1999) Severe ocular and orbital toxicity after intracarotid etoposide phosphate and carboplatin therapy. Am J Ophthalmol 127:230–233
44. Van Dalen JT, Sherman MD (1989) Corticosteroid-induced exophthalmos. Doc Ophthalmol 72:273–277
45. Bixenman WW, Nicholls JV, Warwick OH (1968) Oculomotor disturbances associated with 5-fluorouracil chemotherapy. Am J Ophthalmol 83:604–608

Head and Neck

Arnold C. Paulino · Mary Koshy · Della Howell

Contents

7.1 Introduction

The head and neck region is composed of multiple structures in close proximity that are at risk for acute and late treatment effects. It is the juxtaposition of these sensitive tissues, which include the major organs for sensation (eyes, ears, nose and mouth), mucous membranes, salivary glands, teeth, base-of-skull and associated regions of brain and the hypothalamic-pituitary axis, which places multiple critical structures at risk for radiation damage. Approximately 40% of rhabdomyosarcomas arise in this region. Ewing's sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, nasopharyngeal carcinoma, lymphoma, neuroblastoma, hemangioma and histiocytosis also occur in the head and neck. Consequently, late effects secondary to local treatment such as radiotherapy (RT) and surgery, as well as systemic therapy, are expected following treatment for tumors originating in this area. The current chapter reviews the pathophysiology and clinical manifestations of late effects in the head and neck region, outlines methods for screening and detection and suggests interventions that can be used for their management.

7.2 Pathophysiology

7.2.1 Normal Organ Development

At birth, the skin and mucous membranes, salivary glands, taste buds, bones and connective tissues, deciduous incisor crowns and auditory apparatus are all formed. These tissues of the head and neck region arise in the embryo from branchial arches, beginning

Table 7.1. Radiotherapy doses and types of chemotherapy attributed to late effects in head and neck region

Late effect	Radiotherapy dose	Type of chemotherapy
Bone		
Hypoplasia	RT dose ≥30 Gy [23, 28, 33, 49]	
Skin		
Necrosis/ulceration	RT dose ≥70 Gy [7]	
Teeth		
Growth disturbances	RT dose ≥20 Gy [33, 56]	Cyclophosphamide Vincristine Vinblastine [18, 30, 33, 35, 36, 44, 47, 54, 57]
Salivary gland		
Xerostomia	RT dose ≥30 Gy [5, 16, 23]	
Ear		
Sensorineural hearing loss	RT dose ≥40 Gy [25, 48]	Cisplatin (cumulative dose ≥ 360mg/m^2) Carboplatin [6, 13, 60]

in the fourth week of gestation. Ectoderm, mesoderm and endoderm, along with migrating neural crest cells and myoblasts, give rise to the specialized structural and functional components of this region [42].

Sixty-five percent of the growth of the mandible, maxilla and alveolar ridge takes place from birth to puberty, with remaining growth completed by age 20. During childhood (age 4 through adulthood), mandibular growth is primarily forward, while the maxilla grows vertically. The permanent dentition is developing as well throughout childhood, with the more visible front teeth developing during the preschool years. Dental development may not be completed until 16 years of age [13]. Thus, therapy anytime during childhood can affect dentition. Long-term effects are dependent upon developmental status at the time of chemotherapy and radiotherapy. Manifestation of these effects becomes apparent with expected growth.

7.2.2 Organ Damage and Developmental Effects of Cytotoxic Therapy

The head and neck comprise a complex region with multiple tissue types, including mucosa, skin, subcutaneous tissue, salivary gland tissue, teeth, bone and cartilage. Each has a unique response to cytotoxic therapy. In general, two types of effects are seen. Acute effects that occur during or shortly after the course of treatment usually involve tissues that divide rapidly, resulting in erythema and pseudomembrane vs. ulceration of mucosa, erythema and desquamation of skin, reduced serous output from salivary glands and reduction of taste acuity. Cell populations in "late-reacting" tissues proliferate slowly and may not manifest injury until months to years after treatment. Early changes within these tissues may also occur but are usually not detected by standard methods of observation. Late changes, however, can occur in all organs. Table 7.1 shows some of the more common late toxicities in relation to radiotherapy dose and type of chemotherapy.

7.2.2.1 Skin and Mucous Membranes

Skin and mucosa exhibit early epithelial damage and delayed permanent vascular injury that are dependent on the total radiation dose, the fraction size and the volume of irradiated tissue. Early radiation injury to the skin is directly attributable to the effect of ionizing radiation on the stratum germinativum cells [20]. Release of vasoactive substances results in increased capillary permeability and dilatation that

manifest as skin erythema [55]. An increase in melanin- containing cells at 2–3 weeks enhances pigmentation. Moist desquamation that occurs 3–4 weeks from the initiation of treatment has been found to correlate with the development of severe delayed telangiectasias [2].

Late radiation effects are primarily caused by fibrosis and vascular damage, particularly to small vessels. Arterioles become narrow as a result of myointimal proliferation and destruction of capillaries and sinusoids [19]. Delayed histologic manifestations of these changes include fibrin deposition, ulceration and fibrosis. Telangiectasias are caused by endothelial cell depletion and basement membrane damage that causes capillary loops to contract into distorted sinusoidal channels.

Stomatotoxicity resulting from chemotherapeutic agents, such as methotrexate, Adriamycin, 5-fluorouracil, bleomycin and cytosine arabinoside, is not associated with long-term effects. However, when administered in conjunction with radiotherapy, the acute injury may be enhanced, resulting in an increased risk for long-term damage.

7.2.2.2 Bone and Connective Tissue

Irradiation of growing bone causes injury to actively dividing mesenchymal cells, osteoblasts and endothelial cells [20]; it also causes impairment of the osteoid formation. The long-term injury observed in irradiated growth centers includes atrophy, fibrosis of marrow spaces and a lack of osteocytes. Impaired vascularity and fibrosis of both periosteum and endosteum can occur.

The soft tissues may also be affected by radiation. Fibrosis occurs as a consequence of increased fibroblast proliferation, combined with collagen deposition, in children whose craniofacial structures are irradiated [21]. Hypoplasia also occurs. Mucosal atrophy, reduced tissue vascularity and tumor effects predispose to osteoradionecrosis, chondronecrosis and soft tissue necrosis, particularly with high radiation dose/time and large irradiated volume. Interstitial implants and intraoral techniques further enhance the likelihood of such outcomes.

7.2.2.3 Salivary Glands and Taste Buds

The parotid, submandibular and sublingual glands are the major salivary glands. Other (minor) salivary glands are variably distributed throughout the oral cavity and pharynx. In the resting state, saliva production comes primarily from the submandibular gland. With food intake, 60% of the saliva may originate from the parotid gland. The composition of saliva produced is characteristic of the specific gland. Parotid saliva production is primarily serous, while the minor salivary glands secrete a predominantly mucous fluid that is more vicious. The submandibular and sublingual glands produce mixed mucous and serous secretions. Radiation damages the serous cells to a greater extent than it does the mucous cells and epithelium of ducts. Histopathologic changes 10–12 weeks after initiation of RT to doses of 50–70 Gy consist predominantly of serous acini loss, mild fibrosis, dilatation and distortion of ducts and aggregation of lymphocytes and plasma cells [7]. There is little evidence that chemotherapy has a long-term effect on salivary gland function [39].

Modification in taste occurs as a result of changes in oral mucosa and saliva [38]. Patients retain the perception of sweet and salt more readily than that of sour and bitter. Dietary changes thus enhance dental decay in an environment already conducive to caries production [4]. Although the taste buds are considered relatively radioresistant, some taste alterations may be caused by damage to the microvilli.

7.2.2.4 Teeth

RT effects on dentition are influenced by the developmental stage of the tooth, with the most severe disturbances occurring in children younger than six years of age [9, 34, 56]. Prior to morphodifferentiation and calcification, irradiation may result in agenesis. Direct irradiation at a later stage may cause microdontia, enamel hypoplasia, incomplete calcification of enamel and arrested root development. Chemotherapeutic agents, such as cyclophosphamide, vincristine and vinblastine, have also been shown to affect dentition, resulting in hypodontia,

enamel hypoplasia, microdontia and root malformation [1, 11, 18, 30, 33, 35, 36, 44, 47, 54, 57].

7.2.2.5 Ear

Children who present with primary tumors of the head and neck area or brain frequently encounter radiation to the external, internal and middle ear during the course of their treatment [45]. There can be effects on the otic structures, both during the treatment sessions and months to years following therapy. The immediate effect on the ear is desquamation of the columnar epithelium, which lines the ears and covers the ossicles, leading to edema of the mucosa within the ear. Altered production of cerumen, in conjunction with epithelial desquamation, leads to plugging of the ear canals that may persist long after completion of therapy. More chronic effects from fibrosis and scarring can lead to chronic radiation otitis and hearing loss. Hearing loss secondary to radiation therapy is usually permanent and can be sensorineural or conductive, depending on the structures affected by the radiation. Direct effects of radiation on the cartilaginous structures can lead to stenosis or necrosis of the ear canal. Chondronecrosis may occur in the cartilage of the external ear as well.

Cisplatin and carboplatin have sensorineural effects, and these are most prominent in the high frequency ranges (which can be affected significantly by radiation – see Chapter 8).

7.3 Clinical Manifestation of Late Effects

7.3.1 Skin and Mucous Membranes

Mucosal atrophy after conventionally fractionated doses of 60–70 Gy over a period of 6–7 weeks is common, but necrosis, chronic ulceration and bone exposure rarely occur unless the delivery of dose is accelerated or the total dose exceeds 70 Gy in 7 wks [7]. Thrombosis of small blood vessels in the submucosa results in ischemia and the consequent appearance of ulcers and telangiectasias. This condition may become apparent as soon as six months after irradiation or as late as 1–5 years and is irreversible. Scarring and fibrosis of the nasal mucosa can alter sinus drainage and predispose patients to persistent rhinosinusitis. Children may complain of symptoms of chronic sinusitis, which include chronic nasal discharge, postnasal drip, headache and facial pain and headache. Smell acuity is significantly affected by radiation treatment of the olfactory mucosa, and, although this is not usually voiced as a specific complaint, it can contribute to decreased appetite and poor nutrition.

Severe skin reactions, including permanent hyperpigmentation, telangiectasias and skin ulcerations, are rarely seen with the use of modern day megavoltage RT, unless the skin is intentionally treated with a high dose. Doxorubicin and actinomycin can interact with radiation to produce severe skin reactions and may contribute to late skin effects. When these drugs are given early in the course of radiation such reactions may be seen after low doses of 20–30 Gy. If they are delivered after radiation, the phenomena of "radiation recall" may occur, in which skin reactions appear in the treated field [14, 26]. Skin often remains chronically dry due to damage to the sebaceous and eccrine glands. The sebaceous glands are as radiosensitive as the basal epithelial cells of hair follicles; eccrine glands are less sensitive [27]. Epilation within the treatment field usually occurs 2–3 weeks into the course of radiation treatment. The permanency of the epilation depends on the total dose of radiation delivered to the hair follicles, and this, in turn, depends on the treatment technique and beam energy. Single fraction doses of 7–8 Gy or more and total doses (after fractionated therapy) of greater than 40 Gy can result in permanent hair loss. After chemotherapy, hair begins to regrow within 1–2 months. It may be lighter in color and have a finer texture [20]. Microscopic analysis of hair samples of patients receiving chemotherapy has shown trichorrhexis, fragmentation, decrease in diameter and depigmentation of the hair shaft, all of which may account for the changes in color and texture [46].

7.3.2 Bone and Connective Tissue

Clinical manifestations of radiation include hypoplasia, deformities, fracture and necrosis. The craniofacial development of children is affected, resulting in reduced temporomandibular joint mobility, growth retardation and osteoradionecrosis [10]. Impaired growth of the mandible and facial bones can contribute to malocclusion. Chemotherapy may also affect the growing skeleton, although with limited long-term consequences. In the immature rat, the growth plate becomes thicker with methotrexate and thinner with doxorubicin. These agents do not appear to have a major effect on the ultimate height of treated children.

Varying degrees of facial asymmetry, including hemifacial microsomia and other craniofacial abnormalities, may necessitate interventions, including bimaxillary osteotomies and reconstruction with prostheses. The clinical effects of chemotherapy and radiation on dental and craniofacial development will be discussed later in this chapter. Radiation has been associated with malocclusion, reduced mobility of the temporomandibular joint, fibrosis, soft tissue necrosis and osteoradionecrosis. Eventual fibrosis of the temporomandibular joint results in muscle pain and headaches [11]. Tumor invasion of the temporomandibular joint, surgery and the use of large daily fractions further increase the risk of radiation-induced trismus. Combined modality therapy has a greater impact on facial structures when radiation doses are high; children receiving doses of 24 Gy or less to the temporomandibular joint have not demonstrated clinical signs of trismus [37]. The facial skeleton appears to be the most susceptible to high radiation doses before age six and at puberty, which are critical times of skeletal development. In a study of 26 children receiving a mean dose of 54 Gy for either nasopharyngeal cancer or rhabdomyosarcoma, cephalometric measurements utilizing CT showed deviations in the cranial vault, the anterior and mid-interorbital distances and lateral orbital wall length, compared with normal skulls [12]. The age at which RT is given is the most important factor determining orbital growth retardation in retinoblastoma. The orbit has three growth spurts, the first between 0–2 months, the second between 6–8 months and the third during adolescence. Radiation in children younger than 6 months of age is more damaging to orbital growth than at an older age [32]. Maxillary and mandibular hypoplasias are common dentomaxillofacial defects after chemoradiation. Linear cephalometric values suggest that the growth of the mandible may be more affected than that of the maxilla [41].

Rhabdomyosarcoma of the head and neck is a condition in which the long-term side effects of combined modality therapy has been extensively studied. Clinical or radiographic dentofacial abnormalities have been observed in 80% of patients with head and neck rhabdomyosarcoma at a median follow up of 12.2 years [18]. Abnormalities included enamel defects, bony hypoplasia/facial asymmetry, trismus, velopharyngeal incompetence, tooth/root agenesis and disturbance in root development. Bony hypoplasia and disturbance in root formation were the most common findings. The largest report on late effects in pediatric head and neck rhabdomyosarcoma comes from IRS II and IRS III, in which 213 patients were followed for a median length of 7 years. Seventy-seven percent had one or more late sequelae, including poor statural growth, facial and nuchal asymmetry, dental abnormalities and vision/hearing dysfunction [52]. Late side effects in children treated with combined modality therapy for head and neck rhabdomyosarcoma are usually seen within the first 10 years after treatment [49], given that most will have experienced their pubertal growth by that time. Bony hypoplasia of the orbit was noted in 50–60% of patients treated for orbital rhabdomyosarcoma in IRS-I and IRS-III [29, 53]. In both of these studies, orbital bone growth was inversely related to age at irradiation, which is reasonable, given that the growth potential is greater in younger children. The cosmetic effects become more apparent as normal growth proceeds in adjacent unirradiated areas.

In 1983, Guyuron et al.. reported on 41 patients who had been treated as children with RT to the head and face. They noted that hypoplastic development of soft tissue and bone was a common finding [28]. Irradiation of the cranial base was often correlated with soft tissue deficits in the upper face and mid

face. Soft tissue was more vulnerable to RT than growing facial bones, with a threshold dose as low as 4 Gy (in contrast to 30 Gy for facial bones). In 1984, Jaffe reported on the maxillofacial abnormalities seen in 45 patients who had been treated as children with megavoltage RT for lymphoma, leukemia, rhabdomyosarcoma and miscellaneous tumors [33]. Forty-three of the 45 patients also received chemotherapy (including vincristine, actinomycin-D, cyclophosphamide, methotrexate, 6-mercaptopurine, prednisone, procarbazine or nitrogen mustard in various combinations). In 82% of the radiated patients, dental and maxillofacial abnormalities were detected, including trismus, abnormal occlusal relationships and facial deformities. The most severe radiation deformities were seen younger patients who received higher radiation doses. Those who received median doses of only 24–30 Gy for leukemia and Hodgkin's disease did not have facial deformities or temporomandibular joint deficits. In contrast, 50% of the patients with rhabdomyosarcoma who received a median dose of 55 Gy developed trismus, nasal voice, caries and maxillary/mandibular and facial deformities.

In 1986, Fromm evaluated the late effects in 20 patients who, as children, had received radiation therapy and combination chemotherapy with vincristine, dactinomycin and cyclophosphamide (and, in some cases, doxorubicin) for sarcomas of the head and neck [23]. The median follow up was 5.5 years. Age at irradiation was an important factor, as all 16 children younger than 9 years of age developed facial growth abnormalities, while the remaining 4 patients, all of whom were older than 11 years, did not develop deformities. "Mild" deformity was seen in 7 patients, with a median 5.1 yr follow up and a median dose of 40–50 Gy. "Severe" deformities were seen in patients who had received a median dose of 50–60 Gy and were only observed at a median follow up of 8.6 yrs. The length of follow up, as well as total dose received, are important factors in the severity of defects seen in survivors of childhood cancer. Paulino found that 11 of 15 children treated for head and neck rhabdomyosarcoma with RT and chemotherapy developed facial asymmetry in the RT field at doses between 44–60 Gy [49]. Sonis studied 97 patients with acute lymphoblastic leukemia (ALL) who received either chemotherapy alone or with 18–24 Gy cranial RT [56]. The treatment fields routinely included temporomandibular joints, posterior tooth buds and the ramus of the mandible. A significant dose–effect relationship was seen between 18 and 24 Gy (2 Gy/fraction). Children under the age of 5 who received 24 Gy of cranial RT and chemotherapy had was a 90% incidence of craniofacial abnormalities, but no craniofacial abnormalities were seen in children over the age of 5 or in those receiving only 18 Gy of cranial RT and chemotherapy. No craniofacial abnormalities were noted after chemotherapy alone. It is unlikely that chemotherapy alone contributes to bony or soft tissue abnormalities, although it clearly does affect dental development in relation to age at treatment [40, 44].

Radiation therapy has an effect on wound healing that may be critical for those who require a surgical procedure in the irradiated region [13]. RT may also affect the connective tissues and bone, leading to fibrosis and osteoradionecrosis. In the Fromm series, two patients developed temporomandibular joint fibrosis with limitation of jaw motion [23]. Osteoradionecrosis has been well described in the adult head and neck literature; however, little has been written on its incidence in the pediatric population. Osteoradionecrosis usually develops in the mandible and its risk is directly correlated with total radiation dose, fractionation dose, tumor size and bony involvement by the tumor. The risk is also increased in dentulous patients and even more so if these patients receive postirradiation extraction, compared with pre-irradiation extraction. Amifostine may confer radioprotection of craniofacial bone growth inhibition. Pretreatment with amifostine, 20 minutes before 35 Gy RT, resulted in significant preservation of linear bone growth, bone volume and bone mineral density in the rabbit orbital-zygomatic complex, compared with controls [22].

7.3.3 Salivary Glands and Taste Buds

Salivary gland dysfunction may occur when one or more of the major salivary glands are irradiated. Permanent damage can lead to xerostomia, predisposing

to dental caries, decay and osteoradionecrosis. Studies of salivary function in children after RT are limited. Fromm found that 8 of 11 parotid glands that had received >45 Gy to greater than 50% of the volume failed to secrete saliva, whereas all parotid glands receiving <40 Gy retained the ability to secrete [23]. More recent studies in adult patients have shown a lower dose–response effect. Chao found that only 25% of the pretreatment stimulated saliva was present when both parotid glands received a mean dose of 32 Gy; salivary flow rate was reduced by approximately 4% per Gy of the mean parotid dose [5]. Eisbruch found no measurable output or recovery over time in parotid glands receiving >26 Gy mean dose [16].

Chemotherapy for children with acute leukemia alters salivary function [39]. Mansson-Rahemtulla and colleagues showed decreased thiocyanate concentration in saliva following cytotoxic chemotherapy, which can lead to an alteration in function of the salivary peroxidase system, as well as increased oral complications. Patients who undergo bone marrow transplantation are also at risk. Xerostomia, as has been noted in patients with chronic graft-versus-host disease, can persist for as long as a year and results in a high risk for developing dental caries [3].

7.3.4 Teeth

Late effects on dentition in children can be attributed directly to the cytotoxic effects on the growing tooth buds and indirectly to salivary gland damage. Salivary gland damage results in a pronounced shift toward highly acidogenic and cariogenic oral microflora, which promotes dental caries [7].

The severity and frequency of long-term dental complications due to RT are related to the type of RT given, the total dose, the size and location of RT fields and the age of the patient. Growing tooth buds may be arrested with <10 Gy, while doses >10 Gy can completely destroy buds [38]. Root shortening, abnormal curvature, dwarfism and hypocalcification are noted with doses of 20–40 Gy [33, 56].

Age at the time chemotherapy is administered influences the degree of dental effects. Disturbances of dental development noted with chemotherapy include V-shaped and blunted roots [56]. The effects are most pronounced in children less than five years of age. All such children have V-shaped roots, compared with 36% of those older than five years. Blunted roots occur in 12% of children less than five years old and in 9% of those older than five years. Jaffe reported that five of 23 children treated with chemotherapy for non-head and neck region tumors had acquired amelogenesis imperfecta, microdontia of bicuspid teeth and thinning of roots with an enlarged pulp chamber; none of the 23 patients developed craniofacial abnormalities [33]. Similarly, Alpaslan found significant differences in plaque index, enamel hypoplasias, discolorations and agenesis in 30 chemotherapy-treated survivors, compared with matched healthy control subjects [1]. Children treated with RT and chemotherapy likewise develop dental complications. Another study showed that all children with head and neck rhabdomyosarcoma receiving RT to developing teeth, the alveolar portion of the mandible or the lingual surface of the maxilla developed dental abnormalities, including microdontia, root stunting and dental caries [49]. Kaste found radiographically identifiable dental abnormalities, including agenesis, microdontia and root stunting in 77% of children with head and neck rhabdomyosarcoma treated with chemotherapy and RT [34].

Information regarding dental outcome after bone marrow transplants (BMT) is limited [8, 30, 58]. Neuroblastoma patients who received 12 Gy fractionated total body irradiation (TBI)-based or non-TBI-based transplants were not different in the incidence of microdontia and missing teeth [30], although TBI was associated with more severe root defects and a higher chance of permanent damage to teeth. The incidence of tooth abnormalities, including agenesis, was 62.9% in another study in which most of the children were treated with a TBI-based BMT regimen [58]. A study that compared mandibular root surfaces according to treatment regimen showed that patients receiving TBI and chemotherapy had a smaller mandibular root surface area, compared with children receiving chemotherapy alone [15].

7.3.5 Ear

RT has long been associated with various forms of ototoxicity. The exact mechanism of radiation-induced ototoxicity is unknown. Some physicians hypothesize that direct damage to the ossicles and tympanic membrane may lead to conductive hearing loss and fibrosis. Direct damage to the cochlea may also be seen. Other physicians believe that late radiation effects to small vessels cause hypoxia to inner ear structures, leading to hearing loss. Damage to the brainstem through radiation may also lead indirectly to hearing loss.

In categorizing deleterious effects of radiation on the ear, three clinical syndromes are found [25, 48]. The first of these is acute radiation otitis. The effects of acute radiation otitis can be seen during or shortly after the completion of radiation. It is associated primarily with erythema of the tympanic membrane and external canal and occasionally with middle ear effusion and tinnitus. Radiation doses equal to or greater than 30 Gy have been implicated. According to some studies, 15–30% of pediatric patients will be affected. Acute radiation otitis is usually self-limiting but in severe cases requires further therapy. The second, and most common, clinical syndrome is that of chronic radiation otitis. Clinically, patients present with dry cerumen, thickened tympanic membrane and, occasionally, slight hearing loss (both conductive and sensorineural). Chronic radiation otitis usually occurs several months after RT has been completed. Radiation doses of 45 to 65 Gy are required, and in some studies this syndrome has been found in up to 70% of patients receiving radiation therapy [48]. The third, and most rarely seen, clinical syndrome is late radiation-associated deafness. This is seen in cases of radiation to the brainstem and ear. Patients experience an irreversible, unilateral, profound hearing loss, which may progress over weeks or months to the contralateral ear. Symptoms tend to occur 3–10 years following RT.

Specific antineoplastic agents have been shown to enhance the ototoxic effects of radiotherapy. In particular, the platinum based agents, cisplatin and carboplatin, have well-documented effects on hearing, and radiation has been shown to be synergistic in terms of ototoxicity. Children with primary brain tumors, osteosarcoma, germ cell tumors and neuroblastoma are most at risk for this added ototoxicity, because they are more likely to receive platinum-based chemotherapy and may require RT as well. The exact mechanisms of ototoxicity related to chemotherapy are not known, but they seem to affect the cochlea, specifically the outer hair cells in the organ of Corti. Cisplatin ototoxicity has been reported in 9–91% of patients, depending on the dose, duration and circumstances surrounding its use. The initial effects are on high frequency hearing (above 8000 Hz), but lower frequencies can also be affected at higher doses. In one study, 14 of 25 children who received a cumulative cisplatin dose of 474 mg/m^2 developed hearing loss in the 250–2000 Hz range, while only four of 29 children had hearing loss in the same range with a cumulative dose of 410 mg/m^2 [6]. Hearing loss with cisplatin is irreversible and symmetric bilaterally. Cohen et al. have shown that the threshold for high-frequency hearing loss in patients receiving cisplatin is lower than for patients who have brain tumors treated with RT [6]. Information regarding the effects of timing the treatment with platinum-based chemotherapy and RT on patients has not been well characterized. Walker hypothesized that RT given concurrently with or prior to cisplatin administration was associated with a worsening of hearing [60].

More recent advances in RT may lead to fewer ear-related, radiation-induced effects. Intensity-modulated radiation therapy (IMRT) and 3D Conformal Radiotherapy (3D CRT) have been associated with reduced ototoxicity in pediatric patients receiving RT and cisplatin for the treatment of medulloblastoma [31]. Due to the precise delivery of RT with the conformal techniques, patients can receive full doses to the target volume while receiving lower doses to the auditory structures [24, 50].

7.4 Detection and Screening

The successful evaluation, diagnosis and management of late effects require a multidisciplinary approach. All children with head and neck cancers need prolonged follow up by a pediatric oncologist and

radiation oncologist. They must also have access to specialists in endocrinology, ophthalmology, otolaryngology and dentistry. In addition, psychological counseling should be available, as some of these children have suffered trauma secondary to cosmetic changes from tumor and/or treatment. Abnormalities in any of the head and neck or dental structures should be noted at diagnosis and prior to treatment. Children with head and neck cancers should receive an annual assessment of growth, pubertal status and growth function, as well as frequent ophthalmologic and dental exams.

The initial dental exam for children who have received chemotherapy and RT should consist of a full mouth series of radiographs, including periapical, bitewing and panoramic views of the teeth. Asymptomatic patients are often found on radiographic exam to have dental disease. Horizontal and vertical alveolar bone loss, retained root tips, deep caries and periapical pathoses can usually be visualized only on intraoral radiographs [51]. It is critical to assess crown and root development, as abnormalities can predispose a tooth to premature loss. Changes in root development are critically important to recognize, as they may affect decisions regarding the removal of permanent teeth. To assess abnormal tooth and root development, it is recommended that patients receive a dental exam every six months, with special attention to early caries, periodontal disease and gingivitis. Careful evaluation of root and crown status is required before tooth extraction, endodontic and orthodontic procedures. With time, the risk of periodontal bone loss increases; it is, therefore, critical that proper periodontal prophylaxis be offered to patients, including professional cleaning and meticulous oral hygiene. When areas of the periodontium exposed to radiation are treated, or in cases where the risk of infection is increased with trauma, antibiotics may be given.

Radiation-induced changes in salivary pH and quantity produce an environment conducive to the development of caries. Xerostomia and a high carbohydrate diet can predispose the pediatric cancer patient to radiation-induced caries. Frequent dental visits to identify early caries, periodontal disease, infection, gingival recession and soft tissue ulcers are important. Salivary flow studies are helpful in assessing xerostomia, and salivary substitutes may be offered to symptomatic patients. Nutritional counseling on the importance of avoiding fermentable carbohydrates and maintaining excellent oral hygiene is critical. Mouth rinsing is essential and daily topical fluoride applications (either as a solution for mouth rinsing, a gel delivered on a tray or brushed on as a paste or gel) are all effective in reducing the risk of radiation caries [17].

In children who have received high doses of radiation to the developing facial bones and soft tissues, the use of screening to identify craniofacial abnormalities and problems with jaw movement is important for early detection and management. Trismus, crepitus, limited mandibular movement and abnormal growth associated with the temporomandibular joint may be present [37].

Routine ear, nose and throat evaluation, including inspection of the oral mucosa for ulcers, indirect and direct laryngoscopy and nasopharyngoscopy may be included in the screening process to ensure a thorough assessment of the mucosa. It is important to look for nasal scarring, as this may interfere with the normal movement of mucus and sinus drainage, leading to recurrent sinusitis. The soft tissue of the head and neck should be evaluated for muscle hypoplasia, fibrosis and ulceration. Irradiated skin often has impaired vascularity and the resultant "thin skin" is highly susceptible to minor trauma.

Both an otoscopic exam and inspection of the auricle are necessary to rule out the presence of otitis externa and chondronecrosis, respectively. Detailed inspection of the ear canal can detect cerumen impaction and tympanic scarring, both of which can lead to conductive hearing loss. In addition, the patient should be evaluated for the possible presence of otitis media or tympanic membrane perforation. In children receiving cisplatin or high-dose radiation to the inner ear, pure tone audiometry should be done at baseline and every 2–3 years to evaluate for sensorineural hearing loss [43]. Finally, the physician following a child cured from cancer should always be aware of the possibility of secondary malignancies, particularly in irradiated fields.

7.5 Management of Established Problems and Rehabilitation

7.5.1 Oral Cavity

One of the best ways to manage late effects of the teeth is preventative care. Ideally, all patients should undergo a dental evaluation and treatment of any existing dental problems prior to undergoing treatment for their cancer. Patients who are younger at diagnosis and who have received higher radiation doses will require more watchful attention for future problems. Patients should have dental exams and cleanings every six months, and these should include fluoride applications [17]. For those who develop malocclusion or other structural abnormalities, consultation with an orthodontist who has experience in the management of childhood cancer survivors who have undergone irradiation is preferred. All patients should have at least a baseline Panorex examination prior to dental procedures to evaluate their root development, since root thinning and shortening occur fairly frequently. Symptomatic treatment of temporomandibular joint dysfunction may be required and involve exercises and pain control.

When major periodontal disease is present, care should be taken to minimize trauma to the oral cavity. Prophylactic antibiotics may be required prior to specific dental procedures in patients who have received high doses of radiotherapy to the extraction or procedure site. Oral infections that occur after procedures should be aggressively treated with antibiotics. Care should be taken to avoid tight sutures and trauma during use of orthodontics.

Patients should be evaluated yearly for xerostomia. Symptomatic care with saliva substitutes, moistening agents and sialogogues such as pilocarpine may be required. Fungal infections are more likely to occur in patients with xerostomia, so special care should be taken to treat with appropriate antifungal medications, either topically or systemically.

7.5.2 Bone and Connective Tissue Disease

Many bone and connective tissue late effects may require extensive surgical correction, often staged procedures, spanning many months to years. A craniofacial team, consisting of a head and neck plastic surgeon and neurosurgeon may be necessary in restoring function and cosmesis to an affected child.

Patients who have experienced radiation to the region requiring operation will also experience poor wound healing and increased susceptibility to infection. Patients who develop infections of the soft tissue regions will require not only aggressive antibiotic therapy, but also possible surgical debridement and supportive care of pain and swelling. Soft tissue and bone necrosis can be devastating to the patient, both physically and psychologically, so measures should be taken to prevent trauma to areas affected by radiation.

Chronic sinusitis is more likely to occur in patients who have a history of atopy or hypogammaglobulinemia. Aggressive management of sinus infections with the guidance of ENT specialists is required. Patients should have their sinuses evaluated at least yearly by history and physical exam, and CT of the sinuses should be obtained as clinically indicated.

7.5.3 Ears

Younger patients and those who have received higher radiation doses are more likely to experience sclerotic side effects and eustachian tube dysfunction. They are also at greater risk for developing sensorineural hearing loss. Patients should have audiograms or brainstem auditory evoked response (BAER) tests performed yearly, or as clinically indicated. Speech and language evaluations should be performed at the end of treatment and as needed for clinical concerns. Those children with hearing loss will require routine speech and language therapies. Special educational interventions may be required as well, including alternative learning methods, individualized education plans (IEP) and preferential seating in the classroom. Table 7.2 lists various amplification and assisted living devices currently available. The use of a hearing aid can help amplify any residual hearing. Personal

Table 7.2. Amplification and assisted listening devices for children with hearing loss

Amplification
Conventional analog hearing aid
Digital hearing aid
Bone conduction hearing aid
Bone-anchored hearing aid
Assisted listening devices and personal systems
FM trainers
Telephone devices with volume controls and couplers for hearing aids
Closed captioning television
Signaling devices

devices, such as FM trainers, can aid in reducing the signal-to-noise ratio in various listening situations, e.g., in the classroom, where, at times, there may be significant background noise.

For those suffering with chronic otitis, ENT referral is indicated. Treatment usually includes antibiotic therapy, myringotomy and/or the placement of pressure-equalizing tubes. Chronic cerumen and obstruction of the ear canal will require routine cleaning and the use of agents to soften the cerumen. Some patients may require treatment for otitis externa with the use of topical otic drops. These patients should avoid submersion in water without protective earplugs.

References

1. Alpaslan G et al. (1999) Disturbances in oral and dental structures in patients with pediatric lymphoma after chemotherapy: a preliminary report. Oral Surg Oral Med Oral Pathol 97:317–321
2. Bentzen SM, Overgaard M (1991) Relationship between early and late normal tissue injury after postmastectomy radiotherapy. Radiother Oncol 20:159–165
3. Berkowitz RJ, Feretti GA, Berg JH (1988) Dental management of children with cancer. Pediatr Ann 17:715–725
4. Bonnani G, Perazzi F (1965) Variations in taste sensitivity in patients subjected to high energy irradiation for tumors of the oral cavity. Nucl Radiol 31:383–397
5. Chao KS et al. (2001) A prospective study of salivary function sparing in patients with head and neck cancers receiving intensity modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys 49:907–916
6. Cohen BH et al. (1990) Ototoxic effect of cisplatin in children with brain tumors. Pediatr Neurosurg 16:292–296
7. Cooper JS et al. (1995) Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys 31:1141–1164
8. Dahllof G et al. (1988) Disturbances in dental development after total body irradiation in bone marrow transplant recipients. Oral Surg Oral Med Oral Pathol 65:41–44
9. Dahllof G et al. (1989) Effect of chemotherapy on dental maturity in children with hematological malignancies. Pediatr Dent 11:303–306
10. Dahllof G et al. (1994) Disturbances in the oral cavity in pediatric long-term survivors after different forms of antineoplastic therapy. Pediatr Dent 16:217–223
11. Dahllof G et al. (1994) Histologic changes in dental morphology induced by high-dose chemotherapy and total body irradiation. Oral Surg Oral Med Oral Pathol 77:56–60
12. Denys D et al. (1998) The effects of radiation on craniofacial skeletal growth: a quantitative study. Int J Pediatr Otorhinolaryngol 45:7–13
13. Donahue B et al. (1994) Head and neck. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (eds) Survivors of childhood cancer. Mosby, St Louis
14. Donaldson SS et al. (1974) Adriamycin activating a recall phenomenon after radiation therapy. Ann Intern Med 81: 407–408
15. Duggal MS (2003) Root surface areas in long-term survivors of childhood cancer. Oral Oncol 39:178–183
16. Eisbruch A et al. (1999) Dose, volume and function relationships in parotid glands following conformal and intensity modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 45:577–587
17. Epstein JB et al. (1996) Effects of compliance with fluoride gel application on caries and caries risk in patients after radiation therapy for head and neck cancer. Oral Surg Oral Med Oral Pathol 82:268–275
18. Estilo CL et al. (2003) Effects of therapy on dentofacial development in long-term survivors of head and neck rhabdomyosarcoma: the Memorial Sloan-Kettering Cancer Center experience. J Pediatr Hematol Oncol 25:215–222
19. Fajardo LF, Berthrong M (1988) Vascular lesions following radiation. Pathol Annu 23:297–230
20. Fajardo LG, Berthrong M, Anderson RE (2001) Radiation pathology. Oxford University Press, New York
21. Fiorillo A et al. (1999) Radiation late effects in children treated for orbital rhabdomyosarcoma. Radiother Oncol 53:143–148

22. Forrest CR et al. (2002) Efficacy of radioprotection in the prevention of radiation-induced craniofacial bone growth inhibition. Plast Reconstr Surg 109:1311–1323
23. Fromm M et al. (1986) Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck: experience at a single institution with a review of the literature. Cancer 57:2070–2076
24. Fukunaga-Johnson N et al. (1998) The use of 3D conformal radiotherapy (3DCRT) to spare cochlea in patients with medulloblastoma. Int J Radiat Oncol Biol Phys 41:77–82
25. Goldwein JW et al. Late radiation-associated deafness in children treated for medulloblastoma and brainstem tumors, a newly recognized sequelae of radiation treatment. Oncolink website, University of Pennsylvania
26. Greco FA et al. (1976) Adriamycin and enhanced radiation reaction in normal esophagus and skin. Ann Intern Med 85:294–298
27. Guggenheimer J et al. (1977) Clinicopathologic effects of cancer chemotherapeutic agents on human buccal mucosa. Oral Surg Oral Med Oral Pathol 44:58–63
28. Guyuron B et al. (1983) Effect of irradiation on facial growth: a 7- to 25- year follow-up. Ann Plast Surg 11:423–427
29. Heyn R et al. (1986) Late effects of therapy in orbital rhabdomyosarcoma in children: a report from the Intergroup Rhabdomyosarcoma Study. Cancer 57:1738–1743
30. Holtta P et al. (2002) Long-term adverse effects on dentition in children with poor-risk neuroblastoma treated with high-dose chemotherapy and autologous stem cell transplantation with or without total body irradiation. Bone Marrow Transplant 29:121–127
31. Huang E et al.. (1998) Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys 41:77–82
32. Imhof SM et al. (1996) Quantification of orbital and midfacial growth retardation after megavoltage external beam irradiation in children with retinoblastoma. Ophthalmology 103:263–268
33. Jaffe W et al. (1984) Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: effects of treatment with chemotherapy and radiation to the head and neck. Pediatrics 73:816–823
34. Kaste SC et al. (1995) Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. Med Pediatr Oncol 25:96–101
35. Kaste SC et al. (1998) Dental abnormalities in children treated for neuroblastoma. Med Pediatr Oncol 30:22–27
36. Lindvall AM et al. (1972) The effect of roentgen irradiation on the formation of enamel and dentin in maxillary rat incisors. Scand J Dent Res 80:253–263
37. Maguire A et al. (1987) The long-term effects of treatment on the dental condition of children surviving malignant disease. Cancer 60:2570–2575
38. Marcial V (1989) The oral cavity and oropharynx. In: Moss WT, Cox JD (eds) Radiation oncology. Mosby-Year Book, St Louis
39. Mansson-Rahemtulla B et al. (1992.) Analysis of salivary components in leukemia patients receiving chemotherapy. Oral Surg Oral Med Oral Pathol 73:35–46
40. Minicucci EM et al. (2003) Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. Leuk Res 27:45–50
41. Moller P, Perrier M (1998) Dento-maxillofacial sequelae in a child treated for a head and neck rhabdomyosarcoma in the head and neck. A case report. Oral Surg Oral Med Oral Pathol 86:297–303
42. Moore K (1977) The developing human, 2nd edn. Saunders, Philadelphia
43. Nagy JL et al. (1999) Cisplatin ototoxicity: the importance of baseline audiometry. Am J Clin Oncol 22:305–308
44. Nunn JH et al. (1991) Dental caries and dental anomalies in children treated by chemotherapy for malignant disease: a study in the North of England. Int J Pediatr Dent 1:131–135
45. Ondrey FG et al. (2000) Radiation dose to otologic structures during head and neck cancer radiation therapy. Laryngoscope 110:217
46. Pai GS et al. (2000) Occurrence and severity of alopecia in patients on combination chemotherapy. Indian J Cancer 37:95–104
47. Pajari U, Lanning M, Larmas M (1988) Prevalence and location of enamel opacities in children after anti-neoplastic therapy. Community Dent Oral Epidemiol 16:222–226
48. Parsons JA (1984) The effect of radiation on normal tissues of the head and neck. In: Million RR, Cassisi NJ (eds) Management of head and neck cancer. A multidisciplinary approach. Lippincott, Philadelphia, pp 173–207
49. Paulino AC et al. (2000) Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 48:1489–1495
50. Paulino AC et al. (2000) Posterior fossa boost in medulloblastoma: an analysis of dose to surrounding structures using 3-dimensional (conformal) radiotherapy. Int J Radiat Oncol Biol Phys 46:281–286
51. Peterson D, Sonis S (1983) Oral complications of cancer chemotherapy. Nijhoff, Boston
52. Raney RB et al. (1999) Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: a descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and –III. Med Pediatr Oncol 33:362–371
53. Raney RB et al. (2000) Late effects of therapy in 94 patients with localized rhabdomyosarcoma of the orbit: report from the Intergroup Rhabdomyosarcoma Study (IRS)-III 1984–1991. Med Pediatr Oncol 34:413–420
54. Rosenberg SW (1987) Altered dental root development in long-term survivors of acute lymphoblastic leukemia. Cancer 59:1640–1648
55. Rubin P, Casarett G (1968) Clinical radiation pathology. Saunders, Philadelphia

56. Sonis AL et al. (1990) Dentofacial development in long-term survivors of acute lymphoblastic leukemia: a comparison of three treatment modalities. Cancer 66:2645–2652
57. Stene T et al. (1976) The effect of vincristine on dentinogenesis in the rat incisor. Scand J Dent Res 84:342–344
58. Uderzo C et al. (1997) Long-term effects of bone marrow transplantation on dental status in children with leukemia. Bone Marrow Transplant 20:865–869
59. VanLeeuwen BL et al. (2003) The effect of chemotherapy on the morphology of the growth plate and metaphysis of the growing skeleton. Eur J Surg Oncol 29:49–58
60. Walker DA et al. (1989) Enhanced cis-platinum ototoxicity in children with brain tumors who have received simultaneous or prior cranial radiation. Med Pediatr Oncol 17:48–52

Adverse Effects of Cancer Treatment on Hearing

Wendy Landier · Thomas E. Merchant

Contents

8.1 Introduction

Curative therapy for pediatric malignancies often requires the use of therapeutic modalities that have the potential to adversely impact hearing. Monitoring of audiologic function during and after treatment is therefore an essential component of care for patients who have received potentially ototoxic therapy. Since hearing loss can have a significant impact on social, emotional and cognitive function, timely and appropriate interventions should be employed to mitigate the effects of hearing loss in survivors at risk for this common treatment-related complication.

8.2 Pathophysiology

8.2.1 Normal Anatomy and Physiology

The ears are completely formed in utero, and auditory brainstem responses are present at 28 weeks of gestation. Newborns are capable of processing sound and analyzing loudness and pitch; however, continued maturation of auditory structures, related neuronal pathways and the auditory cortex continue throughout infancy and early childhood. Interhemispheric sensory transfer through the corpus callosum takes several years to fully mature [40]. The processing of sounds occurs in the external, middle and inner ears (Fig. 8.1). The pinna funnels environmental sound into the external auditory canal, where it is amplified and directed toward the middle ear. The tympanic membrane then vibrates in proportion to the frequency and intensity of the acoustic wave and transmits the sound to the ossicles, which serve as impedance matching transformers, converting the

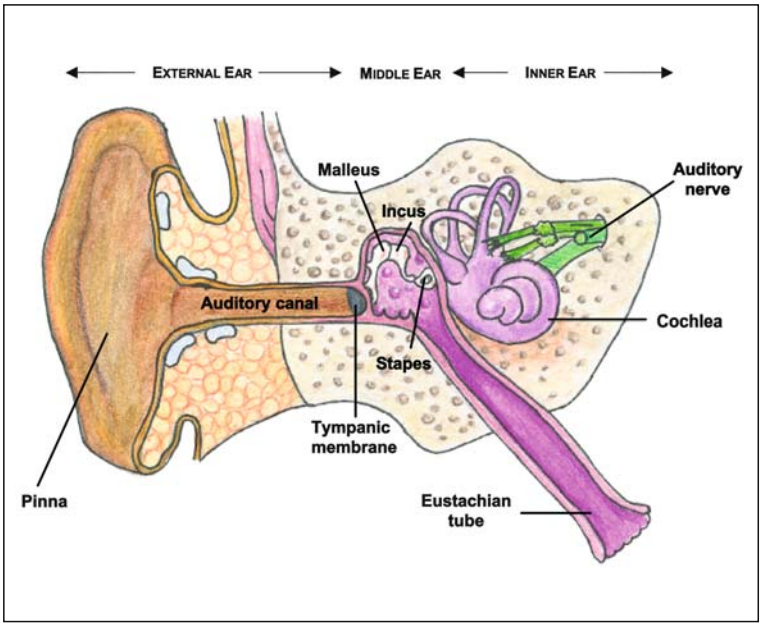


Figure 8.1
Anatomy of the ear

sound into mechanical energy and transmitting it to the inner ear through the oval window. In the inner ear, sound is transmitted through the cochlea by hydraulic waves that stimulate specialized sensory hair cells lining the basilar membrane of the organ of Corti. The hydraulic waves cause displacement of the basilar membrane and bending of the sensory hair cells, resulting in depolarization and release of neurotransmitters, which then stimulate the cochlear branch of the VIIIth cranial nerve. These neural impulses are subsequently transmitted through the medulla, midbrain and thalamus to the auditory cortex of the temporal lobe. In most people, the right ear is dominant; therefore, speech processing usually occurs in the left temporal lobe.

Sound is described in terms of its *intensity* or loudness (measured in decibels) and *frequency* or pitch (measured in Hertz). Normal hearing thresholds are between –10 and 25 dB, and hearing loss is graded on a scale of "mild" to "profound" (Table 8.1). The speech frequencies are between 250 and 2000 Hz, but higher frequencies (>2000–8000 Hz) are critical for speech discrimination, since many of the consonant sounds (e.g. "th," "f," "k," and "s") are in the high-frequency range; therefore, even a "mild" degree of high frequency hearing loss can have a profound effect on a young child who is just acquiring language. *Conductive hearing loss* occurs when transmission of sound from the environment is impaired due to a pathological process in the outer or middle ear. *Sensorineural hearing loss* occurs as a result of pathology involving the cochlea or auditory nerve.

Table 8.1. Degrees of hearing loss

Hearing threshold	Degree of loss
–10 to 25 dB	Normal
26 to 40 dB	Mild
41 to 55 dB	Moderate
56 to 70 dB	Moderately severe
71 to 90 dB	Severe
>90 dB	Profound

Data from: Stach [42 pp. 208–209]

Mixed hearing loss encompasses elements of both conductive and sensorineural hearing loss. In general, hearing loss occurring as a consequence of ototoxic pharmacologic agents is sensorineural in nature; whereas hearing loss resulting from radiation, tumor or surgical procedures is often multifactorial and may include both conductive and sensorineural components.

8.2.2 Ototoxic Effects of Tumor and Therapy: Risk Factors and Incidence

8.2.2.1 Surgery and Tumor

Hearing loss is rarely a presenting symptom in tumors that affect children. Exceptions include nasopharyngeal cancer, parameningeal rhabdomyosarcoma, tumors of the base of skull (chordoma), vestibular schwannoma and metastases that affect the temporal bone, most notably neuroblastoma. Although CNS tumors may come in contact with vital aspects of the auditory system (including the VIIIth nerve and associated vasculature and the brainstem and vestibular nuclei, as well as cortical tracts essential to hearing), hearing loss is not commonly recorded at diagnosis. Surgical management of CNS tumors or musculoskeletal tumors of the head and neck can have a profound and irreversible effect on hearing, especially when essential components of the auditory system are involved with the tumor and surgical resection is required. Transcranial surgery in the region of the middle cranial fossa and suboccipital region can result in bony complications that may lead to mastoiditis and infections. Fortunately, most head and neck tumors are sensitive to radiation and chemotherapy, thus limiting the extent of surgery to biopsy. Tumors of the CNS account for nearly 20% of all neoplasms in children, with the posterior fossa one of the most common locations. Children with medulloblastoma, ependymoma, cerebellar astrocytoma and other tumors that gain access to the lateral recesses and cranial nerves are at risk for transient or permanent hearing loss at the time of resection. Great skill is required to remove tumor from the lateral aspect of the brainstem, through which the VIIIth nerve and vessels may run (Fig. 8.2). Recent efforts in surgery include electromyographic monitoring of cranial nerves at the time of resection to limit neurologic impairment [25].

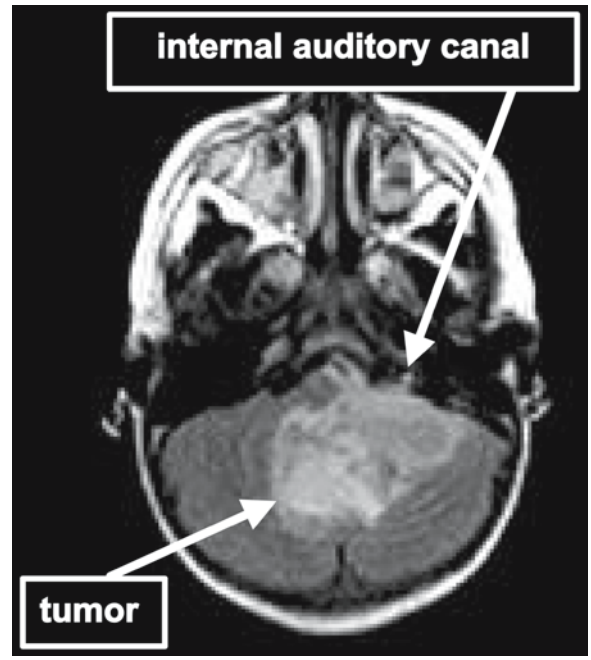


Figure 8.2
Left cerebellopontine angle ependymoma encasing CN VIII with extension into the internal auditory meatus

Children with CNS tumors often present with hydrocephalus that requires emergent evaluation and treatment with temporary ventriculostomy and resection. When the natural flow of CSF cannot be reestablished, permanent ventriculoperitoneal shunting may be required. Rapid loss of intracranial pressure, which may occur after profound blood loss, lumbar puncture, ventriculostomy and tumor resection, has been associated with hearing loss. The mechanism is likely related to the anatomic connection between the CSF spaces and the perilymph of the cochlea (cochlear aqueduct) (Fig. 8.3). Hydrocephalus and its management can influence radiation and chemotherapy-related hearing loss. In one study that included children with localized brain tumors treated with conformal radiation therapy, patients

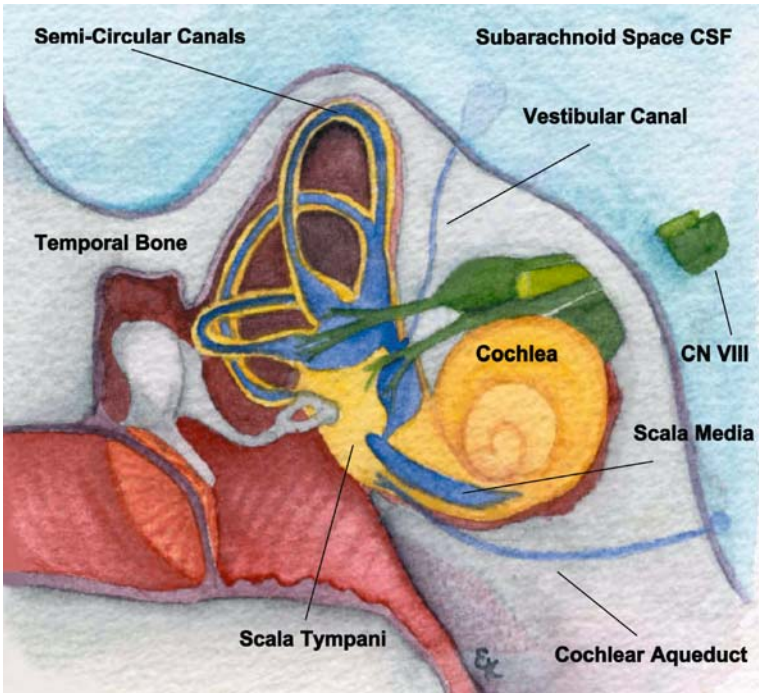


Figure 8.3
Drawing of cochlear duct and anatomic relationships with CSF spaces and auditory system

with CSF shunts and pre-irradiation ototoxic chemotherapy had the greatest change in hearing thresholds. Among patients who did not receive chemotherapy, hearing impairment after radiation alone was apparent at low and intermediate frequencies only in shunted patients with supratentorial tumors who received doses exceeding 32 Gy over a six-week period. Additionally, patients with shunts and tumors involving the suprasellar region, hypothalamus and thalamus developed intermediate-frequency hearing loss after radiation regardless of dose [28].

8.2.2.2 Radiation Therapy

Hearing loss is a potential complication of radiation therapy in children. Radiation may affect the conducting system of the ear, with serous otitis media noted as a complication for patients with nasopharyngeal cancer [46] who receive doses in excess of 45 Gy and for children with medulloblastoma who receive more than 36 Gy. The problem can be long-standing, as in the case of patients with nasopharyngeal cancer, although the risk appears to be increased in those with middle ear effusions prior to irradiation [23] (Fig. 8.4). Mucociliary dysfunction is thought to be the primary cause of middle ear effusions during and after radiation therapy; this can be self-limited in nature or, in severe cases, may require treatment with myringotomy [8]. Direct structural damage to the conductive system, including osteoradionecrosis, is rare with modern radiation therapy, although patients who receive high dose irradiation to the ear and temporal bone may be at high risk for complications from localized bone and soft tissue infections arising in the region of the external auditory canal. For this reason, soft tissue infections of the ear should be treated aggressively and instrumentation of the external auditory canal should be undertaken cautiously.

Sensorineural hearing loss can occur as a result of radiation effects from the auditory cortex to the cochlea. Because the doses administered to neural tissue directly or indirectly are generally accepted as safe and below the threshold for neurologic impair-

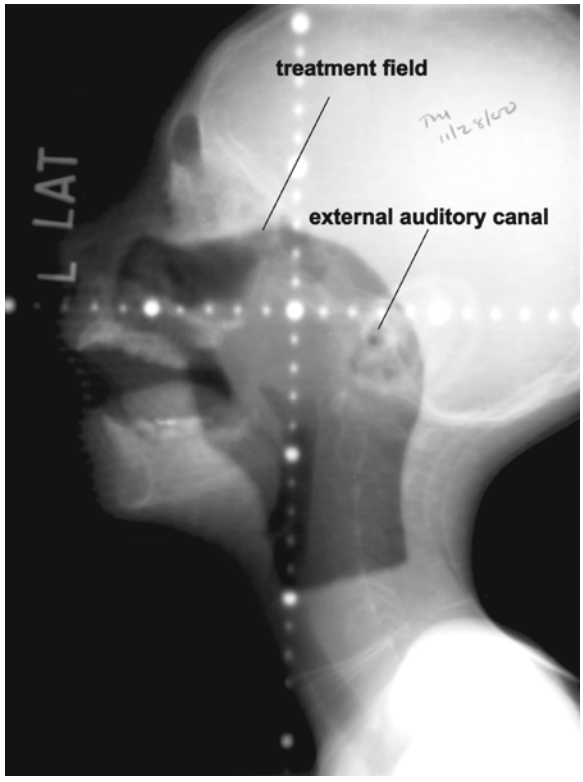


Figure 8.4

Lateral radiation portal film of a child with nasopharyngeal rhabdomyosarcoma

ment, sensorineural effects of radiation are most likely to occur in the cochlea and are usually noted months or years after treatment. Despite recognition of the cochlea as the primary component in sensorineural hearing loss [12], the incidence and time course for injury due to radiation is unknown. Because most children at risk for radiation-related hearing loss also receive ototoxic chemotherapy, the pathophysiology and clinical course of hearing loss is most often described after combined modality therapy. Similar to the effects of ototoxic chemotherapy, the effects of radiation appear to be dose-related, but have been described over a relatively narrow dose range (50–70 Gy) [14], limiting our knowledge of the effects of lower doses when used alone. The combined effects of radiation and chemotherapy – specifically cisplatin and carboplatin [36] – for the treatment of medulloblastoma and other CNS tumors is better understood, with the high incidences of hearing loss reported among children receiving combined modality therapy [19].

8.2.2.3 Pharmacologic Therapy

The primary pharmacologic agents implicated in ototoxicity include platinum chemotherapy, aminoglycoside antibiotics and loop diuretics. These agents are all capable of causing sensorineural hearing loss. The mechanism of aminoglycoside and platinum-related ototoxicity is destruction of cochlear sensory hair cells. These specialized hair cells are arranged tonotopically (in order of pitch) in four rows (one inner and three outer rows) along the organ of Corti, and each hair cell is sensitive to a limited frequency range.

Cisplatin and aminoglycoside antibiotics damage the outer hair cells, whereas carboplatin selectively damages only inner hair cells [44]. The initial hearing loss associated with ototoxic pharmacologic agents usually affects the high frequency ranges. This is because destruction of the sensory hair cells typically begins at the base of the cochlea, where high-frequency sounds are processed, and proceeds towards the apex, where the processing of low frequency sound occurs [34]. Everyone is born with a full complement of auditory sensory hair cells. Once destroyed, these cells cannot regenerate; therefore, hearing loss occurring as a result of sensory hair cell loss is almost always irreversible.

The mechanism of ototoxicity associated with loop diuretics is thought to be related to changes in the fluid and electrolyte balance within the inner ear, resulting in tissue edema within the cochlea and decreased endocochlear potential [35]. Hearing loss resulting from diuretics typically occurs following rapid intravenous administration. Fortunately, this type of hearing loss is usually transient. However, if loop diuretics are administered simultaneously with or shortly after the administration of platinum chemotherapy or aminoglycosides, the likelihood of permanent auditory damage increases as a result of synergism between these agents [2, 43].

Factors placing survivors at highest risk for hearing loss related to pharmacologic therapy include very young age (less than 4 years) at the time of cancer therapy, diagnosis of central nervous system tumor, treatment with multiple ototoxic agents and/or treatment with platinum chemotherapy in combination with radiation to the ear or brain [18, 31, 36]. Many childhood malignancies, including germ cell tumors, central nervous system tumors, osteosarcoma and neuroblastoma, frequently require treatment with platinum-based chemotherapy protocols, and supportive care regimens often employ aminoglycoside antibiotics and loop diuretics [15, 29, 39]. Therefore, the index of suspicion for treatment-related hearing loss should be high for any survivor who received potentially ototoxic therapy. Factors contributing to the risk for ototoxicity include diminished renal function at the time of treatment, rapid intravenous administration of pharmacologic agent(s), prolonged elevated serum trough drug levels [43], co-administration of other ototoxic drugs (e.g. chelating agents, quinine, salicylates [34]) and excessive noise exposure [4]. In addition, genetic susceptibility (e.g. point mutation 1555 A-G in mitochondrial 12S ribosomal RNA, glutathione S-transferase genetic polymorphisms) may play a role in predisposing certain patients to drug-induced ototoxicity [1, 32]. Further, the potential impact of new agents with ototoxic properties (e.g. tirapazamine [38]) should be kept in mind when assessing patient risk.

The incidence of ototoxicity is well documented in children receiving platinum chemotherapy [37], and is dose-related, with an inverse relationship to age at therapy [45]. Brock et al. [3] studied 29 children off therapy for at least two years who had received "standard dose" (60–100 mg/m^2/course) cisplatin-containing chemotherapy regimens without brain or ear irradiation. Median age at diagnosis was 2 years, 2 months (range: 1 month–13.5 years) and median cumulative dose was 540mg/m^2 (range: 400–1860 mg/m^2). Moderate to severe sensorineural hearing loss was detected in 48% of these children, with 33% requiring hearing aids; no child demonstrated any recovery of hearing at median 4-year follow-up. Schell et al. [36] studied 177 children and young adults receiving cisplatin (median cumulative dose 360 mg/m^2, range 90–1260 mg/m^2) with and without prior cranial radiation (median dose: 5050 cGy; range 2880–8260 cGy). In irradiated patients, doses as low as 270 mg/m^2 were associated with a high probability of substantial hearing loss, whereas non-irradiated patients demonstrated negligible loss at doses up to 360 mg/m^2; however, as cumulative doses increased to 720 mg/m^2, the risk of substantial shifts in hearing threshold increased to 25%. In a study of 49 patients with osteosarcoma receiving 400 mg/m^2 cisplatin with or without ifosfamide, Meyer et al. [29] reported a significant increase in the incidence of hearing loss (≥30 dB at 2000 or 3000 Hz) in the cisplatin/ifosfamide group, indicative of a synergistic effect between the two agents. MacDonald et al. [24] reported that 50% of children who received Carboplatin at a median dose of 2409 mg/m^2 demonstrated a significant hearing loss at 2000 Hz; in addition, McDonald et al. found that losses in the higher frequencies were predictive of future losses in the speech ranges.

Ototoxicity is also a potential complication of therapy with aminoglycoside antibiotics [27] and loop diuretics [35]. Prospective studies by Fee [10] and Smith et al. [41] reported ototoxic rates of 10–16% for gentamicin and tobramycin. Lerner et al. [22] reported an 11% incidence of ototoxicity associated with gentamicin and a 13% incidence in amikacin-treated patients. An augmented ototoxic effect has been reported with the concurrent administration of cisplatin and gentamicin [33]. Brookhouser [4] described a 6.4% incidence of furosemide-associated ototoxicity and a 0.7% incidence for ethacrynic acid; however, the risk increased significantly when loop diuretics were administered concurrently with aminoglycoside antibiotics [2].

8.2.3 Preventive Measures

The administration of platinum chemotherapy prior to, rather than following, cranial irradiation in children with CNS tumors has been shown to reduce ototoxicity [36]. Newer radiation delivery techniques hold the promise of reducing radiation-related ototoxicity by conforming the prescribed dose to the

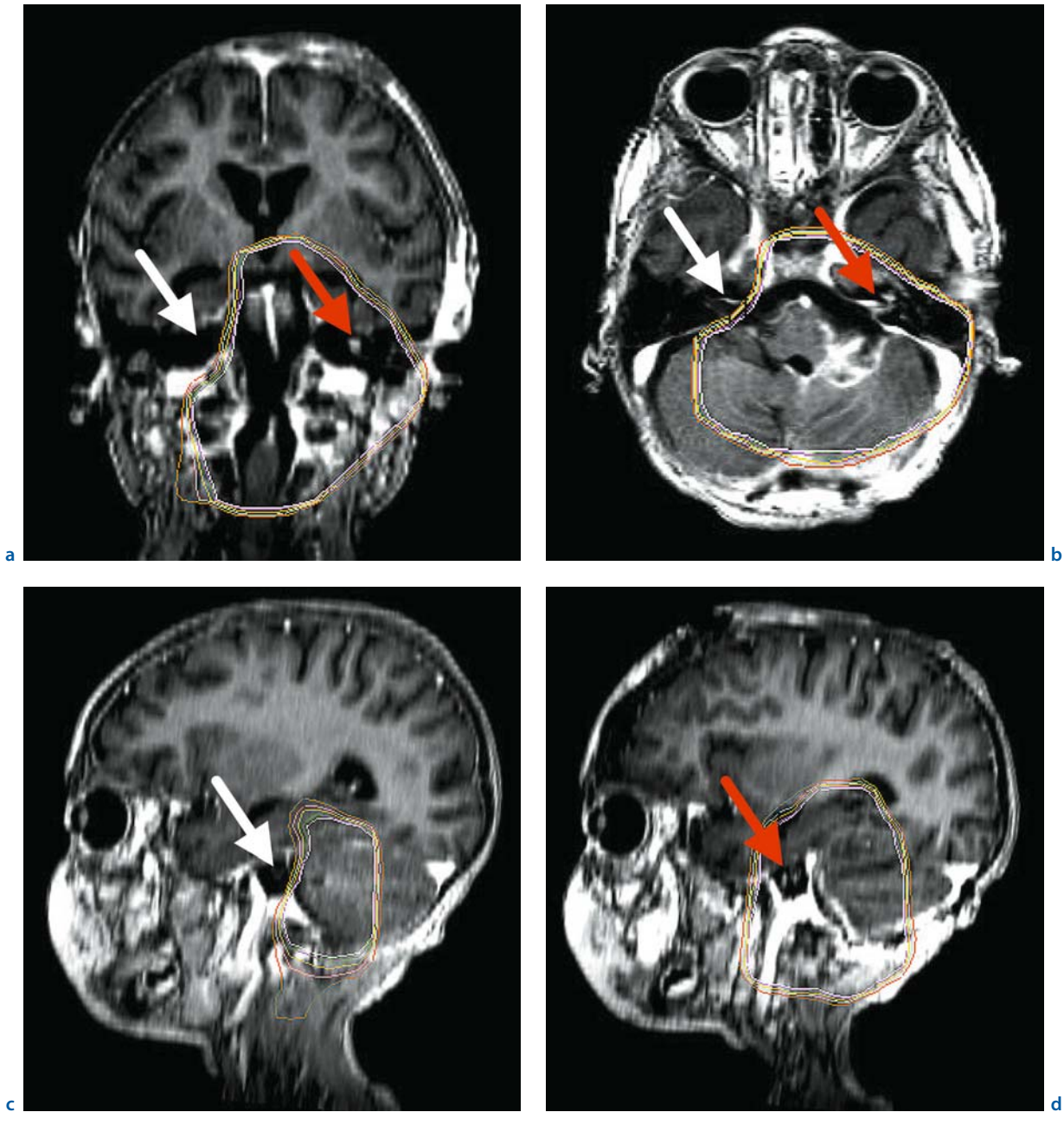


Figure 8.5 a–d

Coronal, transverse and sagittal MR images with 3-dimensional radiation dosimetry, showing the ability of conformal treatment techniques to spare auditory structures not adjacent to tumor bed in a child with cerebellopontine angle ependymoma. (White arrows represent spared cochlea; red arrows represent irradiated cochlea)

Table 8.2. Ototoxicity grading scale

Measure	Grade				
	0 (Normal)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Unacceptable)
Objective	Normal (≤25 dB at all frequencies)	≥30 dB at 8000 Hz	≥30 dB at 4000 Hz	30–35 dB at 2000 Hz	≥40 dB at 2000 Hz
Subjective	Asymptomatic	Asymptomatic	Tinnitus, vertigo, or difficulty hearing in presence of background noise	25–50% of speech signal missed **Hearing aids required**	Requires services in addition to hearing aids
Dose adjustment recommendation for ototoxic agents	No change	↓ dose by 25%	↓ dose by 50%, consider alternative therapy	Delete if alternative therapy available, otherwise continue at 50% dose	Delete

Audiologic testing should include air conduction, with bone conduction added when air conduction exceeds 25dB at any frequency. In most situations, dose modification should be done for sensorineural hearing loss only. For conductive hearing loss, the underlying cause should be investigated and intervention provided. Dose adjustments should not be made for correctable conductive hearing loss.
From: Landier & Larson-Tuttle [21]

region at risk and sparing the cochlea. Using these techniques, the dose to the cochlea can be estimated more accurately to optimize treatment and to collect dose information, which can be correlated with other factors that influence hearing after treatment [17, 28] (Fig. 8.5).

Careful monitoring and appropriate dose modification earlier in the course of therapy, before severe hearing loss has been sustained, is effective in decreasing morbidity (Table 8.2). Additional otoprotective strategies include counseling patients regarding the importance of avoiding other potentially ototoxic agents, including medications (e.g. chelating agents, salicylates) and loud noises (especially ≥85 dB); patients should also be advised to use protective measures (e.g. ear plugs) when in noisy environments in order to prevent co-morbid noise-induced hearing loss [13].

Amifostine (a cytoprotective agent) provided significant otoprotection in a study of adults with advanced ovarian cancer [20]. A pilot study was designed to use amifostine as an otoprotectant in the treatment of high-risk pediatric extragonadal germ cell tumors with high-dose PEB chemotherapy (bleomycin 15 IU/m^2 intravenously on day 1, etoposide 100 mg/m^2/d IV × 5 d, followed by amifostine 825 mg/m^2/d IV × 5 d, and cisplatin 40mg/m^2/d IV × 5 d repeated every 3–4 weeks for 4–6 cycles). Among the 25 patients in the study, four were removed due to ototoxicity, and 18 had 10–60 dB losses at ≥ 500 Hz, requiring amplification in the majority of cases. The investigators concluded that amifostine, as used in the setting of their study, did not provide protection against unacceptable ototoxicity [26]. Although sodium thiosulfate (a rescue agent) has not yet been introduced in cooperative group pediatric trials, it has been reported to provide otoprotection in some limited institutional studies [9, 30].

8.3 Clinical Manifestations

8.3.1 Clinical Manifestations of Ototoxicity Related to Surgery or Tumor

Tumor-related hearing loss is not a common presenting symptom. Notable exceptions include patients with nasopharyngeal tumors or rhabdomyosarcoma involving the middle and inner ear, in addition to patients with eustachian tube dysfunction secondary to mass effect or lymphadenopathy. In the scope of possible side effects and complications first noted after surgery for brain tumors, hearing loss is usually not a priority. Children at risk for hearing loss from surgery often have acquired other deficits that are more apparent or life threatening, which can delay the diagnosis of surgery-related hearing loss. These patients often have deficits involving the abducens (CN-VI) or facial nerve (CN-VII) and, in extreme cases, lower cranial nerves affecting speech and swallowing. Children who require temporary or permanent CSF shunting may experience hearing loss that is also temporary or permanent, as well the opposite, which is hyperacusis (extreme sensitivity to normal levels of sound). Recovery from surgery-related hearing deficits can occur in some cases despite adjuvant irradiation, provided that the nerve has not been transected or the vascular supply permanently disrupted.

8.3.2 Clinical Manifestations of Radiation-Related Ototoxicity

Radiation-related effects on the auditory system may occur during or after treatment. Acute effects are more likely to involve the external auditory canal (radiation dermatitis of the epithelium lining the canal leading to otitis externa) and middle ear (otorrhea with otalgia or mucociliary dysfunction of the middle ear with resultant eustachian tube dysfunction). Cerumen production appears to be increased in some patients during and after radiation, although the contribution from other causes cannot be excluded. Atrophy of the sebaceous glands may occur and is dose-dependent. Soft tissue fibrosis, otosclerosis and even cholesteatoma have been reported. Because radiation therapy is often given in conjunction with ototoxic chemotherapy, separating the effects of the two treatments can be difficult. Since most instances of treatment-related hearing loss occur in close temporal proximity to chemotherapy or combined modality therapy, more ototoxicity is known or observed in this setting. However, radiation therapy alone may result in hearing loss with an onset many years following treatment; therefore, long-term survivors remain at risk for hearing loss. Radiation-related hearing loss may occur during the first year after treatment in patients who also received chemotherapy, and is usually seen two or more years after treatment in patients treated with radiation alone. With newer means of delivering radiation therapy, namely, non-coplanar, individually-shaped beams to avoid the middle ear and cochlea, some of the acute and late effects of treatment appear to be reduced. With additional considerations regarding the timing of radiation and chemotherapy, further reductions in ototoxicity seem to be feasible.

8.3.3 Clinical Manifestations of Ototoxicity Related to Pharmacologic Agents

Hearing loss resulting from ototoxic medications is generally bilateral and symmetrical. Early symptoms may include tinnitus, vertigo and difficulty hearing in the presence of background noise, which is indicative of vestibular injury and high frequency (>2000 Hz) hearing loss. Since consonant sounds are primarily high frequency and vowel sounds are primarily low frequency; a person with high-frequency hearing loss will be able to hear vowel sounds better than consonants. The English language relies heavily on consonant sounds to convey the meaning of words; therefore, the inability to hear high-frequency sounds often results in poor speech discrimination, or a perception of "hearing but not understanding." For people with high-frequency hearing loss, understanding high-pitched voices (e.g. females and children) may be particularly problematic. Increasing the volume of the speaker's voice (e.g. by shouting) is generally not helpful, since this raises the intensity level of vowels and not consonants. As hearing loss progresses, patients may experience difficulty in

hearing sounds within the speech ranges (250–2000 Hz). The impact of even mild high-frequency hearing loss is significant, particularly in young children. It may result in difficulties with speech discrimination and language acquisition and can adversely affect cognitive and social development.

8.4 Detection and Screening

8.4.1 Auditory Screening

It is important to distinguish between auditory "screening" and "testing." Conventional auditory screening typically evaluates the patient's ability to hear pure tones at 1000, 2000 and 4000 Hz in each ear; a score of "pass" (≤ 20 dB) or "fail" (>20 dB) is given. Measurement of otoacoustic emissions is another auditory screening technique often utilized for very young children. A score of "pass" on an otoacoustic emission test verifies that a patient has near-normal (≤30 dB) hearing. However, otoacoustic emissions measure the function of outer ear hair cells only. Since carboplatin affects only inner hair cells, this method of screening should never be used for patients with a history of carboplatin therapy [16]. In general, auditory screening is used to select individuals who need referral for formalized testing and is not appropriate for patients who are known to have significant risk factors for hearing loss; all high-risk patients should be referred for a formal audiometric assessment.

8.4.2 Diagnostic Audiometry

8.4.2.1 Pure Tone Audiometry

The most common method used for diagnostic evaluation of hearing in cooperative patients is pure tone audiometry. The aim is to establish hearing thresholds across a wide range of sound frequencies (usually 250–8000 Hz). This testing is generally done in a soundproof booth; air and bone conduction thresholds are measured and results graphed on an audiogram (Fig. 8.6a), with frequency (in hertz) plotted as a function of intensity (in decibels). Often, a "stair-step" pattern of hearing loss, progressing from the high frequencies down to the speech ranges, is evident on the audiogram of patients with sensorineural hearing loss resulting from ototoxic therapy (Fig. 8.6 b). For patients with a developmental age less than 4–5 years, pure-tone audiometric testing can be performed using behavioral modification techniques, such as conditioned play audiometry or visual-reinforcement audiometry [6].

8.4.2.2 Brainstem Auditory-Evoked Response

For patients unable to cooperate with behavioral testing, hearing can be assessed via brainstem auditory evoked response (BAER, ABR). Electrodes are placed on the skull, and clicks (high frequency) and tone bursts (low frequency) are then presented at intensity levels that elicit an electrophysiological response, recorded as a waveform. The intensity of the stimulus is then lowered until the response is no longer measurable; this level corresponds roughly to the threshold measurements used in pure tone audiometry. Thresholds of 30 dB or lower are generally considered within the normal range. The patient must remain motionless throughout this test; therefore, sedation is almost always required for infants and young children (as reviewed in [42]).

8.4.3 Guidelines for Audiologic Monitoring

The importance of ongoing audiologic monitoring and early dose modification for patients receiving ototoxic therapy cannot be overemphasized. A preventive approach, when possible, is certainly preferable to a remedial one. Audiologic evaluation is recommended as a baseline measure for all patients scheduled to receive ototoxic therapy, then prior to each platinum-based course for patients at high risk for ototoxicity (see section 8.2.2). For lower risk patients, an audiologic evaluation is recommended prior to every other platinum-based course. Therapy should be adjusted, if necessary, based on the grade of hearing loss (Table 8.2), as reviewed in [21].

Survivors who received ototoxic therapy also require ongoing monitoring. Patients who received radiation at a dose of 30 Gy or higher to the ear, infratemporal or nasopharyngeal areas, or to the

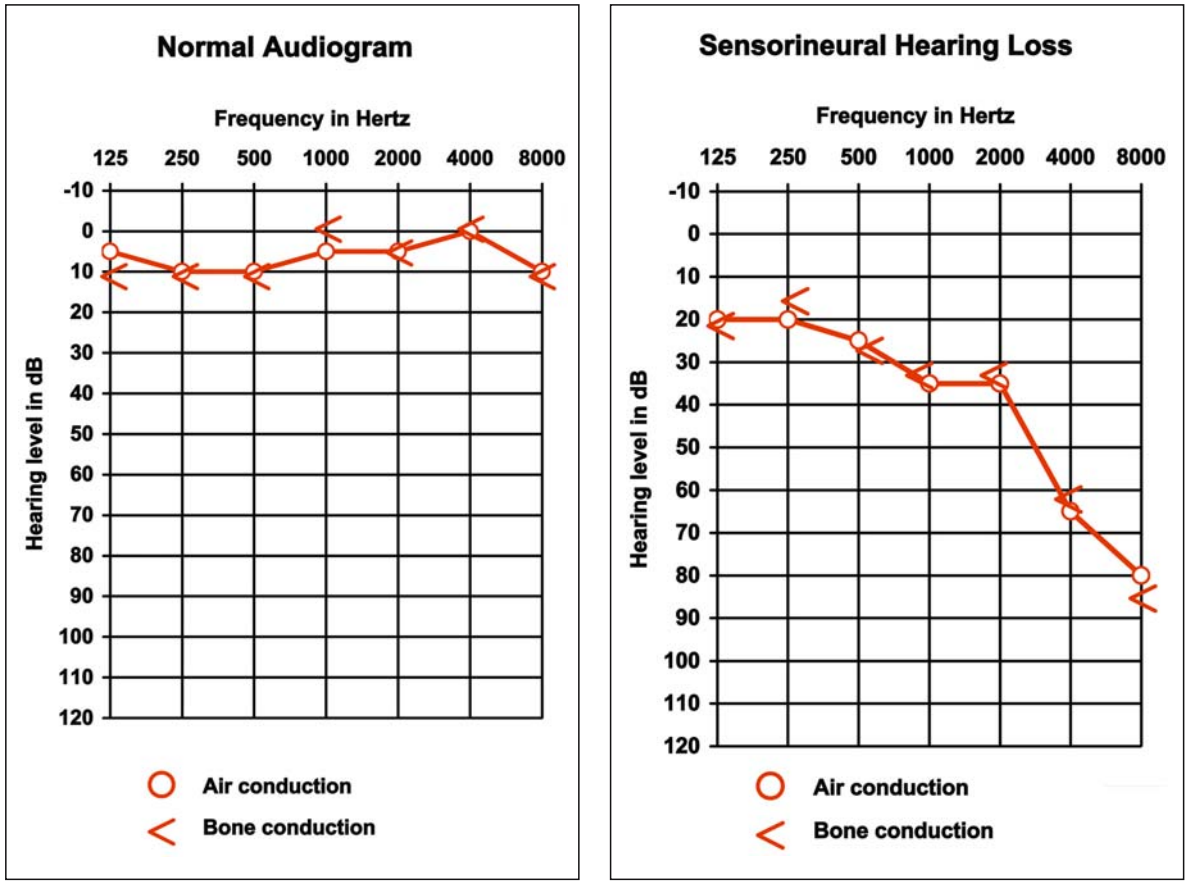


Figure 8.6 a, b

a Normal audiogram. **b** Audiogram demonstrating severe high-frequency sensorineural hearing loss (85 dB at 8,000 Hz and 60 dB at 4,000 Hz). Hz = Hertz; dB = decibels

brain or craniospinal axis, should receive audiologic monitoring on an annual basis for five years following completion of therapy, and, if stable, every five years after that. Patients younger than 10 years of age should continue annual monitoring until they are at least five years off therapy *and* at least 10 years old. Patients who received treatment with platinum chemotherapy (particularly at cumulative cisplatin doses of ≥360 mg/m^2 or carboplatin doses of ≥1000 mg/m^2), those treated with radiation involving the ear at doses less than 30 Gy (including the infratemporal or nasopharyngeal areas, whole brain, craniospinal axis and/or total body irradiation), and patients who received significant exposure to non-platinum ototoxic agents (e.g. aminoglycosides or loop diuretics) should have a baseline audiogram at entry into long-term follow-up. For patients with abnormal audiograms, annual monitoring should continue until hearing loss stabilizes. Testing should be done more frequently if there is evidence of progressive hearing loss, in order to allow for continued adjustment of hearing aids and referral for other interventions. Otherwise, the audiogram should be repeated as clinically indicated.

8.5 Management of Established Problems

The impact of deafness goes beyond the loss of hearing; at its core is the problem of impaired communication that can result in loss of social interaction, with devastating cognitive and emotional consequences for the survivor.

The impact of hearing loss can be especially profound in prelingual children (infants and toddlers); however, hearing loss substantially impacts all patients.

Children with hearing loss are more likely to develop behavioral difficulties than normal-hearing children, due to ineffectual communication and resultant barriers to the establishment of normal discipline and relationships at home and in the classroom. Isolation and social adjustment problems can be significant.

8.5.1 Hearing Aids

Hearing aids are an integral component of the management of hearing loss; however, it is important for the clinician to understand that hearing aids *do not* restore normal hearing. Hearing aids amplify *all* environmental sounds, including background noise, and the quality of aided sound for a patient with sensorineural hearing loss will always be distorted due to sensory hair cell destruction and subsequent loss of the normal ability to process sounds.

All hearing aids have three basic parts. The *microphone* picks up sound waves from the environment and converts them into electrical current. The *amplifier* increases the intensity (volume) of the sound and then sends it to the *receiver*, which converts the amplified electrical impulse back into sound waves and delivers them to the ear.

There are several types of hearing aids available. To accommodate rapid growth, most pre-adolescent children are fitted with a behind-the-ear model. In addition to the hearing aid components, which are contained in a case located behind the ear, the model also has an ear mold, which is fitted into the ear canal. As the child grows, the only component that requires refitting is the ear mold; this is done approximately every 6 months through the age of about 9 years.

Other types of hearing aids include in-the-ear, in-the-canal, and completely-in-the-canal models; amplification provided by these types of aids is limited and may not be adequate for patients with severe hearing loss (as reviewed in [5]).

Patients and parents should be counseled regarding the importance of hearing aid maintenance. Frequent cleaning of the aid is important, and batteries must be changed regularly (usually every 7–14 days). Since young children typically will not report a nonfunctional hearing aid, use of a calendar or other reminder system for battery changes is imperative; parents should also check to be certain that the hearing aid is switched to the "on" position on a daily basis. Close follow-up by an experienced audiologist is essential to provide for ongoing adjustment and fine-tuning of the hearing aid best suited for the patient's needs.

8.5.2 Other Assistive Devices

Besides hearing aids, there are a number of other assistive devices available for patients with hearing impairment. Auditory trainers are particularly helpful in the classroom or daycare setting; these devices employ a transmitter (worn by the teacher or caregiver) and a receiver (worn by the patient). The speaker's voice is transmitted over FM radio waves to a receiver that can either be plugged into the hearing aid or worn as a stand-alone device. The system significantly reduces background noise and is ideal for classroom use.

Additional assistive devices include telephone amplifiers and telephone devices for the deaf (TDD), text pagers, and modified appliances, such as vibratory alarm clocks and smoke detectors. Closed captioning for television is widely available, and the Internet also provides significant communication options for the hearing-impaired (as reviewed in [5]).

8.5.3 Cochlear Implants

Unlike hearing aids that amplify sound, cochlear implants use electronic impulses to stimulate auditory neural pathways in the cochlea, circumventing damaged sensory hair cells and allowing transmission of sound impulses to the brain. Cochlear implants are indicated only for patients with profound (>90 dB) hearing loss who are unable to benefit from powerful, well-fitted hearing aids. The implant's receiver is surgically placed in the mastoid bone and an electrode array is threaded into the cochlea. A microphone worn behind the ear is used to collect environmental sounds that are filtered and digitalized by an external speech processor. The digital impulses then travel across the skull and into the receiver by way of a magnetized transmitter. The signal is relayed to the electrodes that in turn stimulate the auditory nerve, allowing for sound perception by the brain. Sounds processed through a cochlear implant tend to be distorted and mechanical; however, patients with profound hearing loss may derive significant benefit from the procedure. Intensive postoperative speech therapy is always required (as reviewed in [11]).

8.5.4 Communication Methods

Several communication options are available for patients with significant hearing loss. The *auditory-verbal method* is an in-depth educational approach that teaches children to use residual hearing in order to learn to listen and speak. Intensive involvement on the part of the family and the school are required.

Cued speech is a communication method that combines speech-reading (lipreading) with hand signs, clarifying certain words.

Sign language is a unique form of communication with its own grammar and syntax, and is communicated entirely via signs, gestures and facial expressions.

Total communication is a method that combines auditory training with hand signs correlating exactly with the child's primary language (e.g. English). The decision regarding which communication method is best suited for an individual patient is an intensely personal one that should be made by the family. However, for patients whose hearing loss occurs after they have attained substantial language development, the use of methods based on pre-existing language (e.g. the auditory/verbal or total communication methods) are often most practical, as reviewed in [7].

8.5.5 Community and Educational Resources

The Individuals with Disabilities Education Act (IDEA), a public law (PL 105–17) in the United States, recognizes hearing loss as a disability. As a result of the IDEA law, children in the U.S. diagnosed with hearing loss are legally entitled to receive a free and appropriate public education that meets their special needs in the "least restrictive" (e.g. regular or modified classroom) environment. "Part B" of this law provides for other related services, such as speech therapy and assistive devices. All services covered by the IDEA legislation must be provided at public expense under the supervision of the state's educational agency. If the local public school is unable to accommodate the child's needs, services may be provided through a referral agency. A second U.S. law, the Americans with Disabilities Act (ADA; PL 101–336), guarantees people with hearing loss equal access to public events, spaces and opportunities. It is this law that provides the basis for text telephones and telephone amplifiers in public venues, closed captioning for television programs and assistive listening devices in theaters.

8.6 Conclusion

Hearing loss resulting from cancer therapy during childhood can have a profound impact on the survivor's cognitive, social and emotional functioning. Appropriate surveillance and intervention for deficits in audiologic function are an integral part of care for survivors at risk for this potentially debilitating complication.

References

1. Bates DE (2003) Aminoglycoside ototoxicity. Drugs Today (Barc) 39:277–285
2. Bates DE, Beaumont SJ, Baylis BW (2002) Ototoxicity induced by gentamicin and furosemide. Ann Pharmacother 36:446–451
3. Brock PR, Bellman SC, Yeomans EC et al. (1991) Cisplatin ototoxicity in children: a practical grading system. Med Pediatr Oncol 19:295–300
4. Brookhouser PE (2000) Diseases of the cochlea and labrynth. In: Wetmore RF, Muntz HR, McGill TJ (eds) Pediatric otolaryngology: principles and practice pathways. Thieme, New York, pp 327–354
5. Brookhouser PE, Beauchaine KL, Osberger MJ (1999) Management of the child with sensorineural hearing loss. Medical, surgical, hearing aids, cochlear implants. Pediatr Clin North Am 46:121–141
6. Campbell KC, Durrant J (1993) Audiologic monitoring for ototoxicity. Otolaryngol Clin North Am 26:903–914
7. Cherow E, Dickman DM, Epstein S (1999) Organization resources for families of children with deafness or hearing loss. Pediatr Clin North Am 46:153–162
8. Chao WY, Leung HW (1995) Effects of irradiation on the rat middle ear mucosa. A scanning electron microscopic study. Eur Arch Otorhinolaryngol 252:244–248
9. Doolittle ND, Muldoon LL, Brummett RE et al. (2001) Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. Clin Cancer Res 7:493–500
10. Fee WE Jr (1980) Aminoglycoside ototoxicity in the human. Laryngoscope 90 [Suppl 24]:1–19
11. Francis HW, Niparko JK (2003) Cochlear implantation update. Pediatr Clin North Am 50:341–346
12. Gamble JE, Peterson EA, Chandler JR (1968) Radiation effects on the inner ear. Arch Otolaryng 88:156–161
13. Gratton MA, Salvi RJ, Kamen BA et al. (1990) Interaction of cisplatin and noise on the peripheral auditory system. Hear Res 50:211–223
14. Grau C, Moller K, Overgaard M et al. (1991) Sensori-neural hearing loss in patients treated with irradiation for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 21:723–728
15. Hale GA, Marina NM, Jones-Wallace D et al. (1999) Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol 21:115–122
16. Hall JW (2000) Handbook of otoacoustic emissions. Singular, San Diego
17. Huang E, Teh BS, Strother DR et al. (2002) Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys 52:599–605
18. Ilveskoski I, Saarinen UM, Wiklund T et al. (1996) Ototoxicity in children with malignant brain tumors treated with the "8 in 1" chemotherapy protocol. Med Pediatr Oncol 27:26–31
19. Kapoor G, Warrier RP, Shah SJ et al. (1996) Cisplatin and cranial irradiation related hearing loss in children. Proc ASCO 15:1436
20. Kemp G, Rose P, Lurain J et al. (1996) Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. J Clin Oncol 14:2101–2112
21. Landier W, Larson-Tuttle C (2004) Monitoring and management of ototoxicity. In: Altman AJ (ed) Supportive care of children with cancer: current therapy and guidelines from the children's oncology group, 3rd edn. Johns Hopkins University Press, Baltimore, pp 130–138
22. Lerner SA, Schmitt BA, Seligsohn R et al. (1986) Comparative study of ototoxicity and nephrotoxicity in patients randomly assigned to treatment with amikacin or gentamicin. Am J Med 80:98–104
23. Low WK, Fong KW (1998) Long-term post-irradiation middle ear effusion in nasopharyngeal carcinoma. Auris Nasus Larynx 25:319–321
24. Macdonald MR, Harrison RV, Wake M et al. (1994) Ototoxicity of carboplatin: comparing animal and clinical models at the Hospital for Sick Children. J Otolaryngol 23:151–159
25. Mann WJ, Maurer J, Marangos N (2002) Neural conservation in skull base surgery. Otolaryngol Clin North Am 35: 411–424, ix
26. Marina N, Malogolowkin M, London WB et al. (2003) Amifostine does not protect against the Ototoxicity associated with high-dose cisplatin, etoposide and bleomycin (HD-PEB) in pediatric germ cell tumors (PGCT): a PGCT Intergroup Study. Proceedings of the American Society of Clinical Oncology, 31 May - 3 June 2003, Chicago IL, p 798
27. Matz GJ (1993) Aminoglycoside cochlear ototoxicity. Otolaryngol Clin North Am 26:705–712
28. Merchant TE, Gould CJ, Xiong X et al. (2002) Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. 44th annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), New Orleans, LA, 6–10 Oct 2002. Int J Radiat Oncology Biol Phys 54:201
29. Meyer WH, Ayers D, McHaney VA et al. (1993) Ifosfamide and exacerbation of cisplatin-induced hearing loss. Lancet 341:754–755
30. Neuwelt EA, Brummett RE, Doolittle ND (1998) First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. J Pharmacol Exp Ther 286:77–84

31. Parsons SK, Neault MW, Lehmann LE et al. (1998) Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. Bone Marrow Transplant 22:669–674
32. Peters U, Preisler-Adams S, Hebeisen A et al. (2000) Glutathione S-transferase genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. Anticancer Drugs 11:639–643
33. Riggs LC, Brummett RE, Guitjens SK et al. (1996) Ototoxicity resulting from combined administration of cisplatin and gentamicin. Laryngoscope 106:401–406
34. Roland JT, Cohen NL (1998) Vestibular and auditory ototoxicity. In: Cummings CW, Fredrickson JM, Harker LA, Krause CJ, Schuller DE, Richardson MA (eds) Otolaryngology head and neck surgery, 3rd edn. Mosby, St Louis, pp 3186–3197
35. Rybak LP (1993) Ototoxicity of loop diuretics. Otolaryngol Clin North Am 26:829–844
36. Schell MJ, McHaney VA, Green AA et al. (1989) Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 7:754–760
37. Schweitzer VG (1993) Ototoxicity of chemotherapeutic agents. Otolaryngol Clin North Am 26:759–789
38. Senan S, Rampling R, Graham MA et al. (1997) Phase I and pharmacokinetic study of tirapazamine (SR 4233) administered every three weeks. Clin Cancer Res 3:31–38
39. Simon T, Hero B, Dupuis W et al. (2002) The incidence of hearing impairment after successful treatment of neuroblastoma. Klin Padiatr 214:149–152
40. Sininger YS, Doyle KJ, Moore JK (1999) The case for early identification of hearing loss in children: auditory system development, experimental auditory deprivation, and development of speech perception and hearing. Pediatr Clin North Am 46:1–14
41. Smith CR, Lipsky JJ, Laskin OL et al. (1980) Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. N Engl J Med 302:1106–1109
42. Stach BA (1998) Clinical audiology: an introduction. San Diego, pp 208–209; 292–312
43. Stringer SP, Meyerhoff WL, Wright CG (1991) Ototoxicity. In: Paparella MM, Shumrick DA (eds) Otolaryngology, 3rd edn. Saunders, Philadelphia, pp.1653–1669
44. Takeno S, Harrison RV, Ibrahim D et al. (1994) Cochlear function after selective inner hair cell degeneration induced by carboplatin. Hear Res 75:93–102
45. Weatherly RA, Owens JJ, Catlin FI et al. (1991) Cis-platinum ototoxicity in children. Laryngoscope 101:917–924
46. Young YH, Lu YC (2001) Mechanism of hearing loss in irradiated ears: a long-term longitudinal study. Ann Otol Rhinol Laryngol 110:904–906

The Thyroid Gland

Tithi Biswas · Louis S. Constine · Cindy L. Schwartz

Contents

Thyroid dysfunction or deregulation is a clinically significant sequelae of cancer therapy due to the spectrum of physiologic consequences. Primary hypo- or hyperthyroidism may result from direct irradiation of the thyroid gland incidental to the treatment of malignancies such as Hodgkin's disease and head and neck rhabdomyosarcoma. Primary hypo- or hyperthyroidism may also result from central nervous system (CNS) tumors that require spinal axis irradiation [7, 11, 32]. Central hypothyroidism may develop in children with brain tumors treated with cranial irradiation or chemotherapy that includes the hypothalamic-pituitary axis [25]. The development of benign thyroid nodules and malignancy after thyroid radiation therapy (RT) is also a sequela with potential adverse consequences [12, 13, 16, 18, 23, 44].

9.1 Pathophysiology

The hypothyroidism that follows direct thyroid irradiation manifests as an elevated serum thyroid stimulating hormone concentration, with or without a concomitant decreased serum thyroxine concentration. The pathophysiology is not clearly understood, but it is possible that it results from direct radiation damage to the thyroid follicular cells, the thyroid vasculature or the supporting stroma. The endocrine parenchymal cells of the thyroid are fully differentiated cells with a low turnover rate (reverting postmitotic cells) that may have relatively low radiation sensitivity. Conversely, the endothelial cells (EC) of the thyroid may have proliferation cycles shorter than those of endocrine cells. As a result, damage to the EC of the extensive thyroid capillary network may

be an important mechanism for both early and late radiation injury [15]. Less likely mechanisms that could contribute include radiation-induced immunologic cascades or damage from the iodine load administered during lymphangiography (LAG). Support for the latter theory is based on the observation that radioiodine treatment will induce hypothyroidism in patients with autoimmune thyroiditis [3]. Histopathologic changes in an irradiated thyroid gland include progressive obliteration of the fine vasculature, degeneration of follicular cells and follicles and atrophy of the stroma [29]. Because radiation damage is dependant on the degree of the mitotic activity and because the thyroid of a developing child grows in parallel with the body [14], this gland might be expected to show an age-related degree of injury and repair.

9.2 Clinical Manifestations

The common clinical manifestations of hypothyroidism include cold intolerance, constipation, inordinate weight gain, dry skin and slowed mentation. Specific signs include a round puffy face, slow speech, hoarseness, hypokinesia, generalized muscle weakness, delayed relaxation of deep tendon reflexes, cold and dry skin, brittle hair and periorbital edema. The most common clinical picture of hyperthyroidism is similar to that of Graves' disease and usually characterized by a diffusely enlarged thyroid gland, ophthalmopathy and dermopathy.

9.2.1 Hypothyroidism

The incidence of hypothyroidism noted following therapeutic irradiation for Hodgkin's disease (HD) varies, depending on the report. If an elevated serum TSH concentration is the determinant, then 4–79 % of patients become affected. This large range exists because parameters relevant to the induction of hypothyroidism – such as radiation dose, technique and the frequency and types of follow-up testing – differ in the various reports. A recent study by Hancock and colleagues [16] of 1677 children and adults with Hodgkin's disease in whom the thyroid had been irradiated showed that the actuarial risk at 26 years for overt or subclinical hypothyroidism was 47 % (Table 9.1), with the peak incidence occurring 2–3 years after treatment. There are few reports specifically addressing the incidence of hypothyroidism in children as a function of radiation dose. Constine and colleagues [7] noted thyroid abnormalities in four of 24 children (17 %) who received mantle irradiation of 26 Gy or less, and in 74 of 95 children (78 %) who received greater than 26 Gy. The abnormality in all but three children (one with hyperthyroidism and two with thyroid nodules) included an elevated serum TSH concentration with or without low serum T4 concentration. The spontaneous return of TSH to normal limits was observed in 20 of the 75 patients (27 %).

A recent report by Sklar [37] from the Childhood Cancer Study Group showed that the relative risk of hypothyroidism in HD survivors was 17.1, with 28 %

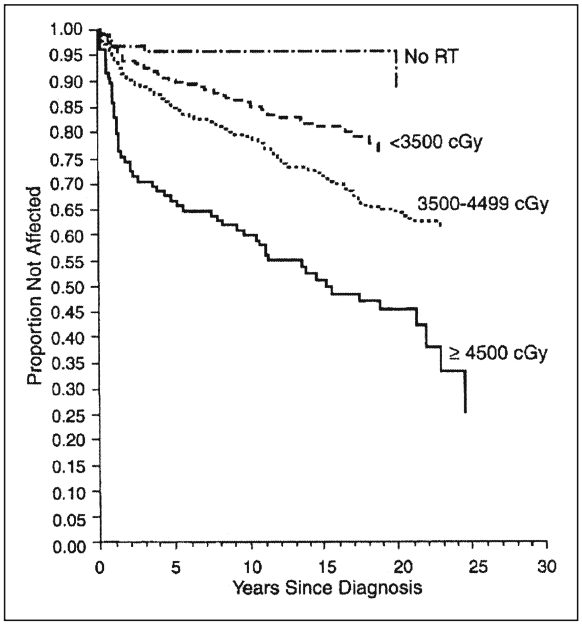


Figure 9.1

Probability of developing an underactive thyroid after diagnosis of HD. Patients are grouped according to dose of thyroid irradiation. RT, Radiation. (From [37], with permission.)

Table 9.1. Thyroid disease after treatment of Hodgkin's disease

Disease	No. of patients/total no.[a]	Actuarial risk (%)		Time to occurrence (years)	
		20 years	26 years	Median	Range
At least one thyroid disease	573/1787	50	63	436	0.2–25.6
	570/1677	52	67	4.6	0.2–25.6
Hypothyroidism	513/1787	41	44	4.0	0.2–23.7
	512/1677	43	47	4.0	0.2–23.7
Graves' disease[b]	34/1787	3.1	3.1	4.8	0.1–17.6
	32/1677	3.3	3.3	4.9	0.1–17.6
Graves' ophthalmopathy[b]	21/1677	–	–	–	–
Silent thyroiditis	6/1677	1.6	0.6	3.7	0.8–15.3
Hashimoto's thyroiditis	4/1677	0.7	0.7	7.9	3.5–15.2
Thyroidectomy	26/1677	6.6	26.6	14.0	1.5–25.6
Thyroid cancer	6/1677	1.7	1.7	13.3	9.0–18.9
Benign adenoma	10/1677	–	–	12.0	1.5–25.6
Adenomatous nodule	6/1677	–	–	17.4	12.7–24.4
Multinodular goiter	4/1677	–	–	14.8	10.8–19.4
Clinically benign nodule	12/1677	3.3	5.1	12.6	2.4–22.6
Clinically benign cyst	4/1677	0.7	0.7	8.1	1.6–16.7
Multinodular goiter[c]	2/1677	0.5	0.5	13.8	10.5–17

[a] The total refers either to all 1787 patients at risk or to the 1677 patients who underwent irradiation of the thyroid region.
[b] Thirty of the 34 patients who had been given a diagnosis of Graves' disease had hyperthyroidism; ophthalmopathy developed in three during a period of hypothyroidism and in one during a period of euthyroidism.
[c] Identified by clinical examination.
(From [16], with permission.)

of the cohort affected. The average time to developing hypothyroidism was five years. In a multivariate analysis, the major risk factors associated with the future development of hypothyroidism were the dose of radiation, female sex and older age at diagnosis. In fact, the actuarial risk of developing hypothyroidism 20 years after a diagnosis of HD was 30% for patients whose thyroid received 35–44.99 Gy and 50% for patients whose thyroid received 45 Gy or more (Fig. 9.1). In patients who were treated with chemotherapy alone, the incidence of hypothyroidism was 7.6%.

Although patients may develop an abnormal thyroid function test within six months of RT, most patients become abnormal between 1–5 years after treatment; however, rare and unexpected new cases can occur more than 20 years after diagnosis of HD [16, 37]. Uncompensated hypothyroidism (decreased serum T4 and elevated serum TSH concentration) occurs in 6–27% of children receiving radiation to the thyroid. In the thyroid dysfunction study by Constine and colleagues, age did not affect the incidence of hypothyroidism but was weakly correlated with the degree of abnormality, as suggested by higher serum TSH concentrations in adolescents compared with younger children [7]. In both Hancock's and Sklar's reports, older age at treatment of HD was a major risk factor for future development of an underactive thyroid. This may reflect the greater sensitivity of the thyroid gland in rapidly growing puber-

tal children, compared with preadolescents; or, it may reflect the fact that the older children generally received a higher radiation dose than the younger children. The iodine load from LAG may be a causal factor in the hypothyroidism observed in patients who are irradiated for Hodgkin's disease. In fact, there is a low, but greater than expected incidence, of hypothyroidism in patients having LAG without neck irradiation. Some recent reviews found that thyroid function was more likely to be abnormal in patients irradiated soon after LAG and mantle irradiation. However, no influence of LAG on thyroid dysfunction was noted in other studies [32, 38, 43]. The role of chemotherapy in producing thyroid abnormalities is less understood. The influence of chemotherapy on the development of thyroid dysfunction among Hodgkin's patients appears to be negligible in most reports [7, 11, 42], although data from England suggest that chemotherapy may add to the frequency of compensated hypothyroidism [25].

Primary hypothyroidism following irradiation of the spinal axis in the course of treating children with CNS tumors is also well documented. Ogilvy-Stuart [25] evaluated 85 such children and found a 32% incidence of compensated hypothyroidism. Constine [6] evaluated eight children treated with 4–10MV photon radiation to the spinal axis (mean dose: 30 Gy). Three demonstrated primary thyroid injury with low serum free-T4 concentration and an exaggerated TSH response to provocative testing with thyrotropin releasing hormone (TRH). Other reports indicate an incidence for compensated hypothyroidism of 20–68%, with overt hypothyroidism being rare [19, 24].

A recent study by Paulino [26] reviewed the incidence of hypothyroidism in children with medulloblastoma treated with lower dose CSI (23.4 Gy) plus chemotherapy (CT), compared with higher dose CSI (36 Gy) alone or in combination with CT. Paulino found that 56% patients developed hypothyroidism (38% primary and 19% central) at a median of 41 months after CSI. Hypothyroidism was more common in patients treated with combined chemotherapy and radiation than in those treated with radiation therapy alone, suggesting that chemotherapy did augment the effects of RT. A recent analysis by the Childhood Cancer Survivor Study (CCSS) [17] showed that the risk of adult survivors of childhood brain tumors developing hypothyroidism was more than twice as great for patients who had received a thyroid radiation dose >25 Gy, compared with the risk of patients who received a radiation dose of <25 Gy, with an RR of 2.7. Another study by Schmiegelow et al. [33] compared CSI with cranial irradiation (CIR) in causing hypothyroidism among survivors of childhood brain tumors. The overall incidence of primary hypothyroidism was 24%, of whom 71% had been treated with CSI, versus 29% who had been treated with CIR. In the CIR cohort, primary hypothyroidism was more common than central hypothyroidism, suggesting that the thyroid was directly affected by scattered radiation from the cranial RT field.

Overall, the role of chemotherapy in causing thyroid dysfunction in survivors of brain tumors remains controversial. The study by Paulino suggests that chemotherapy might be more causative in the induction of hypothyroidism than was previously recognized, but the number of patients was small. Nevertheless, Paulino concluded that the benefit of lowering RT dose was negated by the addition of chemotherapy. Two other reports supported his conclusion [19, 25], but two more studies did not find an association [4, 33].

Patients undergoing a bone-marrow transplant who receive total body irradiation (TBI) are also at risk for thyroid injury due to direct injury to the thyroid gland, rather than to the pituitary-hypothalamic axis. Sklar [36] found that a single dose of 7.5 Gy caused a decrease in serum T4 concentration in 9% patients and an elevated serum TSH concentration in 35%. The frequency of overt hypothyroidism following transplantation is highly variable and depends largely on the conditioning regimen. It was found to be nearly 90% with a 10 Gy, single- dose of TBI [18], but only 15% with fractionated TBI. The frequency of overt hypothyroidism was even less common after conditioning with Bu-Cy [40].

Thyroid abnormalities have been observed among long-term survivors of acute lymphoblastic leukemia (ALL). Robibson [28] collected data on 175 survivors first evaluated seven years after diagnosis. Seventeen

(10%) had thyroid function abnormalities, including five with uncompensated primary hypothyroidism and 11 with compensated hypothyroidism. Eight in the latter group reverted to normal without replacement therapy. No significant association was observed between hypothyroidism and the radiation dose (18 Gy versus 24 Gy), duration of chemotherapy (3 years versus 5 years), or age at the time of irradiation.

9.2.2 Hyperthyroidism

The potential for Graves' disease also appears to be increased after RT for Hodgkin's disease, with a risk that is 7.2–20.4 times the expected risk [16]. In the same childhood cancer survivors study described by Sklar et al., the RR of developing a hyperactive thyroid gland among HD survivors was found to be 8, with 5% of patients diagnosed with hyperthyroidism. The mean time between diagnosis of HD and development of hyperthyroidism was 8 years. A radiation dose of ≥35 Gy was an independent predictor of hyperthyroidism [37]. An immunologic basis has been suggested as an explanation for the apparent higher frequency observed after treatment for Hodgkin's disease, compared with other malignancies in which the neck is incidentally irradiated.

9.2.3 Thyroid Nodules

Extensive data exist on the development of benign thyroid nodules and malignancy after thyroid RT. Representative incidences for thyroid nodules are 6% for malignant and 8–12% for benign lesions following lower dose (less than 15 Gy) external beam RT [8]. The latency period for the development of thyroid cancer following thyroid RT varies from 5–26 years [37]. A recent report from the Late Effects Study Group [44] found that, of 9170 patients who had survived two or more years after the diagnosis of a cancer in childhood, the risk for thyroid cancer was 53 times as great. This risk was associated with both increasing radiation dose and the time from treatment. Sixty-eight percent of the cancers occurred in areas directly within the radiation field, and the thyroid glands of all patients had received at least 1 Gy (via scatter for some patients).

Hancock et al. [16] observed nodularity in 44 of 1677 patients treated for Hodgkin's disease 1.5–25 years after RT. Six patients were diagnosed with malignant nodules, with an RR of 15.6 (95% CI, 6.3–32.5). The other two reports found an RR for developing thyroid cancer among childhood Hodgkin's disease survivors following RT almost identical at 32.7 (95% CI, 15.3–55.3) and 33 (95% CI, 15–62), suggesting that children are at greater risk [2, 31]. Patients treated for neuroblastoma and Wilms' tumor were affected more commonly than those treated for HD; however, patients with the former two cancers were generally younger in age, which may be associated with an increase in risk for thyroid cancer as a second malignancy when data from children are compared with those from adults.

In the recent report by Sklar et al. [37], the incidence of thyroid nodules in HD survivor patients was 9%, with an RR of 27, compared with sibling controls, and 7.5% of these nodules were malignant. There were nine cases of thyroid cancer without any known associated thyroid nodule. The RR of developing thyroid cancer was 18.3, compared with the general population. Their multivariate analysis revealed that an interval ≥10 years since diagnosis, female sex and radiation dose ≥ 25 Gy were independently associated with future development of thyroid nodules.

In Hancock's data [16], the risk for developing thyroid cancer nine to 18 years after RT was 15.6%. In a study by Schneider and colleagues [34], 318 of 5379 patients who had received RT for benign conditions of the head and neck developed thyroid cancer 3–42 years later. Overall, in this setting (low dose RT, generally 2–5Gy, for benign conditions) new nodules develop at a rate about 2% per year, with a peak incidence at 15 to 25 years [10]. It is crucial to review the pathology of any biopsied nodule carefully, because an adenomatous nodule with cytologic atypia can be difficult to distinguish from thyroid carcinoma [5]. The most common type of cancer in this study was papillary carcinoma, which, fortunately, has a high cure rate if detected early [30]. The course of the cancer in these patients was the same as that of thyroid cancer found in other settings [34]. It is important to note that thyroid nodules have been found during surgery or autopsy in as many as 35–50% of a non-

irradiated population, and that clinically palpable nodules are found in 4–7% of normal adults [22, 27, 39, 41].

9.3 Detection and Screening

It is clearly important to obtain a comprehensive history and perform a thorough physical examination in all patients who received direct or scattered RT to the neck. Laboratory screening evaluations for asymptomatic patients should include serum concentrations of TSH and thyroxine (usually, free T4) tests. The measurement of free T4 rather than other tests (usually, total T4 by radioimmunoassay) is recommended because the former is not affected by changes in binding proteins [46]. Although some patients with normal serum-free T4 and TSH concentrations might show an exaggerated TSH response to provocative testing with TRH, the clinical significance of this finding is unclear. Screening for immunologic abnormalities can be performed by examining serum concentrations of antimicrosomal and antithyroglobulin antibodies, but abnormalities in asymptomatic patients are, again, of uncertain clinical significance. Patients with palpable abnormalities of the thyroid gland should undergo ultrasonography (USG) to evaluate the number, location and density of nodules and 99mTc scanning to evaluate the functional status of the nodules. Whether all patients who have received radiation to the thyroid gland should undergo periodic screening with one or the other of these techniques is controversial. Stewart and colleagues performed USG on 30 patients treated with mantle radiation for Hodgkin's disease who did not have palpable abnormalities and found unilateral or bilateral atrophy in eight patients, multiple hypoechoic lesions smaller than 0.75 cm in 18 and dominant cystic solid or complex lesions larger than 0.75 cm in seven patients [41]. Biopsies were not performed. Soberman [39] performed USG on 18 long-term survivors of Hodgkin's disease who had received a mean dose of 34 Gy to the neck 1–16 years (mean 6.4) previously; 16 patients (89%) had abnormalities, including diffuse atrophy (nine cases), solitary nodules (five cases), multiple nodules (six cases) and gland heterogeneity (one case). Only two patients had palpable nodules. Biopsies in four patients revealed multifocal papillary carcinoma in one patient and adenomas in three patients.

We have performed 99mTc scanning in 34 patients who were irradiated to the cervical region for Hodgkin's disease or other malignancy. All patients had an interval of at least five years since radiation treatment, all were euthyroid and all were without palpable thyroid abnormalities. Seven patients (21%) had abnormal scans, and two of these patients were diagnosed with thyroid cancer [30]. Patient numbers are currently too small to make firm recommendations. Although 99mTc scanning is less sensitive than USG, its specificity for detecting clinically-significant nodules is greater.

9.4 Management

The functions regulated by the thyroid gland are particularly important in a growing child. Therefore, early diagnosis and treatment of hypothyroidism, even when subclinical, is required to optimize growth, cognition and progression to puberty [35].

Patients with uncompensated hypothyroidism (low serum concentration of thyroxin) clearly require thyroid replacement therapy. In most institutions, patients with compensated hypothyroidism (elevated serum concentrations of TSH but normal thyroxine) also are treated with thyroid replacement therapy. The rationale for this approach is based on animal studies, which have demonstrated that elevated levels of TSH in the presence of irradiated thyroid tissue can lead to the development of thyroid carcinoma. The observation of thyroid cancer following neck irradiation in humans and the high frequency of elevated serum TSH concentrations in children who have received radiation for Hodgkin's disease have prompted us to institute thyroid replacement therapy in this population. Approaches to decrease the risk of thyroid injury in the setting of RT for Hodgkin's disease have included shielding the gland from irradiation [20] and administering thyroxine during irradiation [1]. The former approach was found to place patients at risk for the inadvertent shielding of dis-

eased cervical lymph nodes, and the latter approach did not prevent subsequent hypothyroidism. Therefore, these approaches are not recommended. Thyroid tissue is routinely protected from the radio-iodides used in MIBG scanning by administering a large dose of cold iodide, but this approach is successful in only 36% of patients. A recent study by van Santen et al. [45] found that administering thyroxine, methimazole (a drug to treat hyperthyroidism) and potassium iodide protects the thyroid gland effectively against radiation damage from Iodine-123/131 during diagnostic and therapeutic MIBG administration in children with neuroblastoma. At 2.6 years follow-up, this combination had successfully protected the thyroid in 85.6% of children. In contrast, the protection afforded by potassium iodide alone was 60%.

Patients with palpable thyroid abnormalities should undergo USG or 99mTc scanning and be evaluated by an endocrinologist and surgeon. If nodules are discovered, then biopsy is necessary. Depending on the results, further therapy may be necessary. The treatment approaches vary in different centers, as recently reviewed by Mazzaferri [21]. For papillary thyroid carcinoma, treatment will generally involve near total thyroidectomy, radioactive iodine and TSH suppression with thyroxine [9]. It remains unclear how best to treat patients who are not receiving replacement hormone and have clinically normal thyroid glands, but who also have nodules detected by USG or 99mTc scanning. Multiple small 2–3 mm carcinomas have been found in irradiated thyroid glands [18]. Because autopsies have shown a high incidence of occult (less than 1 mm) papillary carcinomas, the significance of cancer found in clinically occult lesions is arguable. However, it would seem appropriate to biopsy nodules that are detectable until additional information is available for more definite guidelines.

References

1. Bantle J, Lee C, Levitt S (1985) Thyroxine administration during radiation therapy to the neck does not prevent subsequent thyroid dysfunction. Int J Radiat Oncol Biol Phys 11:1999–2002
2. Bhatia S, Ramsay N, Bantle J et al. (1996) Thyroid abnormalities after therapy for Hodgkin's disease in childhood. Oncologists 1:62–67
3. Braverman LE, Ingbar SH, Vagenakis AG et al. (1971) Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. J Clin Endocrinol Metab 32:515–521
4. Chin D, Sklar CA, Donahue B et al. (1997) Thyroid dysfunction as a late effect in survivors of pediatric medulloblastoma/primitive neuroectodermal tumors: a comparison of hyperfractionated versus conventional radiotherapy. Cancer 80:798–804
5. Carr R, Livolsi V (1989) Morphologic changes in the thyroid after irradiation for Hodgkin's and non-Hodgkin's lymphoma. Cancer 64:825–829
6. Constine LS, Woolf PD, Cann D et al. (1993) Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 328:87–94
7. Constine LS, Donaldson SS, McDougall IR (1984) Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer 53:878–883
8. Constine LS, Rubin P, Woolf PD et al. (1987) Hyperprolactinemia and hypothyroidism following cytotoxic therapy for central nervous system malignancies. J Clin Oncol 5:1841–1851
9. DeGroot LJ, Kaplan EL, McCormick M et al. (1990) Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 71:414–424
10. DeGroot LJ (1989) Clinical review 2: diagnostic approach and management of patients exposed to irradiation to the thyroid. J Clin Endocrinol Metab 69:925–928
11. Devney RB, Sklar CA, Nesbit ME Jr et al. (1984) Serial thyroid function measurements in children with Hodgkin's disease. J Pediatr 105:223–229
12. Donaldson SS, Kaplan HS (1982) Complications of treatment of Hodgkin's disease in children. Cancer Treat Rep 66:977–989
13. Doniach I (1977) Pathology of irradiation thyroid damage. In: DeGrott LJ et al. (eds) Radiation-associated thyroid carcinoma. Grune and Stratton, New York
14. Fisher DA, Dussault JH (1974) Development of the mammalian thyroid gland. In: Greep RO et al. (eds) Handbook of physiology, sect 7, Endocrinology, vol 3, Thyroid. American Physiological Society, Bethesda
15. Fajardo LF, Berthrong M, Anderson RE (2001) Radiation pathology. Oxford University Press, London
16. Hancock S, Cox R, McDougall I (1991) Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 325: 599–605

17. Gurney G, Kadan-Lottick N, Packer R et al. (2003) Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors. Cancer 97:663–672
18. Hawkins MM, Kingston JE (1988) Malignant thyroid tumours following childhood cancer. Lancet 2:804
19. Livesey E, Brook C (1989) Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours. Arch Dis Child 64:593–595
20. Marcial-Vega VA, Order SE, Lastner G et al. (1990) Prevention of hypothyroidism related to mantle irradiation for Hodgkin's disease: preparative phantom study. Int J Radiat Oncol Biol Phys 18:613–618
21. Mazzaferri EL (1993) Management of a solitary thyroid nodule. N Engl J Med 328:553–559
22. Mazzaferri EL, de los Santos E, Rofagha-Keyhani S (1988) Solitary thyroid nodule: diagnosis and management. Mod Clin North Am 72:1177–1211
23. McDougall IR, Coleman CN, Burke JS et al. (1980) Thyroid carcinoma after high-dose external radiotherapy for Hodgkin's disease. Cancer 45:2056–2060
24. Oberfield SE, Allen J, Pollack J et al. (1986) Long-term endocrine sequelae after treatment of medulloblastoma: prospective study of growth and thyroid function. J Pediatr 108:219–223
25. Ogilvy-Stuart A, Shalet S, Gattamameni H (1991) Thyroid function after treatment of brain tumors in children. J Pediatr 119:733–737
26. Paulino AC (2002) Hypothyroidism in children with medulloblastoma: a comparison of 3600 and 2340 cGy craniospinal radiotherapy. Int J Radiat Oncol Biol Phys 53:543–547
27. Pelizzo M, Piotto A, Rubello D et al. (1990) High prevalence of occult papillary thyroid carcinoma in a surgical series for benign thyroid disease. Tumori 76:255–257
28. Robibson LL, Nesbit ME, Sathes HN et al. (1985) Thyroid abnormalities in long-term survivors of childhood acute lymphoblastic leukemia. Pediatr Res 19:266A
29. Rubin P, Cassarett GW (1968) Clinical radiation pathology, vols I and II. Saunders, Philadelphia
30. Sandhu A, Constine LS, Muhs A et al. (2000) Subclinical thyroid disease after radiation therapy detected by technetium 99m scanning. Int J Radiat Oncol Biol Phys 48: 181–188
31. Sankila R, Ganwicz J, Olsen H et al. (1996) Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population based cohort study in five Nordic countries. J Clin Oncol 14:1442–1446
32. Schimpff SC, Diggs CH, Wiswell JD (1980) Radiation-related thyroid dysfunction: implications for the treatment of disease. JAMA 245:46–49
33. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK et al. (2003) VA population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. J Clin Endocrinol Metab 88:136–140
34. Schneider AB, Recant W, Pinsky SM et al. (1986) Radiation-induced thyroid carcinoma: clinical course and results of therapy in 296 patients. Ann Intern Med 105:405–412
35. Sklar CA, Constine LS (1995) Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113–1121
36. Sklar CA, Kim TH, Ramsay NKC (1982) Thyroid dysfunction among long-term survivors of bone marrow transplantation. Am J Med 73:688–694
37. Sklar CA, Whitton J, Mertens A et al. (2000) Abnormalities of the thyroid in survivors of Hodgkins Disease: data from childhood cancer survivor study. J Clin Endocrinol Metab 85:3227–3232
38. Smith RE Jr, Adler AR, Clark P et al. (1981) Thyroid function after mantle irradiation in Hodgkin's disease. JAMA 245:46–49
39. Soberman N, Leonidas JC, Cherrick I et al. (1991) Sonographic abnormalities of the thyroid gland in long-term survivors of Hodgkin's disease. Pediatr Radiol 21:250–253
40. Socie G, Salooja N, Cohen A et al. (2003) Nonmalignant late effects after allogenic stem cell transplantation. Blood 101: 3373–3385
41. Stewart RR, David CL, Eftekhari F et al. (1989) Thyroid gland: US in patients with Hodgkin's disease treated with radiation therapy in childhood. Radiology 172:159–163
42. Sutcliffe S, Chapman R, Wrigley P (1981) Cyclical combination chemotherapy and thyroid function in patients with advanced Hodgkin's disease. Med Pediatr Oncol 9:439–448
43. Tamura L, Shimaoka K, Fhedman M (1981) Thyroid abnormalities associated with treatment of malignant lymphoma. Cancer 47:2704–2711
44. Tucker M, Jones P, Boice J et al. (1991) Therapeutic radiation at a young age is linked to secondary thyroid cancer. Cancer Res 51:2885–2888
45. Van Santen HM, de Kraker J, van Eck BLF et al. (2003) Improved radiation protection of the thyroid gland with thyroxine, methimazole, and potassium iodide during diagnostic and therapeutic use of radiolabeled metaiodobenzylguanidine in children with neuroblastoma. Cancer 98:389–396
46. Woolf P, Lee L, Hamill R et al. (1988) Thyroid test abnormalities in traumatic brain injury correlated with neurologic impairment and sympathetic-nervous system activities. Am J Med 84:201–208

Cardiovascular Effects of Cancer Therapy

M. Jacob Adams · Sarah A. Duffy · Louis S. Constine · Steven E. Lipshultz

Contents

During the past 35 years, advances in the treatment of childhood cancer have allowed many to survive their disease and its treatment. The cardiovascular sequelae that may affect children are clearly a major concern in considering their potential for a normal adult life. Recent data on 33,938 children and adolescents who were treated for cancer in the United States and Scandinavia, and who survived for at least five years, have shed light on the relevance of cardiovascular disease to patient survival [1, 2]. The standardized mortality ratio (SMR) was 10.8, with 67–70% of deaths due to recurrent primary malignancy, 7–12% due to a subsequent malignancy and 8–11% due to non-cancer treatment-related sequelae, including cardiovascular disease (CVD) [2]. The specific SMRs for CVD in the US and Scandinavian populations were also remarkably similar, 8.2 and 5.8, respectively.

Thus, it is clear that cancer therapy, which frequently includes cardiotoxic agents such as anthracyclines and radiation, may cause late cardiovascular effects a few months to decades after therapy. For newer combinations of radiotherapy and anthracyclines, risks are less well known and should be considered at least as damaging as older protocols until more time has elapsed.

Radiation therapy and chemotherapy can cause irreversible cardiac damage. Although many survivors appear well, they may be compensating, either physiologically or by altering their lifestyles, for some degree of heart damage. While it is not known how many will eventually be debilitated by cardiac damage, early recognition and treatment of problems allow survivors to have longer and more symptom-free lives. Early intervention can also help minimize additional damage to the cardiovascular system associated with Western society's lifestyle.

10.1 Pathophysiology

10.1.1 Normal Organ Development

In the third week of gestation, cardiac development begins, and primary morphogenesis is complete by the end of the eighth week. Myocardial cell replication rates are highest in the earlier weeks and decrease as the septum of the heart develops [3]. Cell size remains constant during this period of rapid growth. During most of embryonic development, the heart increases its mass by cell proliferation (hyperplasia) rather than cell enlargement (hypertrophy) [4]. In the late prenatal and early postnatal periods, heart growth is achieved by both hypertrophy and hyperplasia [5]. The adult number of myocytes is present by six months of age. Subsequent growth of the heart occurs almost exclusively by myocyte hypertrophy. Myocytes that die after six months of age are replaced with fibrosis. Such losses are compensated for by hypertrophy of surviving cells.

The pumping action of the heart occurs by synchronized contraction of the myocytes. This contraction is initiated by an electrical stimulus (action potential) that originates in the sinus node and is propagated through the atrioventricular (AV) node and His-Purkinje system to the ventricular myocytes. In order for the action potential to cause an effective contraction of the myocyte, several factors must work optimally. First, the actin and myosin filaments must be in their normal relaxed state. If the myocytes are already stretched (as in anthracycline-induced dilated cardiomyopathy), cross bridging cannot occur as effectively. Second, calcium must be available in the sarcoplasmic reticulum (SR) for release by the action potential into the sarcoplasm. Calcium catalyzes the cross bridging, producing contraction of the myocyte. Third, the myocytes must return to their resting state in order for the next action potential to generate another contraction. Some types of cardiac damage, including anthracycline and radiation-induced cardiomyopathy, impede the return to the resting state, thus decreasing diastolic compliance.

10.1.2 Changes Induced by Cytotoxic Therapy

10.1.2.1 Anthracyclines

The earliest changes seen in cardiac myocytes after exposure to doxorubicin include swelling of the sarcoplasmic reticulum, and mitochondria with occasional nucleolar changes [6, 7]. Large vacuoles that probably distend SR displace mitochondria and contractile elements. Injuries to the mitochondria, SR and sarcolemma affect both calcium transport mechanisms and intracellular calcium concentrations. Those injuries, in concert with the actions of other potential mediators of anthracycline-induced cardiac damage (e.g. free radicals, prostaglandins, histamines and metabolites), result in the morphologic changes noted on endomyocardial biopsies taken from patients undergoing anthracycline therapy, as well as cell death [8, 9].

The major types of myocyte damage described by Billingham and colleagues [8] are myofibrillar loss and vascular degeneration. These changes are graded as follows:

1. Myofibrillar loss or sarcoplasmic swelling in the occasional myocyte;
2. Widespread myofibrillar dropout or definitive cytoplasmic vacuolization in clusters of myocytes;
3. Diffuse injury with marked cellular damage and necrosis.

Electron micrography shows reduction in myofibrillar bundles, myofibrillar lysis, swollen mitochondria and distortion of the Z-line substance. The severity of these changes correlates with total anthracycline dose [10].

Since myocytes rarely proliferate after six months of age, virtually all myocardial growth after this point results from increasing myocyte size. Therefore, the main way to compensate for lost myocytes due to anthracycline therapy is for surviving myocytes to hypertrophy even more than usual in order to maintain normal cardiac output [11]. Lipshultz et al. noted such hypertrophy in conjunction with reduced wall thickness and interstitial fibrosis in myocardial biopsy specimens from children treated with anthracyclines [11]. This suggests that late-onset cardiac failure after anthracycline therapy may be due to the

inability of surviving myocytes to adequately compensate for the demand placed on the heart by the normal growth of the body, pregnancy or other cardiac stresses.

10.1.2.2 Cyclophosphamide

The effects of cyclophosphamide on the heart – specifically, the myocardium – are described primarily in the setting of high-dose preparatory regimens for bone marrow transplant. Left ventricular wall mass and thickness increase as a result of intramyocardial edema or hemorrhage, often in association with a serosanguinous pericardial effusion with fibrinous pericarditis [12]. Multiple areas of myocardial hemorrhage are seen, with extravasation of blood, interstitial edema and multifocal myocardial necrosis [13]. Cyclophosphamide induces endothelial damage causing myocardial edema, and it may also cause myocardial fibrosis [14–16]. Chronic changes have not been described after cyclophosphamide therapy, although it may exacerbate anthracycline-induced cardiotoxicity [17]. Sequential dosing of cyclophosphamide may result in increased myocardial sensitivity to the drug. This is because the median lethal dose (LD50) for cyclophosphamide-induced cardiotoxicity is decreased by glutathione deficiency, which is induced by cyclophosphamide [17]. Other chemotherapeutic agents may cause cardiac damage as well, but the evidence for their effect is much less than for anthracyclines and cyclophosphamide [18, 19]. Nevertheless, they are included in Table 10.1.

10.1.2.3 Radiation

The long-term adverse impact of RT on the heart has been the subject of study since the 1940s [20]. Sequelae can include pericarditis, myocarditis, cardiomyopathy, coronary artery disease (CAD), valvular injury, conduction defects and autonomic dysfunction (Table 10.2). The frequency of RT-related cardiac injury varies because of differences in radiation dosage and techniques employed. Important characteristics that determine risk include total and fractional doses, volume and specific regions of the heart irradiated and relative weighting of the radiation portals. The presence of other risk factors for cardiac disease (e.g. tobacco use, dyslipidemia) and the use of cardiotoxic chemotherapeutic agents, especially anthracyclines, also influence the incidence of cardiac sequelae.

Radiation-associated heart disease generally has a characteristic morphology and pathophysiology. The histological hallmark is fibrosis in the interstitium with normal-appearing myocytes and narrowing of capillary and arterial lumens. Historically, the most common manifestation had been pericardial disease. Dense collagen and fibrin replace the normal adipose tissue of the outer layer of the heart. Fibrosis occurs in the stroma and on the mesothelial surfaces of the pericardium. A protein-rich pericardial fluid is often found, although it usually develops slowly so that cardiac tamponade rarely occurs [21, 22]. Injury to the myocardium is characterized by non-specific, diffuse interstitial fibrosis. Lesions measure from a few millimeters to several centimeters in size, but usually do not encompass the entire myocardium. The severity of fibrosis can be markedly different from one region to another [21, 23]. Collagen not only increases as a whole, but the proportion of type I collagen increases in comparison to type III [24]. These changes are thought to change the compliance of the heart and thus contribute to the significant diastolic dysfunction seen in this population. Cells of the myocardium that are involved with conduction are sensitive to radiation-induced fibrosis as well. Radiation damages the myocardium and pericardium by injuring the capillary endothelial cells, which causes obstruction of the capillary lumen and the formation of thrombi of fibrin and platelets. This leads to ischemia and potentially myocardial cell death and fibrosis.

The pathology and pathophysiology of coronary artery disease after radiotherapy appears to differ, but only slightly, from that of coronary artery disease in the general population. Coronary artery disease (CAD) occurs relative to radiation dose distribution, with the left anterior descending and the right coronary arteries most often affected after anterior-weighted mantle radiotherapy. Before the use of modern techniques, disease of the left main coronary artery occurred more often in those who received

Table 10.1. Potential cardiotoxicity of cancer therapy

Drug	Toxic dose range[a]	Acute toxicity[b]	Chronic toxicity[2]
Doxorubicin[c] (Adriamycin RDF, Doxil)	>550 mg/m^2 (total dose)	Arrhythmias, pericarditis- myocarditis syndrome, myocardial, infarction, sudden cardiac death	Cardiomyopathy/congestive heart failure, conduction abnormalities/arrhythmias
Mitoxantrone (Novantrone)	>100–140 mg/m^2 (total dose)	Congestive heart failure, decreases in left ventricular ejection fraction, myocardial infarction, ECG changes, arrhythmias	
Cyclophosphamide (Cytoxan)	>100–120 mg/kg (over 2 days)	Hemorrhagic cardiac necrosis, reversible systolic dysfunction, ECG changes, CHF	
Ifosfamide (Ifex)		ECG changes, congestive heart failure, arrhythmias	
Cisplatin (Platinol)	Conventional dose	Myocardial ischemia, Raynaud's phenomenon, ECG changes	
Fluorouracil (Adrucil, Efudex)	Conventional dose	Myocardial infarction, angina, cardiogenic shock/sudden death, dilated cardiomyopathy	
Trastuzumab (Herceptin)		Ventricular dysfunction, congestive heart failure	Cardiomyopathy
Paclitaxel (Taxol)	Conventional dose	Sudden death, bradyarrhythmias, myocardial dysfunction, myocardial infarction	
Amsacrine (Amsa-PD)	Conventional dose	Ventricular arrhythmia, ECG changes	Cardiomyopathy
Cytarabine (Cytosar-U)		Congestive heart failure, pericarditis, arrhythmias	
Arsenic trioxide (Trisenox)		Arrhythmias, pericardial effusion	
Interferon Alpha-2A (Roferon)	Conventional dose	Exacerbates underlying cardiac disease, hypotension, arrhythmias	Cardiomyopathy
Interleukin-2 (Aldesleukin)	Conventional dose	Myocardial injury/myopericarditis, ventricular arrhythmias, hypotension, sudden death	Dilated cardiomyopathy
Mitomycin (Mutamycin)	Conventional dose	CHF	Congestive heart failure
Vincristine (Oncovin)	Conventional dose	Myocardial infarction, hypotension, cardiovascular autonomic neuropathy	
Vinblastine (Velban)	Conventional dose	Myocardial infarction, Raynaud's phenomenon	
Busulfan (Busulfex)	Conventional oral daily dose	Endocardial fibrosis, pulmonary fibrosis, pulmonary hypertension, cardiac tamponade	
Chest irradiation	Unclear but those at greatest risk received >35 Gy	Pericarditis/pericardial effusion, non-specific ECG changes	Myocardial Infarction, cardiomyopathy, pericarditis (chronic), conduction abnormalities/arrhythmias, valvular defects

[a] The literature suggests a heightened risk of toxicity at or above the mentioned doses. However, damage can occur at lower doses, especially when other risk factors are present and/or a patient receives more than one cardiotoxic agent.

[b] Acute = < 1 year; Chronic = > 1 year

[c] Other anthracyclines include daunorubicin, idarubicin, epirubicin, carminomycin, detorubicin, esorubicin, marcellomycin, quelmycin, and rodorubicin. Their advantage over doxorubicin on an equimolar basis is still unclear and cardiotoxic dose is not necessarily known for each.

Modified from Table 1 in Simbre et al. [18] with permission from the publisher

Table 10.2. Spectrum of radiation-associated cardiovascular disease

Manifestation	Comments	References
Pericarditis	1. During therapy – Associated with mediastinal tumor and some chemotherapy agents such as cyclophosphamide	[21]
	2. Post therapy – Acute effusion, chronic effusion, pericarditis, constrictive pericarditis	[21]
Cardiomyopathy	1. Fibrosis secondary to microvasculature changes	[21]
	2. Frequently with normal left ventricular dimensions, ejection fraction and fractional shortening as measured by radionuclide scan or echocardiogram	[39]
	3. Can have progressive, restrictive cardiomyopathy with fibrosis. Can cause pulmonary vascular disease and pulmonary hypertension	[39]
	4. Diastolic dysfunction often occurs alone as well as with systolic dysfunction	[39]
Coronary artery disease	1. Premature fibrosis and probable acceleration of atherosclerosis	[27, 31]
	2. Distribution of arteries affected tends to be anterior with anterior weighted therapy	[21]
	3. Lesions tend to be proximal and even ostial	[25, 27, 31]
	4. Apparent increase in lipid profile risk in survivors of the atomic bomb compared to age matched controls	[149]
	5. Increased rates of silent ischemia, clinically unsuspected and clinically suspected acute myocardial infarction (see autonomic effects)	[105]
Valvular disease	1. Predominantly mitral valve and aortic valve affected	[21]
	2. Increased regurgitation and stenosis with increased time since therapy	[32, 154]
	3. Many people with normal valves at completion of therapy demonstrate significant disease 10–20 years later.	[105]
Conduction system/ arrhythmia	1. High rate of complete or incomplete right bundle branch block is suggestive of right bundle branch fibrosis	[104]
	2. Can progress to complete heart block and cause congestive heart failure, requiring a pacemaker	[104]
	3. Complete heart block rarely occurs without other radiation-induced abnormalities to the heart	[103, 104]
	4. Increased left ventricular fibrosis associated with increased high grade ventricular ectopic activity	
	5. Increased right atrial pressure associated with increased risk of atrial arrhythmia	
Autonomic dysfunction	1. Tachycardia, loss of circadian rhythm and respiratory phasic heart rate variability	[105]
	2. The above is similar to a denervated heart, suggesting autonomic nervous system damage	[105]
	3. Decreased perception of anginal pain	[105]
Vascular changes	1. Significant pulmonary artery stenosis and hypoplasia in some, especially in those treated in early childhood.	[39]
	2. Carotid artery and aortic artery increased incidence of fibrosis and atherosclerosis	[150]
	3. Increased incidence of calcification of the aorta in A-bomb survivors	[151, 152]

Modified from Figure 8.15.3 in [113] with permission.

radiotherapy than in the general population [25]. However with the use of modern techniques, the distribution of disease sites is similar to that of the general population [26]. Narrowing of the artery generally occurs proximally and often involves the coronary ostia [25, 27]. The morphology of radiation-associated CAD is no different from that of spontaneous atherosclerosis, except for potentially more fibrosis of the media and adventitia [25, 27–29]. Thus, specifically diagnosing radiation-induced lesions through histology is not possible. The mechanism of radiation-associated coronary artery disease is thought to involve intimal injury and the replacement of the damaged cells by myofibroblasts, deposition of platelets and the other events that usually occur in atherosclerosis.

The cusp and/or leaflets of valves may undergo fibrotic changes, with or without calcification, but the underlying pathophysiology is unknown [30]. Changes to valves on the left side appear to be more common than changes to those on the right, regardless of dose distribution [31, 32]. This suggests that the higher pressures of the systemic circulation play a role in the pathogenesis of radiation-associated valvular disease [32]. It also suggests that such disease is progressive.

10.2 Clinical Manifestations

10.2.1 Anthracyclines

Anthracyclines are the most common class of chemotherapeutic agents associated with adverse effects on the heart. They were first introduced in the late 1960s and early 1970s [33] and are critical in the treatment of many pediatric malignancies [34]. Krischer et al., in their review of the Pediatric Oncology Group (POG) protocols, demonstrated that more than 50% of 12,680 patients treated between 1974 and 1990 received anthracycline chemotherapy [35]. The most commonly used drugs in this class are doxorubicin (Adriamycin), daunorubicin (Cerubidine), epirubicin (Pharmorubicin) and idarubicin (Idamycin) [36].

Childhood cancer survivors have an increased mortality from all causes following the cure of their cancer. In a large cohort of pediatric cancer patients who had survived at least five years after diagnosis, the standardized mortality ratio from all causes was 10.8 [1]. A substantial proportion of the described morbidity and mortality was cardiac in nature (the standardized cardiac mortality ratio was 8.2) [1]. Mortality from anthracycline-induced cardiac failure is substantial, with historic mortality rates as high as 20% after heart failure symptoms develop [37]. As early as the 1970s, the higher risk of cardiac death in anthracycline-treated patients was noted [38].

10.2.1.1 Spectrum of Anthracycline Damage

Heart damage from anthracycline therapy can be divided into three categories: 1) acute changes that occur within a week of infusion, 2) early onset, chronic progressive cardiotoxicity that occurs within one year after completing therapy and 3) late onset, chronic progressive cardiotoxicity that occurs after the first year (Table 10.3). Acute changes can range from minor electrocardiographic (ECG) abnormalities to fatal congestive heart failure. During infusion of an anthracycline, the corrected QT interval (QTc) on the ECG can become prolonged, and the rare patient may develop a ventricular arrhythmia. Echocardiography can reveal left ventricular dysfunction that may be transient. However, some of the changes can become permanent, especially with higher cumulative doses of anthracyclines. Most patients, however, recover at least temporarily. In fact, the risk for chronic cardiac dysfunction may be greatest for those diagnosed by echocardiography with abnormal cardiac function during or immediately following therapy [39]. Nevertheless, the most appropriate and effective methods of on-therapy monitoring, as well as its prognostic value for long-term cardiotoxicity, remains an area of some controversy and active investigation [40]. Data from Krischer et al. illustrate the prevalence of CVD and the importance of developing effective monitoring. In a cohort of 6,493 childhood cancer patients treated with anthracycline, 1.6% developed early, acute congestive heart failure, which prompted permanent discontinuation of anthracycline therapy [35]. None of the 6,187 children treated without anthracycline therapy were reported to have clinical cardiotoxicity.

Table 10.3. Characteristics of different types of anthracycline cardiotoxicity

Characteristic	Acute cardiotoxicity	Early-onset chronic progressive cardiotoxicity	Late-onset chronic progressive cardiotoxicity
Onset	Within the first week of anthracycline treatment	<1 year after the completion of anthracycline treatment	≥1 year after the completion of anthracycline treatment
Risk factor dependence	Unknown	Yes	Yes[a]
Clinical features in adults	Transient depression of myocardial contractility	Dilated cardiomyopathy	Dilated cardiomyopathy
Clinical features in children	Transient depression of myocardial contractility	Restrictive cardiomyopathy and/or dilated cardiomyopathy	Restrictive cardiomyopathy &/or dilated cardiomyopathy
Course	Usually reversible on discontinuation of anthracycline	Can be progressive	Can be progressive

Modified from Table 2 in Simbre et al. [18] with permission from the publisher
[a] Data from Giantris et al. [36] and Grenier and Lipshultz [42].

Many more individuals appear to develop cardiac dysfunction over the long-term than suffer acute decompensation. Children tend to show combined dilated and restrictive pathophysiology [36], while adult patients typically display purely dilated disease [37, 41]. Late anthracycline-related cardiac decompensation has been documented to occur as long as two decades after completion of therapy, but it is unclear whether there is any time limit. In both early and late chronic cardiotoxicity, electrophysiologic changes, left ventricular dysfunction, decreased exercise capacity and clinical congestive heart failure (CHF) may develop [42]. Symptoms of CHF include fatigue, exercise intolerance, cough and dyspnea. Tachycardia, tachypnea, hepatomegaly, rales and a new S3 or S4 heart sound may be noted on physical examination.

Late onset toxicity occurs ≥ 1 year after the completion of therapy; by definition, there must be a latency period before cardiac dysfunction develops [11]. Asymptomatic disease is most common, although some patients may report easy fatigability or dyspnea before being diagnosed. Late-occurring acute, severe disease has been reported but is rare, and it is manifested by deadly arrhythmia or rapid cardiac decompensation [43].

Late-onset anthracycline cardiac dysfunction is a result of damage caused during therapy that is not serious enough to cause symptoms immediately. The myocyte loss and damage that occurs during cancer therapy leads to progressive left ventricular dilation, left ventricular wall thinning and a decrease in contractility [42]. As ventricular contractility diminishes, the ventricle dilates further to maintain cardiac output. These changes produce a chronic elevation in left ventricular wall stress, thereby promoting further left ventricular compromise. Cancer survivors may also unconsciously compensate for anthracycline-induced cardiac damage by choosing less active lifestyles, allowing them to live without symptoms. However, a heart with ventricular dilatation is less likely to compensate further when metabolic demands increase. Acute viral infection and cardiovascular stressors such as pregnancy, surgery or heavy isometric exercise (weightlifting) may tip the already vulnerable heart into acute cardiac failure [44, 45]. In fact, studies have shown an increased risk of cardiac decompensation when additional stress is placed on the heart by growth hormone-induced growth spurts in children with ALL [46], pregnancy-induced hypervolemic weight gain or the increase in cardiac afterload associated with vaginal delivery or weight lifting [43, 47]. Death is likely within months to years after the onset of congestive heart failure, without success-

ful treatment. Thus early recognition and prevention of progression of cardiac dysfunction is key.

Noninvasive monitoring of long-term cancer survivors treated with anthracyclines generally reveals increasing abnormalities over time. Abnormalities can exist in echocardiographic parameters, such as left ventricular (LV) fractional shortening, LV end diastolic dimension, LV afterload (determined by end systolic wall stress), LV contractility (determined by the stress velocity index) [11, 43, 48] and LV diastolic filling phases [48]. Electrocardiographic and exercise stress results can also be abnormal [49, 50]. Some patients with these abnormalities eventually progress to symptomatic CHF. Lipshultz et al. detected late-onset cardiotoxicity in >50% of a cohort of 115 children treated for ALL with doxorubicin, 1–15 years earlier [11]. Cardiotoxicity was evaluated by taking an oral history, 24-hour ambulatory electrocardiogram (ECG) recording, exercise testing and echocardiography. Over half (57%) the patients had abnormal end-systolic wall stress (afterload) or contractility. Patients with excess afterload at the initial evaluation showed less increase in left ventricular wall thickness than expected for somatic growth. In addition, there was a significant increase in age-adjusted afterload during follow-up, with 24 of 34 patients (71%) having higher values on their last study. Similarly, among patients in the National Wilms' Tumor Study who received doxorubicin for their initial treatment, CHF occurred late (greater than one year after therapy) in two-thirds of the CHF cases that developed [51].

In addition to abnormalities of left ventricular structure and function, electrical abnormalities, including lethal conduction blocks or ventricular arrhythmia, may occur during anthracycline therapy or in follow-up. An increased frequency of QTc interval prolongation may occur with higher cumulative doses of anthracyclines [52–54].

10.2.1.2 Risk Factors for Anthracycline-Induced Cardiotoxicity

There are many risk factors that influence anthracycline-induced cardiotoxicity (Table 10.4). Some of the risk factors can be altered. Examples include the type of anthracycline administered, the cumulative dose, the use of cardio-protectants and concomitant mantle radiation [36]. However, patient characteristics, which are not modifiable, also affect the risk of developing cardiomyopathy. These include age at time of treatment, gender, race and length of follow-up. Pre-existing or concomitant medical conditions and treatments can also influence the risk of cardiotoxicity.

Higher cumulative dose has been well established as a risk factor for cardiac damage. An early study reported an incidence of heart failure of 0.15% or less among patients with cumulative doses of 400 mg/m^2 or less, and 7% among patients with cumulative doses of 550 mg/m^2 [37]. In the previously mentioned study of 6,493 children who received anthracyclines on POG protocols from 1974–1995, the risk of cardiotoxicity in children treated with 550 mg/m^2 or more was five times greater than the risk in children treated with lower cumulative doses [35]. In fact, a high cumulative dose of anthracycline was the strongest predictor of cardiotoxicity. Lipshultz et al. found a similar relationship among 115 children treated for ALL with doxorubicin during the previous 1–15 years [11]. Patients receiving 45 mg/m^2 in a single dose were compared to patients receiving 228 mg/m^2 or more in multiple doses. Left ventricular posterior wall thickness adjusted for body surface area was lower in all patients who received doxorubicin, compared with normal controls. Furthermore, left ventricular posterior wall thickness was significantly lower than normal in patients receiving the higher dose of doxorubicin. Children who received a single dose had less impaired function than children who received 228 mg/m^2 or more. Fractional shortening and left ventricular contractility were significantly reduced, and afterload was significantly elevated in all patients in the high-dose group [11]. Afterload is a function of blood pressure, the size of the ventricular cavity and wall thickness; but in these patients, blood pressure and size of the left ventricular cavity were normal. Therefore, increased afterload was attributable to reduced left ventricular wall thickness. Higher cumulative dose of anthracyclines was a significant predictor for both increased afterload and decreased contractility [11]. Similar results were found by Steinherz et al., in their evaluation of 201 survivors who

Table 10.4. Risk factors for anthracycline-induced cardiotoxicity in decreasing order of importance

Risk factors	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 mantle irradiation	Evidence of enhanced cardiotoxicity; not clear whether additive or synergistic
Rate of anthracycline administration	Higher rate was thought to predispose to greater toxicity, but current trials do not support this
Others	Concomitant exposure to cyclophosphamide, bleomycin, vincristine, amsacrine, or mitoxantrone, may predispose to cardiotoxicity. Trisomy 21 and black race have been associated with a higher risk of early clinical cardiotoxicity.

Modified from Table 3 in Simbre et al. [18] with permission from the publisher

had been treated with anthracyclines 4–20 years previously [43]. Echocardiogram revealed the following percentages with decreased cardiac function after the cumulative doses of doxorubicin indicated: 11 % after <400 mg/m^2, 23 % after 400–599 mg/m^2, 47 % after 500–799 mg/m^2 and 100 % after >800 mg/m^2 [43]. The study of the National Wilms' Tumor Study Group found that cumulative dose of doxorubicin increased the patient's relative risk of congestive heart failure by a factor of 3.3 for every 100 mg/m^2 of doxorubicin [51]. Although the risk of cardiotoxicity increases with the cumulative dose of anthracycline administered, the relationship is complex and far from linear [36]. Indeed, reports of cardiac dysfunction in patients treated with <300 mg/m^2 exist [55, 56]. Individuals vary in their susceptibility, and risk may increase over time. Thus, it is important to emphasize that there is no absolutely safe dose of anthracycline.

Younger age at treatment appears to increase the risk of anthracycline-induced myocardial impairment [7, 11, 48, 57, 58]. In one study, children under the age of 4 years at the time of exposure were at a significantly greater risk for developing abnormal cardiac function [11]. A retrospective study of 120 children and adults who had received cumulative doxorubicin doses of 244–550 mg/m^2 for acute lymphoblastic leukemia (ALL) or osteosarcoma during childhood or adulthood showed that younger age at diagnosis was predictive of ventricular dysfunction [48].

Longer follow-up has become important in screening, as both the prevalence and severity of cardiac abnormalities increase over time [48, 59]. In a serial follow-up of 120 doxorubicin-treated patients, those with longer follow-ups were more likely to have reduced left ventricular wall thickness and secondary increased left ventricular afterload [48]. Asymptomatic cancer survivors are at increasing risk for cardiac dysfunction later in life. Patients may develop cardiomyopathy with CHF after years of latency [11, 35, 36, 42, 48, 60]. Although acute episodes can often be treated successfully, cardiac function generally shows a progressive decline even with long-term medication. Studies have shown that, six years after completion of therapy, 65 % of childhood cancer survivors treated with anthracyclines have subclinical cardiac dysfunction that is often progressive [11, 36, 48]. Heart failure frequently develops after an added stress on the heart, such as pregnancy, infection, an unsupervised exercise program or cocaine use. Monitoring cardiac function is thus extremely important during pregnancy or other events that can increase stress on the heart [40].

Girls appear to be more vulnerable than boys to the cardiotoxic effects of anthracycline therapy. In

their review of patients treated on POG protocols from 1974–1990, Krischer et al. reported that being female was an independent risk factor for early cardiotoxicity [35]. Lipshultz et al. also found that female patients were more likely to have late depressed contractility than male patients [48]. In their cohort of 120 children and adults treated for ALL (73%) or osteogenic sarcoma (27%) with doxorubicin (≥ 244 mg/m^2) years earlier, 45% of the female patients (28 of 62) had contractility more than 2 standard deviations below normal, compared with 12% of male patients (7 of 58; P<0.001). In addition, there appeared to be a direct relationship between the cumulative dose and the difference in contractility between male and female patients (the higher the dose, the higher the difference). The findings of Silber et al. also showed the association of increased risk with female gender [61]. In this study, 150 patients underwent one of three procedures: 1) resting and gated nuclear angiography, 2) exercise testing using standard cycle ergometry with electrocardiographic (ECG) monitoring, or 3) both tests. Approximately 38% (32 of 85) of the male patients had abnormalities in one or both of the cardiac function tests, compared with 64% (42 of 66) of the female patients. Similar results were found in the National Wilms' Tumor Studies, from which it was concluded that, given the same level of cumulative doxorubicin dose and radiation therapy, the risk of developing congestive heart failure for girls is about four times greater than for boys [51].

The reason for the sex difference is unclear. One hypothesis is that anthracyclines may be distributed differently in the male and female bodies. Doxorubicin does not distribute well into fat tissue and is metabolized more slowly in the obese [62]. Equal doses of anthracycline given to males and females may lead to higher dose exposure in the hearts of females, because females have more body fat than males of the same body surface area. This hypothesis is supported by Silber's study, which found that the association between cardiac dysfunction and female sex was particularly strong in children older than age 12, when puberty begins to produce larger differences in fat distribution between boys and girls [61].

Rate of administration (continuous infusion versus bolus doses) had previously been suggested as a risk factor for developing cardiotoxicity during and after treatment [36], but recent evidence does not support this. Because continuous infusion reduces peak anthracycline levels, it was thought that this might protect the heart. This method, however, prolongs exposure. Lipshultz et al. reported that serum measurements of cardiac troponin-T were elevated in children who received doxorubicin for ALL by either method and that no significant difference existed in their mean levels. This suggests that neither method provides a protective advantage to the heart [63]. In both groups, multiple echocardiographic measurements showed abnormalities, including a significant decrease in median left ventricular (LV) fractional shortening and LV contractility, and a significant increase in LV peak systolic wall stress. The median follow-up period in this study was only 1.5 years, however. Levitt et al. had similar findings. They showed that late subclinical cardiotoxicity after moderate doses of anthracycline is not alleviated by six-hour infusions [64].

Other patient characteristics may also be risk factors but are not as well documented. In the previously discussed review of children treated on POG protocols from 1974–1990, African-American race was associated with a higher risk of early cardiotoxicity [35]. This link is consistent with the increased morbidity and mortality found in patients of African American ancestry with other forms of cardiomyopathy [60]. However, few studies have examined the effect of racial and ethnic differences in cancer-related cardiotoxicity. Children with certain types of cancers, including Ewing's sarcoma [59], acute nonlymphoblastic leukemia and T-cell leukemia, appear to have an increased risk of cardiotoxicity [42]. This is likely the result of the higher doses of anthracycline used to treat these malignancies. The risk of cardiotoxicity is also higher in children with trisomy 21, even when children with congenital cardiovascular malformations are excluded [65].

10.2.2 Radiation

The functional and structural complexity of the heart is mirrored by the variety of radiation injuries that can occur (Table 10.2). A classification system modi-

Table 10.5. Risk factors for the different manifestations of radiation induced heart disease

Risk factor	Peri-carditis	CM[a]	CAD[b]	Arrhyth-mia	Valvular disease	All causes CD[c]	Reference
Total dose; (>30–35 Gy)	X[d]	X	X	X	X	X	[21, 32, 73, 99]
Fractionated dose; (≥ 2.0 Gy a day)	X	X	X	Likely[e]	Likely	X	[21]
Volume of heart exposed	X	X	X	Likely	Likely	X	[21]
Relative weighting of radiation portals and thus how much radiation is delivered to different parts of the heart and not using subcarinal blocking	X	X	X	Likely	Likely	X	[21, 70]
The presence of tumor next to the heart	X	–[f]	–	–	–	–	[21]
Younger age at exposure	–	X	X	Likely	Likely	X	[21, 48, 70, 141]
Increased time since exposure	–	X	X	X	X	X	[32, 70, 104, 153]
Type of radiation source	X	X	X	Likely	Likely	X	[21]
Use of adjuvant cardiotoxic chemotherapy	–	X	–	X	X	X	[21]
The presence of other known risk factors in each individual such as current age, weight, lipid profile, and habits such as smoking	–	–	X	–	–	X	[21, 26, 73]

– a: CM = cardiomyopathy; b: CAD = coronary artery disease; c: CD = cardiac death; d: X = associations of specific risk factors with specific presentation; e: likely = unknown but likely association; f: – = No known association

fied from Fajardo and Stewart [23] includes: acute pericarditis during irradiation (rare and associated with juxtapericardial tumor); delayed pericarditis that can present abruptly or as chronic pericardial effusion; pancarditis, which includes pericardial and myocardial fibrosis, with or without endocardial fibroelastosis (only after large doses); myopathy in the absence of significant pericardial disease; CAD, usually involving the left anterior descending artery; functional valve injury; and conduction defects. Several parameters (Table 10.5) must be considered in the evaluation of radiation injuries, including: relative weighting of the RT portals and, thus, the amount of radiation delivered to different depths of the heart; the presence of juxtapericardial tumor; volume and specific areas of the heart irradiated; total and fractional radiation dose; the presence of other risk factors – such as age, weight, blood pressure, family history, lipoprotein levels and habits such as smoking – and the administration of specific chemotherapeutic agents.

After anterior weighted radiotherapy to the mediastinum, the rate of hemodynamically important cardiac complications was estimated to be between 15 and 30% within a decade [66]. The prevalence of asymptomatic cardiac abnormalities was probably even higher. A recent study by Adams and colleagues [67] evaluated the cardiac status in 48 asymptomatic survivors of childhood or young adulthood Hodgkin's disease who received between 27.0 and 51.7 Gy of mediastinal irradiation (median 40.0) from 1970 to 1991 via relatively modern techniques (equal weight-

ing of daily treatments, subcarinal blocking, etc.). All but one survivor suffered a significant cardiac abnormality following diagnosis (the median follow-up time was 14.3 years) [67]. It is noteworthy that anteriorly- weighted techniques and RT doses above 25 Gy are seldom used in the current treatment of children with Hodgkin's disease.

10.2.2.1 Coronary Artery Disease and Mortality from All Cardiac Causes

Numerous studies demonstrate that Hodgkin's disease (HD) survivors treated with mediastinal irradiation have an increased risk of fatal CVD [68–71]. Relative risk estimates for all survivors range from 2.2–7.2, compared with age and gender-matched controls from the general population [68–70]. The absolute excess risk of fatal cardiovascular disease is 11.9–48.9 per 10,000 patient years, depending upon patient characteristics [70]. This increased risk becomes statistically significant 5–10 years after radiotherapy [71, 72], and is largely due to fatal myocardial infarctions [70].

Myocardial infarction (MI) may be the most important cardiac concern for survivors treated with radiotherapy since the 1970s. While risk of death from cardiac causes other than myocardial infarction has decreased with the use of subcarinal blocking, the incidence of fatal MI has not changed significantly. This was demonstrated by a study of 2,232 HD patients treated at Stanford during 1960–1991. The study showed that the relative risk of non-MI cardiac death decreased from 5.3 to 1.4 with subcarinal blocking, while the relative risk for fatal MI did not change significantly [70]. This might be explained by the continued exposure of the proximal coronary arteries to radiation despite the protection to the base of the heart afforded by the subcarinal blocking.

The risk of thoracic irradiation should be considered in the context of other cardiovascular risk factors, but information on the prevalence of risk factors in comparison populations is generally lacking. One report that did assess other risk factors [26] demonstrated that patients experiencing an MI also had a higher frequency of elevated cholesterol, tobacco use and obesity than the US population as a whole. In fact, each survivor with an event had at least one other known cardiac risk factor [26]. Unfortunately, risk factor information for those without events was not gathered, so further analysis was not possible. Glanzmann et al. [73] evaluated patients with HD for the risk of fatal myocardial infarction associated with modern techniques of mantle irradiation in the context of known cardiac risk factors: smoking, hypertension, obesity, hypercholesterolemia and diabetes. The total group of survivors had a significantly higher-than-expected incidence of fatal myocardial infarctions and/or sudden death at a mean follow up of 11.2 years (the relative risk of myocardial infarctions alone was 4.2, and the relative risk of either outcome was 6.7). The risk of cardiac events in patients without other known cardiovascular risk factors, however, was not significantly different from that of the age-matched population. This underscores the fact that radiotherapy is only one of several risk factors for cardiovascular disease.

Nevertheless, case reports [25, 74–77] and studies of acute myocardial infarction in young survivors of chest radiotherapy, presumably without other known risk factors, suggest that mediastinal irradiation alone may be sufficient to increase the likelihood of fatal coronary artery disease. Fatal myocardial infarctions have occurred in children as young as 12 years of age after mediastinal radiotherapy [76]. Survivors of childhood (<21 years of age) HD treated between 1961 and 1991 suffered fatal myocardial infarctions 41.5 times more frequently than the age-matched general population [71]. Deaths occurred 3–22 years after therapy. These deaths were limited to those exposed to ≥ 42 Gy of irradiation but 71% of this cohort received ≥ 40 Gy. Although it is uncommon to treat children today with >25–30 Gy, it is unclear whether limiting exposure has impacted the rate of fatal MI in HD survivors [70, 78]. Whatever the case may be with respect to current treatment protocols, the many HD survivors who were treated successfully with the higher doses remain at risk for cardiovascular sequelae.

10.2.2.2 Pericarditis

Historically, pericarditis was the most common sequelae of radiotherapy to the chest, occurring in 20–40% of Hodgkin's disease patients [79–81]. However, reports from one center employing modern techniques – including equally-weighted anterior and posterior fields, daily fraction sizes of 2.0 Gy or less and subcarinal blocking – showed a decrease in the frequency of pericarditis from 20% to 2.5% [80]. Pericarditis can remain clinically silent, or it can present with sudden onset of fever, dyspnea, pleuritic chest pain and/or friction rub, as well as its typical signs of ST and T wave changes and decreased QRS voltage. Early, acute-onset pericarditis occurs during radiotherapy and is usually associated with a large tumor contiguous with the heart. It is thought to be a reaction to necrosis of the tumor and does not have long-term consequences. Delayed pericarditis occurs four months to several years after radiotherapy, although mostly within the first year. Two overlapping forms are seen: delayed acute pericarditis and delayed chronic pericardial effusion. The former presents as described above and may have recurrences. About half of these patients will develop some degree of tamponade, presenting with paradoxic pulse or Kussmaul's sign. Delayed chronic pericardial effusion is usually asymptomatic and is discovered by routine chest radiography revealing an enlarged cardiac silhouette, although a minority will present in tamponade (paradoxical pulse, Kussmaul's sign). Most effusions clear spontaneously in 1–10 months, but it may take up to two years. About 20% of those with delayed pericarditis develop chronic and/or constrictive pericarditis 5–10 years after therapy. The risk for developing chronic pericarditis is substantially greater if pericardial effusion was present previously [82]. Chronic effusive-constrictive pericarditis develops in 10–15% of these patients and may necessitate pericardectomy. Chronic pericarditis can also develop without antecedent acute pericarditis 5–10 years after irradiation [21, 83, 84]. Pancarditis is severe pericarditis combined with significant myocardial fibrosis. This rare complication probably results from at least 60 Gy of irradiation to the mediastinum. Most of these patients have severe, intractable congestive heart failure.

10.2.2.3 Cardiomyopathy

Radiation can cause long-term diastolic and systolic left ventricular dysfunction [85]. This differs from the common, acute transient decrease in ejection fraction that occurs soon after therapy. The relationship between acute and long-term changes is unknown [85]. The predominate characteristics of the long-term changes primarily depend upon concurrent chemotherapy and the prior condition of the heart. Restrictive cardiomyopathy, characterized by diastolic dysfunction, is more common in survivors who have not received an anthracycline [86]. In contrast, dilated cardiomyopathy, characterized by systolic dysfunction, is more common in those who also received an anthracycline.

While clinically evident heart failure is rare in survivors treated with radiotherapy alone, subclinical changes are common and may be progressive. The prevalence varies, depending upon treatment, length of follow-up and method of screening. In a series of 21 asymptomatic adults treated with 20–76 Gy (mean 35.9 Gy) for HD prior to 1983, 57% had an abnormal left and/or right ventricular ejection fraction 7–20 years after treatment (the mean was 14.1 years) [87]. However, these survivors were largely treated with RT techniques considered suboptimal by current standards. For patients treated with modern radiotherapy techniques, the outlook appears improved. Constine et al. [88] evaluated 50 HD survivors who had been treated using modern techniques with 18.5–47.5 Gy (mean: 35.1 Gy) 1–30 years previously (mean: 9.1 years). The results of radionuclide ventriculography revealed that 4% had an abnormal left ventricular ejection fraction and 16% had an abnormal peak filling-rate (which is an indirect measure of diastolic function). Recent studies in survivors of left-sided breast cancer who received adjuvant irradiation also suggest restrictive cardiomyopathy. From these studies it may be inferred that diastolic dysfunction is the primary problem in those who receive radiotherapy to the chest [89, 90]. Overall, the studies suggest that, although diastolic dysfunction associated with chest radiotherapy continues to occur, modern techniques appear to have decreased the rate of systolic dysfunction. The concern is that diastolic dysfunction may

worsen over time and could lead to congestive heart failure [30, 91].

Reports from the 1970s [8, 92–94] first suggested that radiation to the heart in conjunction with anthracycline therapy was associated with greater cardiac toxicity than either modality alone. As previously noted, radiation and anthracyclines damage the myocardium through different pathophysiological mechanisms. In rabbits, the combined effects of radiation and doxorubicin are additive, not synergistic [95]. Studies of long-term childhood cancer survivors [96, 97] and breast cancer survivors [98] have confirmed that combined therapy affects left ventricular systolic function and mortality more significantly than either alone.

10.2.2.4 Valvular Disease

Valvular abnormalities are frequent in survivors of HD treated with mediastinal radiotherapy. Valvular insufficiency seems to be more common, but stenosis is of greater hemodynamic significance, sometimes requiring intervention [32]. In prospective studies of survivors treated with radiotherapy, the frequency of left-sided valvular regurgitation of grade 1 or greater has ranged between 16–40% [99–101]. The largest study to date, which screened 90% of eligible subjects, demonstrated a 24% frequency of left-sided regurgitation in the 116 HD survivors treated with chest radiotherapy +/– chemotherapy between 1980 and 1988, 5–13 years after therapy [101]. This rate of left-sided regurgitation was dramatically higher than the 2% reported in the control population, although the difference was not statistically tested and a comparison of the two groups was not provided. Lipshultz and colleagues also demonstrated that the frequency of aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation in HD survivors treated with modern techniques are each greater than expected in an age-and gender-matched normal population [102]. Except for this last study, given the length of follow-up, most data suggest that a threshold dose for valvular regurgitation is approximately 30 Gy.

Radiation-associated valvular disease appears to be progressive. A review of 38 cases calculated a mean interval to asymptomatic valvular dysfunction of 11.5 years post-therapy, while the mean time to diagnosing symptomatic dysfunction was 16.5 years post-therapy [32]. The one patient for whom annual echocardiograms were available demonstrated progressive thickening of the aortic and mitral valves with development of tricuspid regurgitation. It appears that continued hemodynamic stress increases the likelihood that radiation-associated damage will progress. Signs and symptoms are no different from those of patients in the general population with valvular abnormalities.

Despite the clinical observations suggesting an association between radiation and valvular disease, there is no pathophysiologic mechanism to directly link radiation and valvular disease. Valves in the heart do not have blood vessels so the best understood mechanism of radiation injury does not apply. Furthermore, experimental models of radiation-induced heart disease do not demonstrate valvular lesions. Nevertheless, the literature in humans indicates that valvular disease is increased in survivors of cancer treated with mediastinal radiation [30].

10.2.2.5 Dysrhythmia/ Conduction Abnormalities

Life-threatening arrhythmia and conduction disturbances are rare and occur years after radiation exposure. They are different from the frequent, asymptomatic, nonspecific and transient repolarization abnormalities seen shortly after irradiation [50]. Serious abnormalities reported after radiotherapy include atrioventricular nodal bradycardia, all levels of heart block – including complete heart block [103, 104] – and sick sinus syndrome [66, 104]. In their case series report and review of the literature, Orzan et al. [103] reported that infranodal blocks were more common than nodal blocks, and that right bundle branch block was one of the most common abnormalities. Many, but not all, of the reports reviewed by Orzan, however, involved survivors who had received RT with techniques and doses no longer in use. Unfortunately, only a few prospective studies have reported the incidence of conduction abnormalities. In a study of 134 survivors of childhood cancer treated

with anthracyclines and/or chest irradiation, ventricular tachycardia was significantly greater in those treated with chest radiotherapy than in a group of historical controls, at a mean 5 years after therapy [50]. This increased rate was not seen in those treated with anthracycline without radiotherapy. The frequency of QTc >0.44 seconds was 12.5% in those treated with chest irradiation alone and 18.9% in those treated with irradiation and anthracyclines.

Persistent tachycardia at a fixed rate and loss of circadian variability in heart rate may be common in survivors of childhood HD treated with chest irradiation [67]. This picture is similar to cardiac transplant patients who have a denervated heart. It suggests that there may be autonomic nervous system dysfunction in HD survivors treated with mediastinal radiotherapy, which could lead to the decreased perception of anginal chest pain observed in some of these patients [105]. Symptoms from conduction abnormalities are uncommon but range from palpitations to syncope to sudden death. However, conduction delays, which produce symptoms, rarely occur without some other injury to the heart associated with irradiation [103].

10.3 Detection and Screening

Long-term survivors of childhood cancer who have received potentially cardiotoxic therapies should undergo regular, repeated evaluations of cardiac status, even if the patient is asymptomatic. Patients at highest risk include (but may not be limited to) those who have received anthracyclines, high-dose cyclophosphamide (typically, only those who received it in preparation for bone marrow transplant), and cardiac irradiation (mediastinal, mantle, and possibly spinal, whole lung and left renal bed). Although screening regimens have been suggested for patients treated with doxorubicin and/or irradiation [30, 91, 106, 107], no specific regimen for childhood cancer survivors has ever been tested for efficacy and cost effectiveness. Nevertheless, serial evaluation recognizes the following:

1. As the survivor grows and matures, demands on the heart increase, which a damaged heart at some point may no longer be able to meet;
2. Lifestyle changes may further stress the heart;
3. Cancer therapy-related heart disease may itself be progressive.

Furthermore, survivors need to be screened as they undertake or contemplate changes in their life that increase the workload of the heart, such as beginning a new exercise program, starting growth hormone therapy, becoming pregnant or undergoing anesthesia. Clearly, those patients who have had an abnormal study or a symptomatic cardiac event at any time should have more frequent cardiac screening. The importance of screening all survivors treated with potentially cardiotoxic therapy is underscored by the fact that Lipshultz and colleagues could not find a correlation between patient- or parent-reported symptoms and measures of LV function or exercise tolerance in those treated for ALL with doxorubicin with or without chest irradiation [11].

While the broad range of cancer therapy-related cardiac abnormalities makes it potentially necessary to use multiple diagnostic modalities, cardiac evaluation of the survivor should first begin with a thorough history and physical. The fact that self-reported symptoms without specific questioning do not necessarily correlate well with cardiovascular abnormalities detected by specialized testing makes it essential that information be determined by specific, quantitative parameters (e.g. "Can you walk up two flights of stairs without becoming short of breath?"). Because the manifestations of late anthracycline-related cardiotoxicity include congestive heart failure and arrhythmias, changes in exercise tolerance, dyspnea on exertion, palpitations and syncope should all be evaluated by some screening modality. The history should not only evaluate risk from therapy, but also traditional CVD risk factors (smoking, blood pressure, family history, etc.). Worrisome findings on physical examination include tachypnea, tachycardia, extra heart sounds, rales, hepatomegaly, peripheral edema, diminished peripheral pulse volume and perfusion, any of which is suggestive of congestive failure.

10.3.1 Assessment of Myocardial and Valvular Function

The most common screening methods for anthracycline-associated cardiomyopathy are echocardiograms, radionuclide ventriculography – also commonly referred to as radionuclide angiography (RNA) – and electrocardiograms. These methods are also useful for screening for radiation-associated cardiotoxicity with subtle differences. Echocardiography and RNA are both excellent methods of measuring left ventricular systolic function, but echocardiography has the advantage over RNA of being noninvasive. Echocardiography also has the advantage of being able to evaluate heart structures such as the pericardium and valves. Due to body habitus and bone density, however, trans-thoracic echocardiography is frequently of poor quality in adults.

Fractional shortening (FS) and ejection fraction are reliable echocardiographic measures of left ventricular systolic function. FS is the percentage of change in left ventricular dimension between systole and diastole. Both measurements, however, are dependent on loading conditions, which may vary considerably, particularly during chemotherapy [108, 109]. Load- independent measures of myocyte health and myocardial function can be provided by measurements of wall stress and contractility, i. e. the relationship between wall stress and the heart rate corrected velocity of circumferential fiber shortening [109]. Additionally, anatomic measurements such as posterior wall thickness and left ventricular dimension are useful. Current monitoring recommendations include obtaining echocardiograms of these measurements at regular intervals after therapy [106]. The recommended monitoring interval depends on the cumulative anthracycline dose, other therapies received, the detection of abnormalities, any symptoms the patient may experience and co-existent stressors, such as growth or participation in competitive athletics.

Radionuclide ventriculography determines an ejection fraction that is arguably more accurate than that derived from echocardiography by calculating the change in radioactivity at end diastole to that at end systole. But this measure is also load-dependent, and no load-independent measure of myocyte health exists for this modality. Although it has been recommended as a baseline study to be repeated every five years in anthracycline-treated children (in addition to more frequent echocardiography [99, 107]), further studies are necessary to determine whether RNA is of clinical value for the entire cohort of asymptomatic patients. It is clearly useful for those in whom a good echocardiogram cannot be obtained, which is frequently the case in adults, due to body habitus and bone density. However, it should be noted that the FS on echocardiography and the ejection fraction on RNA are not directly convertible.

A significant difference in anthracycline and radiation associated cardiomyopathy is the type of cardiac dysfunction caused. Although otherwise quite different from other types of dilated cardiomyopathy [128], anthracycline-associated cardiomyopathy resembles dialated cardiomyopathy, because it primarily causes systolic dysfunction. Radiation causes restrictive cardiomyopathy which primarily leads to diastolic dysfunction (i.e. problems with filling the heart). (Restrictive cardiomyopathy may cause systolic dysfunction, but only in its terminal stages.) Both conditions, however, can cause heart failure in the long term. Therefore, it is important to screen for both with the hope that early intervention can delay or prevent heart failure. The problem is that measuring diastolic function noninvasively can only be done through imprecise echocardiographic techniques. In addition to measuring left ventricular (LV) wall-stress, LV fractional shortening and LV wall thickness, we recommend measuring LV mass and LV chamber size, which, if abnormal, may suggest restrictive cardiomyopathy. We also recommend measuring the ratio of peak early filling to peak late filling of the left ventricle (E/A ratio) and other indirect echocardiographic indicators of diastolic function. Echocardiography is also useful for following valvular and pericardial status.

10.3.2 Assessment of Dysrhythmias/ Conduction Abnormalities

Electrical conduction abnormalities and rhythm disturbances may remain silent until fatal. Pertinent ECG findings include prolonged corrected QT inter-

val, atrioventricular conduction delay, ventricular ectopy, low voltage, second-degree AV block, complete heart block, ventricular ectopy, ST elevation (or depression) and T wave changes.

Long term survivors treated with cardiotoxic therapy with left ventricular dysfunction often have 24-hour continuous ECG monitoring performed. How often it should be repeated in asymptomatic survivors without any other abnormalities on cardiac screening is unclear. Steinherz and colleagues have recommended performing 24-hour ECG every five years in long terms survivors who had received anthracyclines, but no formal study backs this recommendation [107].

10.3.3 Assessment of Coronary Artery Disease Risk Factors

All childhood cancer survivors should be screened regularly for coronary artery disease (CAD) risk factors. While those treated with mantle radiation are probably most at risk for CAD, survivors treated with anthracyclines and high-dose cyclophosphamide are also likely to have damaged hearts that can ill afford further damage from a myocardial infarction. Patients who received brain irradiation, especially those with proven growth hormone deficiency or other hypothalamic-pituitary axis dysfunction, may also be at higher risk, compared with other survivors. Risk factors for CAD, such as family history, hypertension, smoking, hyperlipidemia, obesity, diabetes mellitus and a sedentary life-style, should be evaluated at each long-term visit. Counseling to reduce such risk factors is not only appropriate, it is extremely important. Signs and symptoms of pericarditis (fever, dyspnea, pleuritic chest pain, friction rub, ST and T wave changes, decreased QRS voltage), cardiomyopathy, valvular disease (new murmur), arrhythmia (palpitations, syncope) and CAD (left arm and chest pain, diaphoresis, dyspnea) should all raise concern. As in other children, chest pain is usually due to costochondritis (Tietze's syndrome) in young survivors and is characterized by point tenderness, discomfort with inspiration and response to nonsteroidal analgesics. However, because of the sharply increased risk of myocardial infarction in survivors treated with mediastinal irradiation, myocardial infarction should be ruled out in any such patient who presents acutely. Although the possibility of myocardial ischemia is strongly suggested by crushing pain (especially with exercise), diaphoresis, dyspnea and nausea, the absence of these symptoms does not necessarily warrant clearing a survivor. This is because chest irradiation may cause individuals to feel cardiac pain abnormally [105]. Complaints of chest pain, even in young survivors treated with mediastinal irradiation, therefore require additional evaluation.

10.3.4 Exercise Stress Testing

ECHO and ECG exercise testing have been shown to reveal cardiac injury that is not discernible in resting studies [49, 52, 110]. Although more research is required to determine the appropriate use of such studies in chemotherapeutic- or radiation-associated cardiovascular disease [91], it is likely that these tests will be of good predictive value, especially since anthracycline-treated and/or cardiac- irradiated patients appear to decompensate at times of cardiac stress. Exercise stress testing also provides the opportunity to measure maximum oxygen consumption. This parameter is a key prognostic indicator in patients with cardiomyopathy [111]. We, and others, have noticed it to be surprisingly low in long-term survivors of childhood cancer treated with anthracyclines and/or mediastinal radiotherapy [67].

Screening tests for measuring the indirect effects on the cardiovascular system should also be performed periodically. In particular, pulmonary and thyroid function tests should be performed for those at risk for these abnormalities (as a result of e.g. bleomycin, chest irradiation).

10.3.5 Invasive Procedures

In all survivors treated with potentially cardiotoxic therapies, angiography and cardiac catheterization are appropriate for evaluating symptomatic disease (angina and heart failure, respectively). They are not appropriate for routine serial screening in the asymptomatic survivor. According to some experts, however, these procedures should be performed if

any clinically significant cardiac lesion is found, due to the fact that CAD can be asymptomatic and is often present in those who received mediastinal irradiation [112].

10.3.6 Recommendations from Personal Experience

Although data do not exist to support definitive recommendations on test frequency, the Children's Oncology Group suggests screening survivors for cardiovascular abnormalities on a regular basis [106]. One author (S.E.L.) follows survivors of childhood malignancy exposed to anthracyclines and/or mediastinal irradiation on a regular basis (usually, every one to two years) [113]. Echocardiography is performed to assess systolic and diastolic function, valvular and pericardial abnormalities and coronary flow. Serial ECG, Holter monitoring and exercise stress testing are often performed. These tests assess for the prevalence of high-grade ectopy, conduction defects, ischemia and abnormal hemodynamic response to exercise. Lipid profiles, CAD risk profile and thyroid function screening are also usually performed annually on at-risk patients. Pulmonary function tests are performed periodically. Radionuclide angiography is not performed regularly unless a high quality echocardiogram cannot be obtained.

10.4 Preventive Measures

10.4.1 During Therapy

Prevention is the "best treatment" for cardiovascular sequelae. Many treatment protocols now address the dose of cardiotoxic therapy. The treating physician must also monitor the individual's cardiac studies closely for early evidence of enhanced sensitivity, although the specific regimen of monitoring patients while on therapy remains an area of intense debate and research. Other strategies during therapy to prevent long-term cardiac sequelae are still investigational. As discussed above, the method of delivery does not appear to be as promising as was once thought. Replacing conventional anthracyclines with less cardiotoxic analogues or new formulations, such as epirubicin hydrochloride, idarubicin hydrochloride and liposomal anthracyclines is another approach being studied [18]. However, the danger of all these strategies is that the mechanism that protects the heart may also limit antineoplastic efficacy [18].

One approach to preventing or minimizing chemotherapy-induced cardiotoxicity is to add a cardioprotectant. One cardioprotectant that has been proven to be effective in many adult patients is dexrazoxane (Zinecard; Pharmacia & Upjohn, Peapack, NJ) [114, 115]. In a randomized clinical trial of 92 women on the same treatment protocol for advanced breast cancer, dexrazoxane provided significant protection against doxorubicin-induced cardiac toxicity without reducing its antineoplastic effect [114]. Results showed 11 episodes of clinical cardiac toxicity in the control arm and only two in the dexrazoxane arm. In a follow-up study, Speyer et al. concluded that adding dexrazoxane could also allow patients to receive higher cumulative doses of doxorubicin [116]. A similar, but larger, randomized, double-blind trial of 534 patients with advanced breast cancer also demonstrated a significant protective effect, with cardiotoxicity 2.0–2.6 times higher in the group that did not receive dexrazoxane [115]. The most substantial cardioprotective effect was seen at the higher cumulative doses of doxorubicin, but there was a decreased response rate of the breast cancer in one of the trials utilizing dexrazoxane.

Results in children seem promising as well [117–119]. In an open-label, randomized trial involving 38 pediatric sarcoma patients, Wexler et al. [118] showed that dexrazoxane reduced the incidence of short-term subclinical, doxorubicin-induced cardiotoxicity. Eighteen dexrazoxane-treated and 15 control patients were assessed for cardiac toxicity. The study revealed that the dexrazoxane-treated patients were less likely to develop subclinical cardiotoxicity (22% vs 67%, $P<0.01$), despite having received a higher median cumulative dose of doxorubicin (410 vs 310 mg/m^2, $P<0.05$) than control patients. Dexrazoxane-treated patients also had a smaller decline in LV ejection fraction per 100 mg/m^2 of doxorubicin (1.0 vs 2.7 percentage points, $P=0.02$). There were no significant differences in response rate, event-free survival or overall survival. A recent randomized,

multi-centered trial of dexrazoxane in newly diagnosed childhood ALL patients treated with doxorubicin reported a 50% reduction in serum cardiac troponin, indicating significantly reduced acute myocardial injury during therapy [119]. In another study, preliminary results suggest that second cancers are more frequent in those that received dexrazoxane in conjunction with etoposides [120]. Additional clinical trials and longer follow-up are needed to determine whether the short-term cardioprotection provided by dexrazoxane will reduce the incidence of late cardiac complications in childhood cancer survivors, without decreasing survival.

Modern radiotherapy techniques decrease the risk of most radiation-associated cardiac sequelae, but probably do not eliminate them. These modern techniques include 3-dimensional treatment planning, the use of a linear accelerator as the radiation source, equally weighting anterior/posterior portals on a daily basis, the use of a subcarinal block after ≥ 30 Gy and the shrinking field technique. Although permanent complications tend to occur less frequently with a total dose less than 40 Gy, it is not a good idea to systematically limit treatment, since doing so may be inadequate to control disease. Dexrazoxane may also protect against the cardiotoxic effects of radiotherapy, without decreasing therapeutic efficacy.

10.4.2 Post Therapy

Heart-healthy lifestyles should be encouraged in all survivors of cancer treated with potentially cardiotoxic therapies [18]. Activities to be encouraged include maintaining a diet low in saturated and trans fats and implementing a regular exercise program in consultation with a cardiologist and exercise physiologist. Obesity is a major preventable coronary risk factor and its prevalence is greater in survivors of pediatric malignancy, especially ALL [121]. Aerobic exercise can produce symptomatic, physiologic and psychological benefits [122–125]. However, it is important for patients to be monitored by exercise testing to ensure they have stable cardiac status before exercise programs are recommended. Isometric exercises such as weight lifting should generally be discouraged until the results of further studies are available. If they are pursued, it should only be under the direct supervision of a cardiologist and exercise physiologist [18]. Rigid dietary restrictions are not necessary, but the American Heart Association dietary recommendations are appropriate for those of school age and older. Cigarette smoking should be emphatically discouraged, because it may further impair left ventricular function, as well as increase the risk of coronary artery disease. Illicit drug use and alcohol consumption can also impair left ventricular function and should be discouraged as well. Since the lifestyle choices that lead to these problems occur early in life, a major focus of annual visits should be to encourage aerobic exercise and a low-fat diet. In addition, all patients should be educated about the cardiotoxic risks of their treatments, and, when appropriate, about the need for lifelong monitoring of heart function and coronary artery disease risks.

In terms of cholesterol-lowering medications, the recently revised NCEP recommendations provide a well thought-out minimum of care that should be provided for the screening and treatment of increased risk for coronary artery disease [126]. Mediastinal radiotherapy should be considered as an independent risk factor in determining whether an individual's lipid profile suggests the need for treatment. A decision to use medication should be made in consultation with a preventive cardiologist, who ideally should follow the patient at least initially. Based on their increased risk, survivors treated with chest and brain irradiation should be screened with a fasting lipid profile soon after completion of their therapy and on a periodic basis throughout their lives. Screening tests for the indirect effects on the cardiovascular system should also be performed periodically – in particular, for pulmonary function and thyroid function.

10.5 Management of Established Problems

In large part, the management of a manifestation of cancer therapy-related cardiotoxicity is similar to, or the same as, the management of the same condition in the general population [91]. This is probably because the particular disease process, although precip-

itated by a different agent, is the same. But it is also due to the fact that randomized clinical trials targeted at childhood cancer survivors have not been, and are unlikely to be, performed to ascertain cardiac outcomes [127]. Any patient diagnosed with a specific problem needs to be referred to a cardiologist familiar with the cardiotoxicity of cancer therapy for management and ongoing follow-up. Ideally, such a cardiologist should be providing the regular screening discussed in the above section.

10.5.1 Cardiomyopathy, Congestive Heart Failure and Ventricular Arrhythmia

As signs and symptoms of congestive heart failure become evident, therapy clearly becomes necessary. The need to treat survivors with abnormal afterload, contractility and/or fractional shortening, but without symptoms, is less clear. While theoretically advisable to prevent progression, one of the most useful medication classes, angiotensin-converting enzyme (ACE) inhibitors, also appear to decrease the heart's normal growth [127]. Additionally, little is known about most of the medications in this class in regard to development or teratogenicity. There also are no proven long-term benefits to ACE inhibitor therapy in this population [127, 128]. Nevertheless, for reasons to be discussed below, ACE-inhibitor therapy should be considered for survivors with congestive heart failure, as well as for those with asymptomatic changes on their echo, especially if these changes are progressive. Other useful medications include beta-blockers, digoxin and diuretics – specifically, spironolactone, a diuretic that recently has proven in randomized clinical trials to increase survival in congestive heart failure patients [18, 129] although some of these findings are controversal.

Current treatment for subclinical chemotherapy-induced cardiomyopathy, as well as symptomatic congestive heart failure, focuses on correcting the underlying abnormalities, such as increased afterload and decreased contractility. Therapy often includes treatment with angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers that may delay subclinical abnormalities from deteriorating to symptomatic heart failure [18, 130]. Afterload reduction treatment with ACE-inhibitors, such as captopril and enalapril, may alter the course of progressive ventricular dysfunction for patients with or without symptomatic heart failure. In a randomized study of post-myocardial infarction patients with mild to moderate systolic dysfunction, captopril decreased overall mortality by 19 % [131]. A prospective study of 18 doxorubicin-treated, long-term survivors of childhood cancer on enalapril demonstrated improvement that lasted 6–10 years in patients with asymptomatic left ventricular dysfunction and 2–6 years in patients with congestive heart failure [132]. While encouraging in the short-term, the improvement proved only temporary, with decline eventually reoccurring in all patients [132]. This reinforces the theoretical concern, touched on above, about the chronic use of ACE-inhibitors in children with anthracycline-induced thinning of the left ventricular walls. ACE-inhibitors may limit cardiac growth potential by inhibiting cardiac growth factors, and this can result in further thinning of left ventricular walls relative to body surface area, with a subsequent increase in afterload [18]. This concern should be carefully discussed with patients, but should not preclude the use of ACE-inhibitors.

Beta-blockers have been demonstrated to significantly improve the quality of life and to extend the life of patients with congestive heart failure [133–137]. The use of beta-blockers may also be effective in improving the heart function of doxorubicin-treated, long-term survivors of childhood cancer. One study has shown that the left ventricular ejection fraction of patients with doxorubicin-induced cardiomyopathy improved from 28–41 % after treatment with beta-blockers [130]. The effect was similar to the effect in idiopathic cardiomyopathy patients [130].

Treatment for symptomatic chemotherapy-induced cardiomyopathy focuses on providing symptomatic relief and preventing the progression of the underlying abnormalities. However, many anthracycline-treated, as well as mediastinal radiotherapy-treated, long-term survivors with late congestive heart failure have a restrictive cardiomyopathy. As a result, patients may be more severely affected than

their history and physical examination suggest [40]. Careful early invasive assessment of hemodynamics, followed by aggressive, tailored pharmacologic therapy and early heart transplantation, has been beneficial. However, before transplantation is considered, all reversible factors should be treated and the medical regimen should be optimized. Heart transplantation is an option for patients with end-stage cardiac failure, where the goal of transplantation is to improve functional capacity, quality of life and length of life. Rejection is no more likely in cancer survivors than in other transplant patients [138]. Cancer survivors require no significant modification of immunosuppression, and their 2-year survival rate is similar to that of other recipients [138]. The absolute and relative contraindications to this approach include any major systemic condition with the potential to further deteriorate on immunosuppression, recently-treated cancer (not yet reaching 5-year, event-free survival), active rheumatologic disease or any condition that would limit the potential for full rehabilitation, such as cognitive impairment, psychiatric instability, alcohol or drug abuse and repeated non-compliance [18]. The long-term prognosis for patients with advanced heart failure who are treated medically is worse than the extended prognosis for those who undergo transplantation. Unfortunately, the inadequate supply of donor organs, the cost of post-transplant care and the finite lifespan after transplantation require that indications for transplantation be based on the 1- to 2-year prognosis [18, 139]. As further information is obtained regarding troponin and other biochemical markers, and as advancements are made in imaging modalities, the recommendations for screening for transplantation may change [140]. Additional research into cardiotoxicity in long-term survivors should also allow evidence-based studies of lifestyle and medical interventions for preventing and treating cardiomyopathy.

All patients with cardiomyopathy are at risk for ventricular arrhythmias and conduction abnormalities. All such patients should undergo 24-hour ECG monitoring on a regular basis. If arrhythmias are occurring, anti-arrhythmic agents or a pacemaker may be necessary. Pacemakers may be a better option, given that many of the medications used to treat arrhythmias can also depress myocardial function or interfere with other medications.

10.5.2 Coronary Artery Disease

A cardiologist should follow all patients with known coronary artery disease (CAD). Clinical evaluation includes both the regular workup for CAD and a full evaluation to look for other manifestations of cancer therapy-related cardiotoxicity. In the general workup for CAD, resting ECG and ECHO are performed, as well as an ECG stress test (with or without an imaging study with exercise). The presence of ischemic changes and exercise-induced arrhythmias can be detected by an ECG stress test. However, ECG changes on a stress test may not correlate well with the presence of CAD in an already-damaged myocardium. As a result, in addition to the ECG stress test, an imaging study such as RNA or echocardiography may be needed to directly visualize areas of ischemic myocardium or abnormal wall motion that may indicate clinically significant CAD. A problem with RNA is that it lacks the specificity to differentiate ischemic myocardium due to the initial radiation damage from that of other causes. Cardiac catheterization may also be necessary.

Not only are thoracic-irradiated survivors probably most at risk for CAD, they also require some special considerations in their surgical treatment, if and when surgery becomes necessary. Coronary artery bypass surgery may be a better option in this population to relieve acute coronary blockage than percutaneous transluminal coronary angioplasty (PCTA). Complications during PCTA may require placing an emergency coronary artery bypass graft, but under emergent conditions, coronary bypass can be especially difficult due to fibrosis in the mediastinum. Stent results are lacking. Several studies report good long-term results with non-emergent bypass surgery in this population [25, 141, 142].

Irradiated survivors should be screened preoperatively by echocardiography and pulmonary function testing because of the high frequency of coexistent pulmonary dysfunction and valvular problems – 40% in one report [143]. Consideration should be given to repairing comorbidities, even if they are not

severe enough on their own to require intervention. The reason is because repeat surgery can be more difficult in these patients than in general, due to increased fibrosis in the chest [143]. Carotid stenosis should be screened for as well, if the neck was exposed to significant irradiation. Anterior pericardiectomy should be routinely considered with the initial operation on the heart, whether or not there is a thickened pericardium [141]. The choice of bypass graft should be carefully decided, because arterial grafts maintain their patency better than venous grafts but are more likely to have been damaged by irradiation. Despite this concern, internal mammary and thoracic arteries have been used successfully for grafts in this population [142–145].

10.5.3 Valvular Disease

The clinical significance of valvular disease is highly variable. Mild to moderate tricuspid or pulmonary valve regurgitation is often well tolerated. Degeneration of mitral or aortic valves, however, may lead to congestive heart failure and death. All patients with evidence of valvular insufficiency need antibiotic prophylaxis prior to dental or surgical procedures to decrease the risk of bacterial endocarditis. Frequent follow-ups by a cardiologist are necessary to evaluate the type and timing of interventions. Surgical intervention carries the same caveats mentioned above in regards to CAD surgeries. In contrast to earlier reports that patients with radiation-associated valve disease did not do well with surgery [32], a more recent report suggests that patients do well even when valve repair is performed concurrently with coronary artery bypass [146].

10.5.4 Pericarditis

Over half of patients require no treatment for acute pericarditis and another 40% respond to bed rest, nonsteroidal anti-inflammatory medications and mild diuretics. Asymptomatic effusions can be followed while awaiting spontaneous resolution, which may take up to two years. Chronic effusions that cause symptoms and/or hemodynamic abnormalities of cardiac compression should be treated with pericardiectomy instead of pericardiocentesis [147]. Pericardiectomy may decrease the likelihood that radiation-associated effusions will evolve into constrictive pericarditis. Waiting until constriction is present risks greater mortality due to acute dilatation and heart failure. If tamponade is present, pericardiocentesis should be performed under local anesthesia just before pericardiectomy, because of the high risk of general anesthesia in this situation. Treatment is usually successful unless myocardial fibrosis or constrictive pericarditis is present, in which case the prognosis is poor. Hypothyroidism should be excluded prior to surgery, because it is common after mantle irradiation and may cause a chronic effusion. Pericardial fluid and pericardium should be analyzed to exclude infectious agents or tumor invasion.

10.5.5 Other Problems

Autonomic dysfunction may result in hemodynamic instability. For example, induction of general anesthesia in anthracycline-treated patients has been associated with ventricular arrhythmias. Anesthesiologists should be made aware of the patient's prior history and the associated risks [148]. Similarly, ideal care of a woman of reproductive age includes the involvement and education of her obstetrician. Although many cancer patients have tolerated pregnancy and childbirth well, cardiac consultation should be sought prior to pregnancy. Close monitoring throughout pregnancy may be necessary.

All of our patients are pioneers. The cytostatic therapies that cured their cancers may have caused cardiac damage. Careful long-term surveillance, early diagnosis and prompt treatment will allow each patient the maximum opportunity to lead a productive and healthy life.

Acknowledgements. Supported by the National Heart, Lung and Blood Institute (HL70930), National Cancer Institute (CA-79060), and the University of Rochester, James. P. Wilmot Foundation.

References

1. Mertens AC, Yasui Y, Neglia JP et al. (2001) Late mortality experience in 5-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 19:3163–3172
2. Moller TR, Garwicz S, Barlow L et al. (2001) Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries. J Clin Oncol 19:3173–3181
3. Clark EB (1990) Growth, morphogenesis, and function: the dynamics of heart development. In: Moller JH, Neal WA, Lock JE (eds) Fetal, neonatal, and infant heart disease. Appleton-Century-Crofts, New York
4. Clark EB (1989) Effect of increased ventricular pressure on ventricular growth in stage 21 chick embryo. Am J Physiol 257:1455–1461
5. Fishman NH et al. (1978) Models of congenital heart disease in fetal lambs. Circulation 58:354–364
6. Kim DH et al. (1989) Doxorubicin-induced calcium release from cardiac sarcoplasmic reticulum vesicles. J Mol Cell Cardiol 21:433–436
7. Pratt CB, Ransom JL, Evans WE (1978) Age-related Adriamycin cardiotoxicity in children. Cancer Treat Rep 62: 1381–1385
8. Billingham ME, Bristow MR, Glatstein E et al. (1977) Adriamycin cardiotoxicity: endomyocardial biopsy evidence of enhancement by irradiation. Am J Surg Pathol 1:17–23
9. Billingham ME et al. (1978) Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 62: 865–872
10. Ewer MS et al. (1984) A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol 2:112–117
11. Lipshultz SE, Colan SD, Gelber RD et al. (1991) Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 324:808–815
12. Braverman AC et al. (1991) Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol 9:1215–1223
13. Mills BA, Roberts RW (1979) Cyclophosphamide-induced cardiomyopathy. Cancer 43:223–226
14. Gottdiener JS et al. (1981) Cardiotoxicity associated with high dose cyclophosphamide therapy. Arch Intern Med 141: 753–763
15. O'Connell TX, Berenbaum MC (1974) Cardiac and pulmonary effects of high doses of cyclophosphamide and isophosphamide. Cancer Res 34:1586–1691
16. Watts RG (1991) Severe and fatal anthracycline cardiotoxicity at cumulative doses below 400 mg/m2: evidence for enhanced toxicity with multiagent chemotherapy. Am J Hematol 36:217–218
17. Friedman HS et al. (1990) Glutathione protects cardiac and skeletal muscle from cyclophosphamide-induced toxicity. Cancer Res 50:2455–2462
18. Simbre VC, Adams MJ, Deshpande SS et al. (2001) Cardiomyopathy caused by antineoplastic therapies. Curr Treat Options Cardiovasc Med 3:493–505
19. Pai VB, Nahata MC (2000) Cardiotoxicity of chemotherapeutic agents. Drug Safety 22:263–302
20. Leach J (1943) Effect of roentgen therapy on the heart. Arch Intern Med 72:715–745
21. Stewart JR, Fajardo LF (1984) Radiation-induced heart disease: an update. Prog Cardiovasc Dis 27:173–194
22. Stewart JR, Fajardo LF, Gillette SM et al. (1995) Radiation injury to the heart. Int J Radiat Oncol Biol Phys 31:1205–1211
23. Fajardo LF, Stewart JR, Cohn KE (1968) Morphology of radiation-induced heart disease. Arch Pathol 86:512–519
24. Chello M, Mastroroberto P, Romano R et al. (1996) Changes in the proportion of types I and III collagen in the left ventricular wall of patients with post-irradiative pericarditis. Cardiovasc Surg 4:222–226
25. McEniery PT, Dorosti K, Schiavone W et al. (1987) Clinical and angiographic features of coronary artery disease after chest irradiation. Am J Card 60:1020–1024
26. King V, Constine LS, Clark D et al. (1996) Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol Biol Phys 36:881–889
27. Veinot JP, Edwards WD (1996) Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol 27:766–773
28. Fajardo LF (1977) Radiation-induced coronary artery disease. Chest 71:563–564
29. Corn BW, Trock B, Goodman R (1990) Irradiation-related ischemic heart disease. J Clin Oncol 8:741–750
30. Adams MJ, Lipshultz SE, Schwartz C et al. (2003) Radiation-associated cardiovascular disease: manifestations and management. Semin Radiat Oncol 13:346–356
31. Brosius FC, Waller BF, Roberts WC (1981) Radiation heart disease. Analysis of 16 young (aged 15–33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med 70:519–530
32. Carlson RG, Mayfield W, Normann S et al. (1991) Radiation-associated valvular disease. Chest 99:538–545
33. Steinherz LJ, Wexler LH (1998) The prevention of anthracycline cardiomyopathy. Prog Pediatr Cardiol 8:97–108
34. Jemal A, Thomas A, Murray T et al. (2002) Cancer statistics. CA 52:23–47
35. Krischer JP, Epstein S, Cuthbertson DD et al. (1997) Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group. J Clin Oncol 15:1544–1552
36. Giantris A, Abdurrahman L, Hinkle A et al. (1998) Anthracycline-induced cardiotoxicity in children and young adults. Crit Rev Oncol Hematol 27:53–68

37. Von Hoff DD, Layard MW, Basa P et al. (1979) Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 91:710–717
38. Praga C, Beretta G, Vigo PL et al. (1979) Adriamycin cardiotoxicity: a survey of 1273 patients. Cancer Trt Rep 63: 827–834
39. Lipshultz SE, Sallan SE (1993) Cardiovascular abnormalities in long-term survivors of childhood malignancy. J Clin Oncol 11:1199–1203
40. Lipshultz SE, Sanders SP, Goorin A (1994) Monitoring for anthracycline cardiotoxicity. Pediatrics 93:433–437
41. Lefrak EA, Pitha J, Rosenheim S et al. (1973) A clinicopathologic analysis of adriamycin toxicity. Cancer 32:302–314
42. Grenier MA, Lipshultz SE (1998) Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol 25:72–85
43. Steinherz LJ, Steinherz PG, Tan CT et al. (1991) Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 266:1672–1677
44. Ali MK, Ewer MS, Gibbs HR et al. (1994) Late doxorubicin-associated cardiotoxicity in children: the possible role of intercurrent viral infection. Cancer 74:182–188
45. Steinherz LJ, Steinherz PG, Tan G (1995) Cardiac failure and dysrhythmias 6–19 years after anthracycline therapy: a series of 15 patients. Med Pediatr Oncol 24:352–361
46. Lipshultz SE, Vlach SA, Lipsitz SR, Sallen SE, Schwartz ML, Colan SD. Cardiac changes associated with growth hormone therapy in children treated with anthracycline. (Pediatrics. In press, 2004)
47. Davis LE, Brown CE (1988) Peripartum heart failure in a patient treated previously with doxorubicin. Obstet Gynecol 71:506–508 (abstract)
48. Lipshultz SE, Lipsitz SR, Mone SM et al. (1995) Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 332:1738-1743
49. Larsen RL, Barber G, Heise CT et al. (1992) Exercise assessment of cardiac function in children and young adults before and after bone marrow transplantation. Pediatrics 89:722-729
50. Larsen RL, Jakacki RI, Vetter VL et al. (1992) Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults. Am J Cardiol 70:73–77
51. Green DM, Grigoriev YA, Nan B et al. (2001) Congestive heart failure after treatment for Wilms' Tumor: A report from the National Wilms' Tumor Study Group. J Clin Oncol 19:1926–1934
52. Schwartz CL, Hobbie W, Truesdell S et al. (1993) Corrected QT interval prolongation in anthracycline-treated survivors of childhood cancer. J Clin Oncol 11:1906–1910
53. Jakacki RI, Larsen RL, Barber G, Goldwein JW, Silber JH. Cardiac function following cardiotoxic therapy during childhood assessing the damage. In Cardiac Toxicity after Treatment for Childhood Cancer. Eds. Bricker JT, Green DM, D'Angio GJ. NY, NY: John Wiley & Sons, 1993:87–94
54. Bender KS et al. (1984) QT interval prolongation associated with anthracycline cardiotoxicity. J Pediatr 105:442–444
55. Bristow MR, Mason JW, Billingham ME et al. (1978) Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy and cardiac catheterization. Ann Intern Med 88:168–175
56. Cortes EP, Lutman G, Wanka J et al. (1975) Adriamycin (NSC-123127) cardiotoxicity: a clinicopathologic correlation. Cancer Chemother Rep 6:215–225
57. Dearth J, Osborn R, Wilson E et al. (1984) Anthracycline-induced cardiomyopathy in children: a report of six cases. Med Pediatr Oncol 12:54–58
58. Von Hoff DD, Rozencweig M, Layard M et al. (1977) Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am J Med 62:200–208
59. Postma A, Bink-Boelkens MTE, Beaufort-Krol GCM et al. (1996) Late cardiotoxicity after treatment for a malignant bone tumor. Med Pediatr Oncol 26:230–237
60. Nysom K, Holm K, Lipsitz SR et al. (1998) The relation between cumulative anthracycline dose and late cardiotoxicity in survivors of childhood leukemia. J Clin Oncol 16: 545–550
61. Silber JH, Jakacki RI, Larsen RL et al. (1993) Increased risk of cardiac dysfunction after anthracyclines in girls. Med Pediatr Oncol 21:477–479
62. Rodvold KA, Rushing DA, Tewksbury DA (1988) Doxorubicin clearance in the obese. J Clin Oncol 6:1321–1327
63. Lipshultz SE, Giantris AL, Lipsitz SR et al. (2002) Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91–01 Acute Lymphoblastic Leukemia Protocol. J Clin Oncol 20:1677–1682
64. Levitt GA, Dorup I, Sorenson K, Sullivan I. Does anthracycline administration by infusion in children affect late cardiotoxicity? Brit J Hematol 124:463–468
65. Krischer JP, Cuthbertson DD, Epstein S et al. (1998) Risk factors for early anthracycline clinical cardiotoxicity in children: the Pediatric Oncology Group experience. Prog Pediatr Cardiol 8:83–90
66. Pohjola-Sintonen S, Totterman KJ, Kupari M (1990) Sick sinus syndrome as a complication of mediastinal radiation therapy. Cancer 65:2494–2496
67. Adams MJ, Lipsitz SR, Colan SD et al. (2004) Cardiovascular status in long-term survivors of Hodgkin's Disease treated with chest rediotherapy. J Clin Oncol 22:3139–3148
68. Lee CK, Aeppli D, Nierengarten ME (2000) The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience. Int J Radiat Oncol Biol Phys 48:169–179
69. Mauch P, Kalish LA, Marcus KC et al. (1995) Long-term survival in Hodgkin's disease: relative impact of mortality, second tumors, infection and cardiovascular disease. Cancer J Sci Am 1:33–42
70. Hancock SL, Tucker MA, Hoppe RT (1993) Factors affecting late mortality from heart disease after treatment for Hodgkin's disease. JAMA 270:1949–1955

71. Hancock SL, Donaldson SS, Hoppe RT (1993) Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 11:1208–1215
72. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ et al. (1999) Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. Radiother Oncol 51:35–42
73. Glanzmann C, Kaufmann P, Jenni R et al. (1998) Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiother Oncol 46:51–62
74. Radwaner BA, Geringer B, Goldman AM et al. (1987) Left main coronary artery stenosis following mediastinal irradiation. Am J Med 82:1017–1020
75. Rodgers DL (1976) Precocious myocardial infarction after radiation treatment for Hodgkin's disease. Chest 70:675–677
76. Totterman KJ, Pesonen E, Siltanen P (1983) Radiation related chronic heart disease. Chest 83:875–878
77. Angelini A, Benciolini P, Thiene G (1985) Radiation-induced coronary obstructive atherosclerosis and sudden death in a teenager. Int J Cardiol 9:371–373
78. Boivin J-F, Hutchison G, Lubin J et al. (1992) Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 69:1241–1247
79. Pohjola-Sintonen S, Totterman KJ, Salmo M et al. (1987) Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. Cancer 60:31–37
80. Carmel RJ, Kaplan HS (1976) Mantle irradiation in Hodgkin's disease. Cancer 37:2813–2815
81. Martin RG, Ruckdeschel J, Chang P et al. (1975) Radiation-related pericarditis. Am J Cardiol 35:216–220
82. Arsenian MA (1991) Cardiovascular sequelae of therapeutic thoracic radiation. Prog Cardiovasc Dis 33:299–311
83. Applefeld MM (1981) The late appearance of chronic pericardial disease in patients treated by radiotherapy for Hodgkin's disease. Ann Intern Med 94:338–341
84. Byhardt R, Brace K, Ruckdeschel JC et al. (1975) Dose and treatment factors in radiation-related pericardial effusion associated with the mantle technique for Hodgkin's disease. Cancer 35:795–802
85. Cameron EH, Lipshultz SE, Tarbell NJ et al. (1998) Cardiovascular disease in long-term survivors of pediatric Hodgkin's disease. Prog Pediatr Cardiol 8:139–144
86. Tolba KA, Deliargyris EN (1999) Cardiotoxicity of cancer therapy. Cancer Invest 17:408–422
87. Burns RJ, Bar Shlomo BZ, Druck MN et al. (1983) Detection of radiation cardiomyopathy by gated radionuclide angiography. Am J Med 74:297–301
88. Constine LS, Schwartz RG, Savage D et al. (1997) Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. Int J Radiat Oncol Biol Phys 39:897–906
89. Hardenbergh PH, Munley MT, Bentel GC et al. (2001) Cardiac perfusion changes in patients treated for breast cancer with radiation therapy and doxorubicin: preliminary results. Int J Radiat Oncol Biol Phys 49:1023–1028
90. Gyenes G, Fornander T, Carlens P et al. (1996) Myocardial damage in breast cancer patients treated with adjuvant radiotherapy: a prospective study. Int J Radiat Oncol Biol Phys 36:899–905
91. Adams MJ, Hardenbergh P, Constine LS et al. (2003) Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol 45:55–75
92. Merrill J, Geco FA, Zimber H et al. (1975) Adriamycin and radiation: synergistic cardiotoxicity. Ann Intern Med 82: 122–123 (abstract)
93. Kinsella TJ, Ahmann DL, Giuliani ER et al. (1979) Adriamycin toxicity in stage IV breast cancer: possible enhancement with prior left chest radiation therapy. Int J Radiat Oncol Biol Phys 5:1979–2002
94. Fajardo LF, Eltringham JR, Stewart JR (1976) Combined cardiotoxicity of adriamycin and x-radiation. Lab Invest 34:86–96
95. Eltringham JR, Fajardo LF, Stewart JR et al. (1979) Investigation of cardiotoxicity in rabbits from adriamycin and fractionated cardiac irradiation: preliminary results. Front Radiat Ther Oncol 13:21–35
96. Pihkala J, Saarinen U, Lundstrom U et al. (1996) Myocardial function in children and adolescents after therapy with anthracyclines and chest irradiation. Eur J Cancer 32A:97–103
97. Leonard GT, Green DM, Spangenthal EL et al. (2000) Cardiac mortality and morbidity after treatment for Hodgkin disease during childhood and adolescence. Pediatr Res 47:46A (abstract)
98. Shapiro CL, Hardenbergh PH, Gelman R et al. (1998) Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. J Clin Oncol 16:3493-3501
99. Glanzmann C, Huguenin P, Lutolf UM et al. (1994) Cardiac lesions after mediastinal radiation for Hodgkin's disease. Radiother Oncol 30:43–54
100. Gustavsson A, Eskilsson J, Landberg T et al. (1990) Late cardiac effects after mantle radiation in patients with Hodgkin's disease. Ann Oncol 1:355–363
101. Lund MB, Ihlen H, Voss BM et al. (1996) Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study. Heart 75:591–595
102. Adams MJ, Lipsitz SR, Colan SD et al. (2004) Cardiovascular status in long-term survivors of Hodgkin's Disease treated with chest rediotherapy. J Clin Oncol 22:3139–3148
103. Orzan F, Brusca A, Gaita F et al. (1993) Associated cardiac lesions in patients with radiation-induced complete heart block. Int J Cardiol 39:151–156
104. Slama MS, Le Guludec D, Sebag C et al. (1991) Complete atrioventricular block following mediastinal irradiation: a report of six cases. PACE 14:1112–1118

105. Hancock SL (1998) Cardiac toxicity after cancer therapy. Research issues in Cancer Survivorship Meeting, 3 Mar 1998. National Cancer Institute, Bethesda, Maryland
106. Childrens Oncology Group (2004) Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. http://www.survivorshipguidelines.org/. (electronic citation)
107. Steinherz LJ, Graham T, Hurwitz R et al. (1992) Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the cardiology committee of the Children's Cancer Study Group. Pediatrics 89:942–949
108. Lipshultz SE, Colan SD (1993) The use of echocardiography and Holter monitoring in the assessment of anthracycline-treated patients, Cardiac Toxicity after Treatment for Childhood Cancer. Wiley-Liss, New York, pp 45–62
109. Colan SD, Borow KM, Neuman A (1984) Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load independent index of myocardial contractility. J Am Coll Cardiol 4:715–724
110. Weesner KM (1991) Exercise echocardiography in the detection of anthracycline cardiotoxicity. Cancer 68:435–438
111. Mancini DM, Eisen H, Kussmaul W et al. (1991) Value of peak exercise oxygen consumption for the optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 83:778–786
112. Orzan F, Brusca A, Conte MR et al. (1993) Severe coronary artery disease after radiation therapy of the chest and mediastinum: clinical presentation and treatment. Br Heart J 69:496–500
113. Adams MJ, Constine LS, Lipshultz SE (2001) Radiation. In: Crawford MH, DiMarco JP (eds) Cardiology. Mosby International, London, pp 8.15.1–8
114. Speyer JL, Green MD, Kramer E et al. (1988) Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. N Engl J Med 319:745–752
115. Swain SM, Whaley FS, Gerber MC et al. (1997) Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 15:1318–1332
116. Speyer JL, Green MD, Zeleniuch-Jacquotte A et al. (1992) ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol 10:117–127
117. Bu'Lock FA, Gabriel HM, Oakhill A et al. (1993) Cardioprotection by ICRF187 against high dose anthracycline toxicity in children with malignant disease. Br Heart J 70:185–188
118. Wexler LH, Andrich MP, Venzon D et al. (1996) Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 14:362–372
119. Lipshultz SE, Rifai N, Dalton VM et al. (2004) The effect of Dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. New Engl J Med 2004; 351:145–153
120. Schwartz CL, Tebbi CK, London WB et al. (2003) Enhanced toxicity in pediatric Hodgkin disease (HD) patients treated with DBVE or DBVE-PC and Dexrazoxane (DXR). Blood 102:11–16 (abstract)
121. Hinkle AS, Truesdell SC, Proukou CB et al. (1998) Cardiotoxicity related to cancer therapy. Prog Pediatr Cardiol 8:145–155
122. Heart Failure Guideline Panel (1994) Heart Failure: evaluation and care of patients with left ventricular systolic dysfunction. Clinical Practice Guideline #11. US Department of Health and Human Services, Agency for Health Care Policy and Research (report)
123. Guidelines for the evaluation and management of heart failure (1995) Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). Circulation 92:2764–2784
124. Hunt SA, Baker DW, Chin MH et al. (2001) ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in Collaboration With the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. Circulation 104:2996–3007
125. Miller TL, Horgan S, Lipshultz SE. Exercise rehabilitation of pediatric patients with cardiovascular disease. Prog Pediatr Cardiol. (In press 2004)
126. Expert Panel on Detection , Evaluation, And Treatment of High Blood Cholesterol In Adults (2001) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 285:2486–2497
127. Lipshultz SE, Lipsitz SR, Sallan SE et al. (2003) Treatment for asymptomatic anthracycline-induced cardiac dysfunction in childhood cancer survivors: the need for evidence: in reply (letter). J Clin Oncol 21:3377–3378
128. Lipshultz SE, Colan SD (2004) Cardiovascular trials in long-term survivors of childhood cancer. J Clin Oncol 22: 769–773
129. Pitt B, Zannad F, Remme WJ et al. (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators (comment). N Engl J Med 341:709–717
130. Noori A, Lindenfield J, Wolfel E et al. (2000) Beta-blockade in adriamycin-induced cardiomyopathy. J Cardiac Failure 6:115–119
131. Pfeffer MA, Braunwald E, Moye LA et al. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 327:669–677

132. Lipshultz SE, Lipsitz SR, Sallan SE et al. (2002) Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol 20:4517–4522
133. Packer M, Bristow MR, Cohn JN et al. (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 334:1349–1355
134. Woodley SL, Gilbert EM, Anderson JL et al. (1991) Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. Circulation 84:2426–2441
135. Fisher ML, Gottlieb SS, Plotnick GD et al. (1994) Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. J Am Coll Cardiol 23:843–950
136. Olsen SL, Gilbert EM, Renlund DG et al. (1995) Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Col Cardiol 25:1225–1231
137. Waagstein F, Bristow MR, Swedberg K (1993) Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 342:1441–1446
138. Dillon TA, Sullivan M, Schatzlein MH et al. (1991) Cardiac transplantation in patients with preexisting malignancies. Transplantation 52:82–85
139. Stevenson LW, Warner SL, Steimle AE et al. (1994) The impending crisis awaiting cardiac transplantation. Modeling a solution based on selection. Circulation 89:450–457
140. Herman EH, Zhang J, Lipshultz SE et al. (1999) Correlation between serum levels of cardiac troponin-T and the severity of chronic cardiomyopathy induced by doxorubicin. J Clin Oncol 17:2237–2243
141. Hicks GL Jr (1992) Coronary artery operation in radiation-associated atherosclerosis: long-term follow-up. Ann Thorac Surg 53:670–674
142. Gharagozloo F, Clements I, Mullany C (1992) Use of the internal mammary artery for myocardial revascularization in a patient with radiation-induced coronary artery disease. Mayo Clin Proc 67:1081–1084
143. Handa N, McGregor CG, Danielson GK et al. (1999) Coronary artery bypass grafting in patients with previous mediastinal radiation therapy. J Thorac Cardiovasc Surg 117:1136–1142
144. Van Son JA, Noyez L, van Asten W (1992) Use of internal mammary artery in myocardial revascularization after mediastinal irradiation. J Thorac Cardiovasc Surg 104: 1539–1544
145. Reber D, Birnbaum DE, Tollenaere P (1995) Heart diseases following mediastinal irradiation: surgical management. Eur J Cardiothorac Surg 9:202–205
146. Mittal S, Berko B, Bavaria J et al. (1996) Radiation-induced cardiovascular dysfunction. Am J Cardiol 78:114–115
147. Morton DL, Glancy D, Joseph WL et al. (1973) Management of patients with radiation-induced pericarditis with effusion: a note on the development of regurgiation in two of them. Chest 64:291–297
148. Huettemann E, Junker T, Chatzinikolaou KP et al. (2004) The influence of anthracycline therapy on cardiac function during anesthesia. Anesth Analg 98:941–947
149. Kodama K, Fujiwara S, Yamada M et al. (1996) Profiles of non-cancer disease in atomic bomb survivors. World Health Statistics Quarterly- Rapport Trimestriel de Statistiques Saintaires Mondiales 49:7–16
150. Warda M, Khan A, Massumi A et al. (1983) Radiation-induced valvular dysfunction. J Am Coll Cardiol 2:180–185
151. Shimizu Y, Kato H, Schull W et al. (1992) Studies of mortality of A-bomb survivors: mortality 1950–1985, part 3. Non-cancer mortality based on the revised doses. Radiat Res 130:249–266
152. Shimizu Y, Pierce DA, Preston DL et al. (1999) Studies of mortality of atomic bomb survivors, report 12, part II. Non-cancer mortality: 1950–1990. Radiat Res 152:374–389
153. Perrault DJ, Levy M, Herman JD et al. (1985) Echocardiographic abnormalities following cardiac radiation. J Clin Oncol 3:546–551
154. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Col Cardiol 2003; 42:743–749

Pulmonary Effects of Antineoplastic Therapy

Andrea S. Hinkle · Cindy Proukou · Yuhchyau Chen

Contents

Long-term follow up of children and adolescents treated with chemotherapy and/or radiation has demonstrated the potential for significant impact on pulmonary function and thoracic development. Both radiation therapy (RT) and chemotherapy can acutely and chronically affect lung function. Thoracic irradiation in children can cause developmental abnormalities including inhibited growth of the thoracic cage resulting in impairment of pulmonary function. Other effects of direct radiation on the lungs include pneumonitis and fibrosis. Pulmonary effects of cytotoxic drugs usually present as acute effects and less frequently as long-term effects, but there is the potential for significant late morbidity and mortality. Although treatment approaches have been adapted to provide optimal therapy with minimal toxicities, for some diseases therapies continue to include potentially pulmonary toxic agents and modalities. Knowledge of these agents and an understanding of lung physiology and how it may be altered by therapy facilitate appropriate clinical care and monitoring of long-term survivors.

11.1 Pathophysiology

11.1.1 Development of the Lung

Lung development begins on day 26 of gestation and continues through the toddler years. There are five phases in development. The embryonic period extends from day 26 through 52 of gestation. During this time, the primitive lung bud arises from the foregut, elongates caudally and branches to form the major airways. The pseudoglandular phase encompasses the time from day 52 through the end of 16

weeks gestation. During this phase of development, the process of branching continues and the smaller airways are formed. Fetal breathing movements are identified as early as eight weeks, and by the end of this phase, the two lobes of the left lung and three lobes of the right lung can be identified. Cartilage and smooth muscle cells are present, and about half of the epithelial cell types that will eventually comprise the mature lung are identifiable. The canalicular phase of development extends from weeks 17 through 26. It is during this phase that the airway branching is completed. Interstitial tissue decreases, and prospective gas exchange regions begin to appear. A differentiation process occurs in the cuboidal epithelial cells, and Type I and II pneumocytes appear. Type I pneumocytes are the functional exchange unit of the lung, while Type II pneumocytes produce surfactant, a phospholipid substance that serves to decrease surface tension within the Type I cell and prevent it from collapsing. Vascularization of the lung occurs throughout development, and, at this point, the capillaries can be found in close proximity to the pneumocytes. The saccular phase of development extends from 24 weeks through 36 weeks gestation. During this time, there is continued thinning of the connective tissue between the potential air spaces, further maturation of the Type II pneumocytes and increased surfactant production. Primitive alveoli, lined by both Type I and Type II pneumocytes, can now be identified as pouches in the walls of the saccules and respiratory bronchioles. The alveoli phase of development extends from 36 weeks gestation through about 3 years of age. At birth, there are few alveoli present, but potential airspaces are present as smooth-walled ducts and saccules with thickened septa. Inflation of the saccules occurs at birth. The septa become thin and grow into air spaces, forming partitions within the pouches. Within a few months the infant's alveoli resemble those of the adult, with greatly increased surface area available for gas exchange. Completion of the vascularization process during this time results in single capillary networks associated with each area of gas exchange [105, 136]. After birth, minor structural changes continue to occur. The alveolar surfaces become more complex, and the alveoli become more numerous with the increase in body size. The most rapid phase of pulmonary growth probably occurs within the first years of life, followed at 4–6 years of age by a slow growth phase. The number of alveoli that will be present in adulthood is reached at approximately eight years of age, after which the alveolar surface face enlarges by increases in volume or size [57, 135]. Radiographic measurement of lung diameters demonstrates linear growth during childhood and a spurt at puberty [129].

11.1.2 Pathophysiologic Changes Induced by Cytotoxic Therapy

Lung disease may be obstructive, restrictive, or interstitial or a mixed picture. Most long-term toxicity is the result of interstitial disease, which involves inflammation and fibrosis of the alveolar walls and changes in the capillary endothelium and alveolar epithelial lining cells, as described below. The histologic hallmarks of interstitial lung disease are proliferation of fibroblasts and excessive deposition of collagen [122]. Interstitial lung disease also may impact the small airways. As alveolar-capillary membrane destruction is an integral part of interstitial disease, pulmonary function tests demonstrate a decrease in the measured diffusing capacity [122].

Pulmonary disease after chemotherapy or radiation therapy may also have obstructive or restrictive components. Obstructive diseases result from airway narrowing. This may be due to bronchospasm, mucus or luminal narrowing as a result of edema and inflammation or scarring [88]. Airway narrowing due to disease can be detected as a decrease in expiratory airflow. Pulmonary function tests demonstrate a decrease in the ratio of the volume exhaled in 1 second (FEV_1) to the total exhaled forced vital capacity (FVC).

Restrictive lung diseases occur as a result of alterations in the elasticity of the pulmonary system [38]. Restrictive diseases can originate in the lung or from structural anomalies of the chest wall. In the healthy lung, collagen and elastin fibers contribute to the formation of an organized web, which has a significant ability to stretch and recoil [38]. Disruption of this organization from inflammation and fibrosis occurs

as a result of injury and response to cytotoxic therapy, thereby decreasing the elasticity of the lung and resulting in restrictive disease. Restrictive lung disease may also occur as a result of growth impairment of the lung or musculoskeletal structures, a condition which may occur as well after cytotoxic therapy. Children are more vulnerable to chronic respiratory damage from impairment of the normal growth and development of the lungs and the thoracic cage. In the child, cytotoxic therapy may impair the proliferation and maturation of alveoli, leading to inadequate alveoli number and lung growth, and resulting in chronic respiratory insufficiency. Inhibition of growth of the thoracic cage (i.e. muscle, cartilage and bone) can limit chest wall compliance, with resultant restrictive problems. Therefore, younger children are more at risk than adults or adolescents for developing chronic toxicity, a situation that results in long-term pulmonary effects that need to be considered in appropriate follow-up, monitoring and counseling.

In restrictive respiratory disease, pulmonary function testing demonstrates an increased FEV1/FVC ratio with an increased maximal expiratory airflow. With more advanced restrictive disease, total lung capacity, vital capacity and lung volumes are decreased, with evidence of uneven distribution of ventilation [88].

Pneumonitis and pulmonary fibrosis are the two most important consequences of irradiation of the lung. Pulmonary fibrosis occurs in almost 100% of patients receiving high doses of radiation, but it may not be of clinical significance if the volume is small. The clinically significant presentation of pulmonary toxicity is usually pneumonitis, due to its prevalence and potential morbid outcome. The presentation varies with the type of lung injury present. Often there are complaints of a nonproductive cough, fever and dyspnea. However, the presentation can also be quite acute with respiratory insufficiency and acute respiratory distress syndrome (ARDS). Other presentations include bronchospasm, pleural effusion, bronchiolitis obliterans, pulmonary veno-occlusive disease, sarcoidosis, pulmonary alveolar proteinosis, pneumothorax and pulmonary hemorrhage.

The pathogenesis of pulmonary toxicity is largely based on animal experimentation. However, it is believed to occur through one of four mechanisms of injury: 1) DNA damage from the drug or radiation itself, 2) damage inflicted by free radical generation, 3) allergic response to the cytotoxic agent and 4) subsequent injury induced by the inflammatory response to the primary damage itself. Pulmonary fibrosis, which mediates many of the long-term effects, can arise from collagen deposits that occur after cellular damage. In addition, the breakdown of actual lung tissue can trigger an inflammatory reaction that activates increased production of elastin by actin-expressing smooth muscle cells. This also results in pulmonary fibrosis. While there are several postulated means of injury to the pulmonary tissue, the common finding in all is diffuse alveolar damage. The cytotoxic changes start as endothelial blebs in the alveolar capillaries and lead to capillary leak syndrome. These are then associated with interstitial edema. There is destruction and a resulting decrease in number of Type I pneumocytes, as well as reactive changes and proliferation of Type II pneumocytes. More recently, progress has been made in understanding the molecular and cellular events after radiation lung injury, leading to clinically and histologically recognizable changes. The process appears to be dynamic and to involve proinflammatory cytokines, profibrotic cytokines, chemokines and adhesion molecules in modulating and recruiting immune cells to the sites of radiation lung injury [20]. Long-term effects on the lungs are the result of this complex process.

Chemotherapy. Drug-related pulmonary disease may be the result of toxicity, allergy or idiosyncrasy [70]. Toxicity, with a dose response, has been shown for bleomycin, chlorambucil and the nitrosoureas. Pulmonary damage, likely mediated through allergic mechanisms, is caused by cyclophosphamide, methotrexate, procarbazine and bleomycin. Pulmonary disease has also been associated with mitomycin, cytosine arabinoside, the vinca alkaloids and alkylating agents.

Bleomycin may be the most commonly recognized cause of pulmonary toxicity. Lung injury following low-dose bleomycin has been explained by idiosyncrasy, possibly due to genetically impaired drug me-

tabolism. The lung is vulnerable to bleomycin injury because it has low levels of bleomycin hydrolase [69] that inactivates bleomycin. Mouse data demonstrate that strain sensitivity to bleomycin is related to different levels of bleomycin hydrolase activity [58]. Hence, individual variations in bleomycin sensitivity may be explained at least in part by genetically determined levels of bleomycin hydrolase activity. The pathogenesis of bleomycin injury has been studied extensively [24, 53, 65]. Free radical formation and oxidative damage play a role in bleomycin-induced lung injury. Fibrosis after bleomycin therapy develops under the influence of immune processes that include activation of effector cells, including alveolar macrophages, and release of cytokines. Tumor necrosis factor may play a pivotal role [73, 94]. Pathology demonstrates endothelial and Type I cell necrosis with Type II hyperplasia and hyaline membranes. Bleomycin-induced pulmonary effects usually occur during or within a year of treatment.

Alkylating agents, such as the nitrosoureas, are known to cause late onset pulmonary fibrosis. The pathology of the fibrosis noted after nitrosourea therapy demonstrates less inflammation than bleomycin-induced fibrosis, but consistency in Type I depletion and Type II hyperplasia with excess collagen deposition. The formation of free radicals and lipid peroxidation of phospholipid membranes may also be the mechanism by which cyclophosphamide and mitomycin damage the capillary endothelium [25]. Permeability increases, resulting in interstitial edema. Hyaline membranes form as plasma proteins, and fluid enters the alveoli through the denuded epithelium. Type I pneumocytes swell, become necrotic and are replaced by cuboidal cells. Proliferation of fibroblasts then occurs. This process may evolve slowly, with fibrosis increasing over a period of years. Interstitial pneumonitis (either the desquamative type that appears to be an earlier stage or the usual type with fibrinous exudation, hyaline membranes and interstitial fibrosis) is also seen with alkylating agents. This pneumonitis may lead to the development of chronic pulmonary fibrosis that is characterized by the enhanced production and deposition of collagen and other matrix components. Pulmonary veno-occlusive disease, with vasculitis and intimal fibrosis resulting in pulmonary hypertension, has been reported with bleomycin and mitomycin [30].

Radiotherapy. Relatively similar histopathologic changes and resultant physiologic abnormalities are found in the lung following radiotherapy and chemotherapy. Injuries resulting from radiation to the lung are most likely present in all patients, even after very small doses of radiation. Studies of the immunological regulation of inflammation after radiation in animals have revealed a complex interaction between local tissues, resident cells and circulating immune cells, mediated through chemokines, adhesion molecules, inflammatory cytokine and fibrotic cytokines. Chemokine monocyte chemotactic protein-1 (MCP-1) [61], adhesion molecules (intercellular adhesion molecule-1 [ICAM-1]) [51, 64] and interferon-inducible protein-10 (IP-10) [61] appear to be involved in initiating radiation lung injury [16, 20, 49, 51, 61, 64, 111, 116, 134]. Afterward, there appears to be a cascade of proinflammatory cytokines and fibrotic cytokines [117]. In the first few days to weeks after irradiation, ultrastructural alterations in the capillary endothelial lining become evident. The cells become pleomorphic and vacuolated and may slough, thereby producing areas of denuded basement membrane and occlusion of the capillary lumen by debris and thrombi [46, 71, 78, 102]. There is exudation of proteinaceous material into the alveoli, leading to impairment of gas exchange. Studies have shown that radiation-induced lung injury is characterized by alveolar infiltrates of mononuclear cells, primarily $CD4^+$ T cells and macrophages/monocytes (mononuclear alveolitis), and that there is a relative scarcity of neutrophils [36, 40], a common marker for infectious processes. Lavage fluids obtained from bronchoscopy have confirmed this finding in patients with active pneumonitis [75, 89, 111]. In a few weeks the interstitial edema organizes into collagen fibrils, which eventually leads to thickening of the alveolar septa. These exudative changes may resolve in a few weeks to a few months. However, depending on the volume of lung parenchyma irradiated, the total dose and the dose per fraction, the changes can result in an acute radiation pneumonitis. Although no specific lesion is entirely characteristic of pneumonitis, current evi-

dence suggests that damage to the type II pneumocyte and to the endothelial cell is closely linked to the pneumonitic process [99, 137, 138, 147]. The type II pneumocyte, which produces surfactant and maintains patent alveoli, has been well studied. After radiation exposure a rapid decrease in the content of cytoplasmic surfactant-containing lamellar bodies occurs, followed by the ultimate sloughing of some of the cells into the alveolar lumen [97, 98]. Changes in the surfactant system that lead to alterations in alveolar surface tension and low compliance are most likely a direct result of the radiation [99, 118, 119], although it has been postulated that the changes indirectly result from exudation of plasma proteins [47]. Endothelial cell damage results in changes in perfusion and permeability of the vessel wall. Endothelial leakage and increased permeability allow immune cells to undergo transendothelial migration and extravasation from the vascular compartment into the alveolar space.

Late lung injury is characterized by progressive fibrosis of the alveolar septa, which become thickened by bundles of elastic fibers. The alveoli collapse and are obliterated by connective tissue. Studies in animals have confirmed the protective effect of fractionation, indicating a significant degree of recovery of lung tissue between fractions [128, 146]. The mechanisms of chronic injury may be related to the effects of radiation on the pulmonary vasculature (endothelial cells) or somatic cells. The nature of the triggering event in the pathogenesis of radiation-related lung fibrosis is complex. The classic hypothesis that fibrosis is a connective tissue replacement process following parenchymal cell death has been challenged and the exact mechanisms of early injuries leading to the late effects are not entirely understood. Cytokine-mediated multicellular interactions that initiate and sustain the fibrogenic process take place within hours to days after radiation in animal research models. Experimental data suggest that the progression of the initial lung injury to the pneumonitic phase may be the result of a cytokine and cellular interaction, which subsequently regulates the fibrotic phase of the presentation [20, 115–117]. In addition, it has been recently hypothesized that chronic hypoxia, and the perpetual injury to normal tissue through reactive oxygen species, may also be a contributing mechanism to chronic and progressive fibrosis [144].

11.2 Clinical Manifestations

11.2.1 Long-Term Effect in Pediatric Population

Potential pulmonary complications of therapy leading to a range of respiratory manifestations have been reported by the Childhood Cancer Survivor Study. Study participants were asked whether they had ever been told by a physician, or other healthcare professional, that they have or had a particular diagnosis, e.g. pulmonary fibrosis. This self-report study demonstrated that long-term survivors described a statistically significant increased relative risk of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen, abnormal chest wall, exercise-induced SOB, bronchitis, recurrent sinus infection and tonsillitis for all time periods, including during therapy, from the completion of therapy to 5 years off therapy and >5 years after therapy. Significant associations existed between the development of fibrosis and treatment with radiation therapy, and between the use of supplemental oxygen, recurrent pneumonia, chronic cough and pleurisy and treatment with radiation therapy and/or multiple chemotherapy agents [84].

Pulmonary toxicity is frequently reported in survivors of Hodgkin's disease, but it also complicates the cure of survivors of germ cell tumors, rhabdomyosarcoma, neuroblastoma, bone tumors and acute lymphoblastic leukemia (ALL) [14, 50, 56, 62, 66, 86, 90, 91]. Although many of the patients that have been studied received radiation therapy, the intensified use of chemotherapy accounts for all or some of the toxicity in subsets of survivors. Detected pulmonary abnormalities are generally restrictive. Although some reports described subclinical findings, it remains to be seen whether there will be clinical manifestations with longer follow-up.

11.2.2 Radiotherapy: Clinical Presentations

When radiation therapy is the only modality used, radiation pneumonitis follows the completion of the definitive course of treatment. Cough, pink sputum, dyspnea and pleuritis are common complaints during the subacute pneumonitic phase, which occurs generally 1–3 months after completion of radiation. When chemotherapy has been used, as in total body irradiation (TBI) and BMT-conditioning regimens, reactions can occur during treatment. The fibrotic phase of radiation injury starts 3–6 months after completion of radiation and is progressive. The clinical manifestations of fibrosis are worsening dyspnea, increasing probability of oxygen dependence and declining pulmonary function test results.

11.2.2.1 Subacute Radiation Pneumonitis

Subacute pneumonitis is a pneumonopathy that usually occurs 1–3 months after the completion of radiation. It is well described in the adult literature after the treatment of lung cancer [5, 6, 109], but little of the data from such studies are relevant to modern pediatric cancer therapies. Pneumonitis can occur unexpectedly, with little or no warning. Because of this, many attempts have been made to identify clinical risk factors. The factors that influence risk include total lung radiation dose, irradiated lung volume exceeding 20 Gy vs 25 Gy vs 30 Gy, mean lung dose, fractionation of radiotherapy, daily fraction size, performance status, pre-treatment pulmonary function, gender, low pre-treatment blood oxygen and high C-reactive protein [44, 54, 59, 68, 110, 112, 123].

Symptoms of subacute pneumonitis syndrome include low-grade fever and nonspecific respiratory symptoms such as congestion, cough and fullness in the chest. In more severe cases, dyspnea, pleuritic chest pain and nonproductive cough may be present. Later, small amounts of sputum, sometimes blood-stained, may be produced. Physical signs in the chest are usually absent, although a pleural friction rub or pleural fluid may be detected. Evidence of alveolar infiltrates or consolidation is sometimes found in the region corresponding to pneumonitis. This results from an acute exudative edema that is initially faint but may progress to homogenous or patchy air-space consolidation. Frequently there is an associated volume loss in the affected portion of the lung. CT studies of the lung have been used to evaluate lung density in this situation. Because of its sensitivity to increased lung density, CT has been favored for radiographic detection of pulmonary damage in humans [72, 77, 141]. CT findings demonstrate a well- defined, dose-response relationship [76]. Four patterns of radiation-induced changes have been defined in lung on CT: homogenous (slight increase in radiodensity); patchy consolidation; discrete consolidation; and solid consolidation [72]. These patterns, corresponding to both pneumonitic and fibrotic phases, have varying timetables and may appear weeks to years after radiotherapy.

11.2.2.2 Radiation Fibrosis

In contrast to the acute reaction, chronic effects of cytotoxic therapy may be observed from a few months to years following treatment, even though histologic and biochemical changes are evident sooner. Pulmonary fibrosis develops insidiously in the previously irradiated field and stabilizes after 1–2 years.

The clinical symptomatology related to the radiographic changes is proportional to the extent of the lung parenchyma involved and pre-existing pulmonary reserve. After thoracic radiation, restrictive changes gradually develop and progress with time [46]. Gas exchange abnormalities occur approximately at the same time as the changes in lung volumes. These abnormalities consist of a fall in diffusion capacity, mild arterial hypoxemia that may manifest only with exercise and a low or normal $PaCO_2$ level. The changes appear to be consistent with a parenchymal lung defect and ventilation–perfusion inequality that results in a component of effective shunt [47]. Radionuclide evaluations have demonstrated that under perfusion, rather than under ventilation, is the cause of these inequalities, reflecting radiation injury to the microvasculature [106, 107, 143]. Larger doses of irradiation cause reductions in lung compliance that start at the time of pneumonitis and persist thereafter [104]. The compliance of the

chest wall is usually much less affected in adults and adolescents than in young children, in whom interference with growth of both lung and chest wall leads to marked reductions in mean total lung volumes and diffusion capacity (DLCO) [153]. Whole-lung irradiation in doses of 11 to 14 Gy has resulted in restrictive changes in the lungs of children treated for various malignancies [10, 74, 85]. Consequently, RT in younger children, particularly those younger than 3 years old, results in increased chronic toxicity [85].

One to two years after radiation, clinical symptoms stabilize and are often minimal if fibrosis is limited to less than 50% of one lung [149]. A mild deterioration in pulmonary function may be demonstrated as fibrosis develops. There is a reduction in maximum breathing capacity that is particularly evident in patients with bilateral radiation fibrosis. Tidal volume usually decreases and breathing frequency tends to increase, resulting in an overall moderate increase in minute ventilation [126]. Most studies have found these changes to persist indefinitely, with little recovery unless there are concurrent improvements in pulmonary function with lung tumor response [37, 41, 45]. Functional compensation by adjacent lung regions [97] limits the effect of radiation on pulmonary function tests when small volumes of lung are irradiated. Dyspnea and progressive chronic cor pulmonale leading to right heart failure may occur when >50% of a lung is irradiated.

Radiologic changes consistent with fibrosis are seen in most patients who have received lung irradiation, even if they do not develop acute pneumonitis (Fig. 11.2). Chest radiographs have linear streaking, radiating from the area of previous pneumonitis, and sometimes extending outside the irradiated region, with concomitant regional contraction, pleural thickening and tenting of the diaphragm. The hilum or mediastinum may be retracted with a densely contracted lung segment, resulting in compensatory hyperinflation of the adjacent or contralateral lung tissue. This is usually seen 12 months to two years after radiation. When chronic fibrosis occurs in the absence of an earlier clinically evident pneumonitic phase [99, 113, 127], chest radiography generally reveals scarring that corresponds to the shape of the radiation portal. Eventually, dense fibrosis can develop, especially in the area of a previous tumor [114]. CT is currently favored to image regions subjected to RT [72, 77, 141]. Magnetic resonance imaging (MRI) is being explored and may have promise in accurately distinguishing radiation fibrosis from recurrent tumor [43]. Although radiation tolerance doses may be exceeded, not all patients will develop complications, given that the sensitivity to radiation varies from patient to patient.

11.2.2.3 Radiation Tolerance Doses and Tolerance Volumes

It must be noted that these phenomenon are dose and fraction-dependent, as well as volume dependent. Scattered changes can be seen at 5.0 Gy, but lesions become widespread at lethal doses of irradiation. The effects of lethal radiation doses on the lung parenchyma may not become evident until weeks to months after exposure. With high doses exceeding clinical thresholds (8.0–12.0 Gy, single dose), pulmonary reactions clinically express themselves as a pneumonitic process 1–3 months after the completion of thoracic irradiation. Lethality can occur if both lungs are irradiated to high doses (8.0–10.0 Gy, single dose) or if threshold doses of drugs are exceeded. Recovery from pneumonitis usually occurs, however, and is followed almost immediately by the second phase of fibrosis, which progresses with time.

The clinical pathologic course is biphasic and dependent upon the dose and volume of lung exposed. Lower doses of lung irradiation (less than 7.0 Gy, single dose) produce subclinical pathologic effects that can be expressed by added insult, such as infection or drugs.

Single Dose, Whole Lung Volume. Total-body irradiation (TBI) in the setting of bone marrow transplantation (BMT) and half-body irradiation (HBI) initially used single doses of 8.0–10.0 Gy, without lung correction factors (for lung density) [40–43, 45–48, 52, 53, 57, 63, 65]. Death resulting from interstitial pneumonitis was often attributed to secondary opportunistic infection after BMT for leukemia. Pulmonary failure 1–3 months later was mistaken for lymphangitic carcinomatosis after HBI. At autopsy, radiation

pneumonopathy became evident. Studies of fatal pneumonitis following TBI and HBI conducted by Keane et al. [65] and Fryer et al. [40] provided precise dose–response curves for injury, both with and without lung inhomogeneity correction. The threshold dose for fatal pneumonitis was 7.0 Gy with the TD_5 (tolerance dose for 5% probability of death) at 8.2 Gy, the TD_{50} at 9.3 Gy and the TD_{90} at 11.0 Gy, corrected for pulmonary transmission. The dose response is so sharp that a difference of 2.0 Gy could change zero mortality to 50% lethality. Decreasing the dose rate from 0.5 to 0.1 Gy per minute decreases the incidence of injury from 90% to 50% [40, 65].

Fractionated Dose, Whole Lung Volume. The tolerance of the whole lung to fractionated doses of radiation is well described, particularly in Wilms' tumor patients [10, 74, 85, 101, 153]. In the absence of chemotherapy and with daily doses of 1.3–1.5 Gy, the TD_5 is 26.5 Gy and the TD_{50} is 30.5 Gy. Young children experience more chronic toxicity at lower doses than older children and adults because of interference with lung and chest wall development, in addition to fibrosis and volume loss. After 20 Gy, mean total lung volumes and DLCO are reduced to 60% of predicted values [153]. Even within the dose range currently used for whole lung irradiation (11–14 Gy), restrictive changes occur [10, 74, 85].

Fractionated Dose, Partial Lung Volume. Clinical tolerance of partial lung volumes to fractionated radiation is not well quantified. There are, however, some relevant data from Mah and colleagues [77]. They showed that, using an increase in lung density within the irradiated volume on CT in the post-treatment period as an endpoint, each 5% increase in effective dose was associated with a 12% increase in the incidence of pneumonitis. Doses above 30 Gy over a period of 10–15 days, and 45–50 Gy over a period of 25–30 days, caused radiographic changes in 30–90% of patients. The need for a clinical guideline in estimating radiation injury prompted the collaborative work by a task force to address the normal tissue tolerance in the standard, fractionated radiation setting. Information was obtained from a diverse group of patients afflicted with various diseases of the thoracic region, but mostly from patients with Hodgkin's disease, lung cancer or a disease requiring large-volume irradiation (hemibody or total body radiation) [33]. The doses agreed on by the physicians in the task-force are shown in Table 11.1.

Table 11.1. Lung tolerance dose (TD) in fractionated radiotherapy

Lung volume	TD 5/5[a]	TD 50/5[b]
1/3	4500 cGy	6500 cGy
2/3	3000 cGy	4000 cGy
3/3 (whole lung)	1750 cGy	2450 cGy

[a] The probability of 5% complication within 5 years of treatment
[b] The probability of 50% complication within 5 years of treatment

11.2.3 Chemotherapy: Clinical Manifestations

As increasing numbers of patients are cured with chemotherapy, reports of agents responsible for acute, and possibly chronic, pulmonary toxicity are expanding. Drug-related lung injury is most commonly an acute phenomenon, occurring during or shortly after the chemotherapeutic agent(s) are administered [25]. Three typical patterns of pulmonary toxicity have been described: pneumonitis or fibrosis, acute hypersensitivity (or inflammatory interstitial pneumonitis) and noncardiogenic pulmonary edema. Hypersensitivity reactions are rare but can be induced by such agents as methotrexate, procarbazine, bleomycin, BCNU and paclitaxel. Cough, dyspnea, low-grade fevers, eosinophilia, "crackles" on exam and interstitial or alveolar infiltrates are noted. These reactions occur during therapy and usually resolve with discontinuation of the offending drug and, potentially, corticosteroid use. Noncardiogenic pulmonary edema, characterized by endothelial inflammation and vascular leak, may arise upon initiation of treatment with methotrexate, cytosine arabinoside, ifosfamide, cyclophosphamide and interleukin-2 [25, 70, 132]. All-trans retinoic acid (ATRA) syndrome occurs in 23–28% of patients receiving

ATRA. Pulmonary edema has also been described in patients treated with bleomycin who are exposed to supplemental oxygen. These acute reactions generally have a good prognosis. Hypersensitivity reactions and non-cardiogenic pulmonary edema are unlikely to result in late-onset pulmonary toxicity.

Drug-induced pneumonitis or fibrosis has a similar clinical presentation to that described after RT. Bleomycin, the nitrosoureas and cyclophosphamide are most commonly the etiologic agents, although methotrexate and vinca alkaloids have also been implicated [25]. This syndrome is particularly worrisome because symptoms may not be detectable until months after a critical cumulative dose has been reached or exceeded. In addition, persistent subclinical findings may indicate a potential for late decompensation.

Bleomycin. The incidence of bleomycin pulmonary toxicity is 6–10%, with a mortality of 1–2%. One study in children with rhabdomyosarcoma exposed to bleomycin demonstrated an incidence of toxicity of 70% based on decreased DLCO [62]. A risk factor for bleomycin-induced pulmonary toxicity is the cumulative dose with a 10% risk at doses of 400–500 IU/m^2 [13, 120] although injury may occur at doses as low as 20 IU/m^2. The elderly [13] and children or adolescents [39] may be more sensitive, especially when bleomycin is administered in conjunction with RT. Of children treated for Hodgkin's disease with 70–120 IU/m^2 of bleomycin [39], 9% had grade 3 or 4 pulmonary toxicity, according to DLCO. Three patients (5%) had clinical symptomatology, and one patient died. Only one patient had received RT. Although pediatric trials now use a significantly lower maximal dose than many adult studies, 80% of the drug is excreted by the kidney, which can result in an increased risk of toxicity due to renal insufficiency [100, 130]. Other chemotherapeutic agents, such as cisplatin, cyclophosphamide, doxorubicin, methotrexate and vincristine [8, 108] may also increase risk. Exposure to high levels of oxygen or to pulmonary infection, especially within a year of treatment, is associated with a risk for immediate progressive respiratory failure [42]. Risks associated with surgery after treatment with bleomycin may be due to fluid overload [31]. These risks may persist for longer periods of time. There may be a potential increase in pulmonary toxicity with the use of granulocyte colony stimulating factor (G-CSF), which mediates via the increased numbers of neutrophils [7, 26].

Patients with acute bleomycin toxicity most commonly present with dyspnea and a dry cough. Fine bibasilar rates may progress to coarse rales involving the entire lung. Radiographs reveal an interstitial pneumonitis with a bibasilar reticular pattern or fine nodular infiltrates. In advanced cases, widespread infiltrates are seen, occasionally with lobar consolidation [120]. The consolidation may involve only the upper lobes, however. Large nodules may mimic metastatic cancer [81]. Loss of lung volume may occur. Pulmonary function testing reveals a restrictive ventilatory defect with hypoxia, hypocapnia and chronic respiratory alkalosis due to impaired diffusion and hyperventilation [140]. The DLCO is thought by some to be the most sensitive screening tool for bleomycin toxicity [140]. In patients who develop mild toxicity, discontinuation of bleomycin may lead to a reversal of the abnormalities [28], but some patients will have persistent radiographic or pulmonary-function abnormalities [9, 95, 151].

Nitrosoureas. The risk of nitrosourea pulmonary toxicity is age and dose-dependent with patients who have received higher doses of nitrosoureas (e.g. greater than 1500 mg/m^2 in adults and 750 mg/m^2 in children) more likely to present with an interstitial pneumonitis identical to that seen after bleomycin therapy [1]. Fibrosis may be early onset or late onset. Radiation therapy also increases risk, as does underlying pulmonary abnormality, such as chronic obstructive pulmonary disease, although this is rarely a factor in children. Bone marrow transplant patients may develop pulmonary fibrosis with BCNU as one of the contributing etiologies [92]. As part of a preparative regimen including etoposide and melphalan, BCNU at 600 mg/m^2 was associated with unacceptable pulmonary toxicity, but doses of 450 mg/m^2 were tolerated in the acute period [2]. Chemotherapy prior to bone marrow transplant may induce inflammatory changes that render the lung more susceptible to further, potentially irreversible, injury with

Table 11.2. Pulmonary toxicity of commonly used chemotherapy agents

Agent	Toxicity	Risk factors
Bleomycin	Interstitial pneumonitis Fibrosis Non-cardiogenic pulmonary edema	Age, cumulative dose, renal impairment, radiation therapy, oxygen therapy, fluid overload, combination chemotherapy
Nitrosoureas	Interstitial pneumonitis Fibrosis	Age, cumulative dose, combination chemotherapy
Cyclophosphamide	Fibrosis Non-cardiogenic pulmonary edema	Radiation therapy, oxygen therapy, combination therapy
Methotrexate	Interstitial pneumonitis Non-cardiogenic pulmonary edema Fibrosis Bronchospasm	No clearly identified risk factors No clearly identified risk factors No clearly identified risk factors No clearly identified risk factors
Busulfan	Fibrosis	Potentially dose, combination chemotherapy, radiation therapy
Cytosine arabinoside	Non-cardiogenic pulmonary edema	No clearly identified risk factors

high dose therapy [11]. Although pulmonary fibrosis has been most commonly associated with BCNU, it has been described after other nitrosoureas as well [12, 29]. Bibasilar rales with a bibasilar reticular pattern may be seen on chest radiograph, and restrictive ventilatory defects are seen. Abnormalities may be restricted to the upper lobes. A decreased diffusion capacity may precede all other signs [124]. Discontinuation of therapy may alter the course of BCNU-induced pulmonary disease. However, once pulmonary infiltrates are noted, the disease may be irreversible [150]. In a documented study, 47% of survivors of childhood brain tumors treated with BCNU and radiation died of lung fibrosis, 12% within 3 years of treatment and the remainder 6–17 years post treatment. Additional patients were known to have pulmonary fibrosis and remained at risk for late decompensation. In this study, age was a risk factor. The median age of the patients who died was 2.5 years, and the median age of survivors 10 years. All patients treated under the age of 5 years had died [93].

Cyclophosphamide. Fibrosis after treatment with cyclophosphamide is rare, with a reported incidence less than 1%. However, Makipemaa and colleagues [79] found that four of 15 children treated with high-dose cyclophosphamide without mediastinal RT had significantly decreased forced vital capacities; two of these children also had a decreased FEV_1. In addition, one of the children had pulmonary fibrosis and a chest deformity. Two children who received more than 50 g/m^2 of cyclophosphamide had delayed (greater than 7 years) fatal pulmonary fibrosis, with severe restrictive lung disease. Severely decreased anteroposterior chest dimensions in these patients were attributed to inability of the lung to grow in accordance with body growth. Fibrosis may also develop late after prolonged treatment with relatively low doses of cyclophosphamide. Although there may be recovery if symptoms occur during therapy and the drug is discontinued and treatment instituted with corticosteroids, the course may be one of progressive fibrosis.

Other Agents. Acute pulmonary effects have occurred with cytosine arabinoside (noncardiogenic pulmonary edema) [3, 52] and vinca alkaloids in association with mitomycin (bronchospasm or interstitial pneumonitis) [24, 48], but delayed pulmonary toxicity has not been described. Hypersensitivity reactions to the antimetabolites (methotrexate,

mercaptopurine and azathioprine) may cause either a desquamative interstitial pneumonitis or an eosinophilic pneumonitis [70, 141, 145]. Recovery usually occurs within 10–45 days after methotrexate-induced pulmonary toxicity [131].

However, long-term follow-up of 26 childhood-leukemia survivors revealed that 17 (65%) patients had one or more abnormalities of vital capacity, total lung capacity, reserve volume or diffusion capacity [125]. All children with these deficiencies were diagnosed and treated before age eight. The findings have also been attributed to an impairment of lung growth, which normally proceeds exponentially by cell division during the first eight years of life. Other studies have also demonstrated long-term changes in pulmonary function in survivors of ALL treated without spinal radiation or bone marrow transplant [91].

Busulfan can result in late pulmonary fibrosis, with no consistently identified risk factors. Unlike many other agents, the risk does not appear to be dose-related. The clinical and pathologic picture is like that of bleomycin-induced fibrosis. The mortality from busulfan fibrosis is high [1]. Although reports of pulmonary toxicity with other agents are rare, pneumonitis and fibrosis should be considered in the differential of patients presenting with respiratory symptoms. New agents may also present a risk for late pulmonary toxicity. See Table 11.2. [1, 82].

11.2.4 Chemotherapy–Chemotherapy Interactions

In considering the risk of pulmonary toxicity from chemotherapy, the potential for chemotherapy–chemotherapy interactions must be taken into account. Toxicity is seen at much lower doses than expected with drug combinations such as nitrosoureas and cyclophosphamide [133], bleomycin and cisplatin, or vincristine, doxorubicin and cyclophosphamide [8, 70, 108]. Vinca alkaloids appear to cause pulmonary toxicity only in the presence of mitomycin [24, 70].

11.2.5 Radiation and Chemotherapy Combinations: Interaction and Tolerance

Many antineoplastic agents potentiate the damaging effects of radiation on the lung. Phillips [102] and Wara [146] demonstrated that dactinomycin administration lowered the radiation dose threshold for pneumonitis. Testing the effects of commonly used chemotherapeutic agents, Phillips and colleagues [103] reported that the administration of dactinomycin, cyclophosphamide and, to a lesser extent, vincristine enhanced the lethal potential of thoracic irradiation. The effect of dactinomycin was seen when given as long as 30 days before irradiation, but it was not seen when given 30 days after the irradiation. The administration of bleomycin and lung irradiation together produces lung toxicity that is more common and severe than when either agent is given alone. Catane [18] found pulmonary toxicity in 19% of patients, and it was fatal in 10%. This toxicity appears to be maximal when bleomycin is given concurrently with radiation [32]. Although 500 IU of bleomycin without RT can be lethal in 1–2% of patients, as little as 30 IU can be fatal when given with RT. The effects of RT are also potentiated by doxorubicin. In addition to the enhanced toxicity observed in skin, intestines and heart, the lung also appears to be very sensitive to this combination [17, 19]. Of 24 patients with lung cancer treated with low-dose doxorubicin and RT, 13 developed pneumonitis [142].

11.3 Detection and Screening

Pulmonary disease occurring in patients treated for cancer can present a diagnostic problem because of the multiplicity of possible etiologies. Progressive cancer, infections, emboli, allergy, irradiation or drugs (and their interaction) can be causative. Clinical findings, radiologic studies and pulmonary function tests can be nonspecific; however, these factors represent measurable endpoints to quantify toxicity.

11.3.1 Measurable Endpoints

Symptoms. Fever, cough and shortness of breath are the most common symptoms of radiation-induced pneumonopathy. Temperature, respiratory rate, frequency of cough and the nature of sputum produced should all be recorded. Varying degrees of dyspnea, as well as orthopnea, can be present, depending on the severity of pulmonary damage. To standardize grading in the literature, the grading criteria in Common Terminology Criteria for Adverse Events (CTCAE), published by National Cancer Institute and National Institute of Health [23], have been expanded to be useful for the long-term survivor.

Sign. The principal signs of both acute and delayed radiation-induced pneumonopathy are the increase in respiratory rate percussion of a pleural effusion, auscultation of rales or rhonchi and, in severe cases, cyanosis.

Radiography. Plain anteroposterior (AP) and lateral chest films are useful when disease involves a large volume of lung. The acute pneumonitic phase manifests as a fluffy infiltrate, and the late fibrotic phase can follow the intermediate phase of contraction. However, routine chest radiography has a low level of reliability in detecting small volumes of pneumonopathy, particularly if they are located close to the chest wall. Chest radiography also lacks the ability to quantify the volume of affected lung, versus the total lung volume.

When chronic fibrosis occurs, chest radiography generally reveals scarring that corresponds to the shape of the radiation portal. CT scans have the capability of presenting three-dimensional images and calculating three-dimensional volumes of functional lung in a defined range of Hounsfield units. One can also detect small infiltrates that may be adjacent to the chest wall, for example, in the case of tangential field RT, where infiltrates are calculated as a percentage of the total lung volume. Mah [76, 77] has shown a quantitative relationship between the volume of abnormality on CT and RT dose (converted to a single-dose equivalent).

Radiographic changes after chemotherapy are often bibasilar fibrosis. Fibrosis confined to the upper lobes has also been described after treatment with BCNU [96] and bleomycin [80].

Pulmonary Function Tests (PFTs). The various PFTs that are available can be divided primarily into those performed in a pulmonary function laboratory and those performed in a nuclear medicine unit. Classic PFTs include measurement of static lung volumes, static and dynamic mechanical properties, airway reactivity, small airway function and gas exchange functions. A wide range of abnormalities in PFTs has been reported during both the acute and chronic phases of radiation-induced pneumonopathy. The abnormalities will, of course, relate to the volume of lung irradiated as well as the dose. Decreases have been noted in vital capacity, inspiratory capacity, total lung capacity, residual volume and FEV_1. Decreases in lung compliance have also been measured.

The goal of the classic PFTs is to determine the pattern of pulmonary disease that affects the patient in order to provide definitions of restrictive, obstructive and interstitial disease. Restrictive patterns are generally found after RT or chemotherapy injury, with reductions in the vital capacity, lung volumes and total lung capacity. Combined obstructive restrictive patterns may be seen, resulting in reduced lung volumes, but fibrotic injury also reduces airway patency. Finally, there is abnormal gas transfer because of the change in the alveolar capillary barrier. This can be measured by the carbon monoxide–lung diffusion test and, in more severe cases, will also be reflected in elevated arterial oxygen and carbon dioxide levels.

The basic evaluation that is most valuable in studying patients who have had lung injury consists of the measurement of maximum inspiratory and expiratory pressures, forced vital capacity and the FEV_1, as well as the FEV_1/FVC%. The findings usually indicate whether there is an obstructive or restrictive pattern and to what degree pulmonary function is impaired. The evaluation consists of a screening spirometry panel, followed by an examination of static lung volume, such as total lung capacity, functional residual capacity and residual volume. Finally,

it is essential to perform a carbon monoxide diffusion test to measure the degree of alveolar–capillary block. Diffusion results should be corrected for anemia. Combining these various measurements into a grading system of pulmonary function is difficult.

All these tests are quantitative but must be related to the expected level of function in a person of the same age and size, or preferably to measurements performed before the anticancer therapy was begun, if the measurements were not affected by tumor itself. Abnormal PFTs prior to treatment, which are commonly observed in lung cancer patients with severe COPD, may also alert the practitioner to patients at higher risk for pulmonary toxicity. PFTs may be impossible to obtain in younger children or in children who cannot cooperate. PFTs must be interpreted in the context of the patient's clinical status. In addition, PFT abnormalities may be present in the absence of clinical symptoms and may herald the development of clinical disease. However, they are not predictive of the development of clinical disease, which may also develop despite normal PFTs.

Nuclear Medicine Tests. In evaluating radiation-induced pneumonopathy, qualitative and quantitative radionuclide studies have been applied in some institutions. They consist of perfusion studies, ventilation studies, gallium scans and quantitative ventilation-perfusion scintigraphy. These nuclear studies have been primarily for research interests and have not been routinely applied to the clinical management of patients.

A perfusion scan is usually obtained with micro-aggregated albumin labeled with ^{99m}Tc, or similarly labeled microspheres, which are injected intravenously and imaged in eight views to ensure that the entire lung can be seen. Ventilation studies can be carried out either with ^{133}Xe or ^{127}Xe by inhalation. The wash-in, equilibration and washout phases can be observed, generally through posterior and oblique views. Because of energy and half-life, the ^{133}Xe test is done before the perfusion study and the ^{127}Xe test after the perfusion scan. Generally, both should be employed and, if possible, quantified. The advantage over classic PFTs is that scans will show regional function, which can be correlated with irradiated volume.

In some situations the ventilation study with xenon may be done with krypton; although krypton is more expensive. Finally, aerosols of ^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) can be substituted for an inspiration gas study. The pair of studies (i.e. perfusion and ventilation) is often termed a V-Q scan; the letter V stands for ventilation, Q for perfusion. Gallium scans of the lungs can be useful in assessing and quantifying bleomycin, cyclophosphamide and busulfan chemotherapy injury to the lung. Gallium scans can also be used to separate radiation-induced pneumonopathy from *Pneumocystis carinii* pneumonopathy because the latter will label heavily with gallium.

Quantitative ventilation–perfusion scintigraphy consists of three different studies. The first is ventilation per unit volume; the second is blood flow to ventilated alveoli; and the third is blood flow per unit ventilated lung volume. The second, that is, blood flow to ventilated alveoli, has proven most useful in quantifying RT injury.

Laboratory Tests of Serum or Blood. Clinical studies have reported a number of clinical factors contributing to the risk of developing radiation pneumonitis after therapy. Among these are total lung radiation dose, irradiated lung volume exceeding 20 Gy vs 25 Gy vs 30 Gy, mean lung dose, fractionation of radiotherapy, daily fraction size, performance status, pre-treatment pulmonary function, gender, low pre-treatment blood oxygen and high C-reactive protein and others [44, 54, 59, 68, 110, 112, 123]. Erythrocyte sedimentation rate (ESR) has been evaluated as a potential early marker of pulmonary toxicity from bleomycin [55]. The non-specific nature of this value may make clinical application difficult, as rises would also be expected in infection or recurrent disease. Despite the identification of these clinical contributing factors, research has tended to focus on the development of a reliable and simple diagnostic laboratory test that could predict the risk of post-radiation pneumonitis and, in particular, could be administered prior to the start of therapy.

The usefulness of serum or blood laboratory tests is as yet undefined; there is a need for early biochemical markers of normal-tissue damage that would predict late effects and that would allow the radiation oncologist and medical oncologist to determine whether their treatment is exceeding normal tissue tolerance [113]. If biochemical markers of tissue damage could be detected in the subclinical phase, prior to the accumulation of significant injury, one could terminate therapy or institute treatment to prevent or attenuate later lesions. An ideal marker would be a simple, reproducible positive or negative biochemical test. In the recent years, some circulating cytokine markers have been independently found to be potential predictors of radiation pneumonitis. These include proinflammatory cytokines interleukin 1α (IL-1α) and interleukin 6 (IL-6) [21, 22], fibrotic cytokine- transforming growth factor β (TGF-β) [4] and ICAM [60]. Chen and colleagues recently tested the ability of IL-1α and IL-6 measurements to predict radiation pneumonitis (unpublished data). The predictive power of IL-1α and IL-6 appeared to be strongest for the blood samples collected prior to radiotherapy than during RT. While both inflammatory cytokines can serve as diagnostic testing tools, IL-6 was found to be a more powerful predictor than IL-1α of radiation pneumonitis. The specificity and positive predictive value of IL-6 were as high as 89% for the blood samples collected prior to RT. The application of these cytokine markers in the predictive diagnosis of radiation pneumonitis may prove to have clinical utility in the near future and deserves further investigation.

In addition to cytokines, the release of many substances into the circulation could reflect, and may also predict, the degree of RT and chemotherapy injury to the lung. These include the surfactant apoprotein, procollagen type 3 angiotensin-converting enzyme, blood plasminogen-activating factor and prostacyclin. These various substances have been correlated with either acute or delayed radiation-induced pneumonopathy. Significant additional work is required to evaluate the usefulness of such blood level measurements.

11.4 Management of Established Pulmonary Toxicity Induced by Cytotoxic Therapy

Hopefully in the future, pulmonary toxicity will be prevented rather than managed. Strict attention should be paid to drug doses and cumulative drug–dose restrictions. When RT is given, volumes and doses should be minimized and given in accordance with accepted tolerance. During drug therapy, monitoring of symptoms and signs, PFTs and chest radiographs can aid in detecting problems early, and the causative agent can be withdrawn. After withdrawal of bleomycin, early stages of bleomycin-induced pneumonitis have reversed clinically and radiographically [81].

11.4.1 Precautions for Minimizing Potential Complications

Assessing baseline breathing condition and PFTs prior to therapy is most helpful for patients with underlying pulmonary pathology such as emphysema, COPD and idiopathic lung fibrosis. The detection of abnormalities may allow for better anticipatory guidance and counseling. Counseling on the risks of smoking is imperative for these patients, even in the absence of symptoms or abnormalities on evaluation. Patients should also be aware of the potential risks of general anesthesia and notify physicians of their treatment history if they are to undergo anesthesia. For those with compromised lung condition, therapy should be tailored to minimize injury from cytotoxic agents and radiation damage. When following survivors of cancer, vigilant evaluation of symptoms of respiratory compromise is necessary and should be anticipated when thoracic RT or drugs with known pulmonary toxicity have been used. Depending on the findings and other circumstances, lung biopsy may be considered to confirm fibrosis or exclude the recurrence of cancer. Chronic cough, dyspnea or change in exercise should be further evaluated with chest radiography and PFTs. This is also imperative in patients scheduled for general anesthesia. In the absence of symptoms, chest radiographs and

lung function testing are recommended every 2–5 years. The number of potential pulmonary toxic agents, the cumulative doses and the radiation dose and field size are all factors to be considered in setting follow-up intervals.

11.4.2 Preventative Therapy

The difficult issue in screening is that there is no definitive therapy. Before therapy, the prophylactic administration of steroids has no proven benefit and may present potential risks. A study of inhaled fluticasone propionate, however, demonstrated some potential benefit with reduction of acute pneumonitis in patients treated for breast cancer [83]. Confirmation of this benefit and whether like interventions can reduce long-term pulmonary sequelae requires further study. The role of amifostine as a radioprotector in preventing lung toxicity has been investigated. Amifostine is a sulfhydryl compound that was originally developed as an agent to protect against ionizing radiation in the event of nuclear war [27, 121]. It was also found to protect normal tissues from toxicities of radiotherapy for head and neck tumors [15], alkylating agents and cisplatin [148, 154]. Recent clinical studies have shown a reduction in pneumonitis using amifostine in chemoradiation treatments for lung cancer [5, 67].

There is a lack of studies quantifying the impact of smoking after exposure to chemotherapy and radiation therapy, but it very likely increases the risk of lung damage. In the Childhood Cancer Survivors Study (CCSS), survivors smoked at lower rates than the general population, but more than a quarter reported a history of having ever smoked, and 17% reported currently smoking [34]. Smokers who responded to the study expressed a higher desire to quit than the general population. Interventions have been developed and studied to decrease smoking and improve smoking cessation in long-term survivors [35, 139].

11.4.3 Therapy for Established Toxicity

Corticosteroids play a useful role in the relief of symptoms from pneumonitis caused by a variety of drugs and RT. Severe symptoms necessitating treatment can be relieved markedly and rapidly by corticosteroids in half of affected patients [87, 151, 152]; however, prevention or reversal of the fibrotic phase does not occur. Supportive care with bronchodilators, expectorants, antibiotics, bed rest and oxygen can be beneficial for relief of symptoms in pneumonitis and fibrosis. In cases of radiation or chemotherapy-induced pneumonitis in which corticosteroids have been used, it is important to withdraw steroids very slowly to avoid reactivation.

11.5 Future Studies

We have come to appreciate the complexity of interstitial pneumonitis from cancer therapy, now seen as a process involving an active communication and interaction between resident cell types of the lung parenchyma and circulatory immune and inflammatory cells. There is increasing evidence of immune cells augmenting pneumonitis through complex autocrine, paracrine and systemic regulatory mechanisms critically orchestrated by cytokines [20, 117].

Further investigation of the molecular mechanisms involved in pneumonitis and fibrosis will allow for timely intervention and proper protection. Substances such as interferons that oppose or inhibit fibrosis-promoting growth factors potentially may be used during therapy, resulting in the desired enhanced therapeutic ratio. Chemoprotective agents are being investigated for their ability to reduce the toxicity of chemotherapy, including lung injury. It is essential, of course, that they do not disturb the efficacy of the treatment. Improvement of radiotherapy targeting and normal tissue sparing, such as three-dimensional conformal radiotherapy and intensity modulated radiotherapy (IMRT), will minimize radiation to non-target normal lung tissue. Novel interventions, such as mechanisms to increase the level of bleomycin hydrolase in susceptible patients or viral-mediated transfer of a bleomycin resistance gene,

may hold promise for future applications in clinical treatment. What may prove to be the most important is the recognition of those at enhanced risk for long-term pulmonary toxicity as a result of their genotype. Understanding of such risk factors could lead to therapy tailored to an individual risk profile.

References

1. Abid S, Malhotra V, Perry M (2001) Radiation induced and chemotherapy induced pulmonary injury. Curr Opin Oncol 13:1–16
2. Ager S, Mahendra P, Richards EM, Bass G, Baglin TP, Marcus RE (1996) High-dose carmustine, etoposide and melphalan (BEM) with autologous stem cell transplantation: a dose-toxicity study. Bone Marrow Transplant 17:335–340
3. Anderson BS, Cogan BM, Keating MJ (1984) Subacute pulmonary failure complicating therapy with high dose ara-C in acute leukemia. Cancer 56:2181–2184
4. Anscher MS, Kong F-M, Andrews K (1998) Plasma transforming growth factor ß1 as a predictor of radiation pneumonitis. Int J Radiat Oncol Biol Phys 41:1029–1035
5. Antonadou D, Throuvalas N, Petridis A (2003) Effect of amifostine on toxicities associated with radiochemotherapy in patients with locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 57:402–408
6. Antonia SJ, Wagner H, Williams C (1995) Concurrent paclitaxel/cisplatin with thoracic radiation in patients with stage III A/B non-small cell carcinoma of the lung. Semin Oncol 22:34–37
7. Azoulay E, Herigault S, Levame M, Brochrd L, Schlemmer B, Harf A, Delclaux C (2003) Effect of granulocyte colony stimulating factor on bleomycin-induced acute lung injury and pulmonary fibrosis. Crit Care Med 31:1442–1448
8. Bauer KA, Skarin AT, Balikian JP (1983) Pulmonary complications associated with combination chemotherapy programs containing bleomycin. Am J Med 74:557–563
9. Bellamy EZ, Husband JE, Blaquiere RM (1985) Bleomycin related lung damage: CT evidence. Radiology 156:155–158
10. Benoist MR, Lemerle J, Jean R, Rufin P, Scheinmann P, Paupe J (1982) Effects on pulmonary function of whole lung irradiation for Wilms' tumor in children. Thorax 37: 175–180
11. Bhalla KS, Wilczynski SW, Abushamaa AM, Petros WP (2000) Pulmonary toxicity of induction chemotherapy prior to standard or high-dose chemotherapy with autologous hematopoietic support. Am J Resp Crit Care Med 161:17–25
12. Block M, Lachowiez RM, Rios C (1990) Pulmonary fibrosis associated with low-dose adjuvant methyl-CCNU. Med Pediatr Oncol 18:256–260
13. Blum RH, Carter SK, Agre K (1973) A clinical review of bleomycin – a new antineoplastic agent. Cancer 31:903–914
14. Bossi G, Cerveri I, Volpini E, Corsico A, Baio A, Corbella F, Klersy C, Arico M (1997) Long-term pulmonary sequelae after treatment of childhood Hodgkin's disease. Ann Oncol 8 [Suppl 1]:19–24
15. Brizel DM, Wassernan TH, Henke M (2000) Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 18:3339–3345
16. Burger A, Loffler H, Bamberg M, Rodenmann HP (1998) Molecular and cellular basis of radiation fibrosis. Int J Radiat Biol 73:401–408
17. Cassady JR, Richter MP, Piro AJ (1975) Radiation-Adriamycin interactions: preliminary clinical observations. Cancer 36:946–949
18. Catane R, Schwade JG, Turrisi AT (1979) Pulmonary toxicity after radiation and bleomycin: a review. Int J Radiat Oncol Biol Phys 5:1513–1518
19. Chan PYM, Kagan AR, Byfteld JE (1979) Pulmonary complications of combined chemotherapy and radiotherapy in lung cancer. Front Radiat Ther Oncol 13:136–144
20. Chen Y, Okunieff P, Ahrendt SA (2003) Translational research in lung cancer. Semin Surg Oncol 21:205–219
21. Chen Y, Rubin P, Williams J (2001) Circulating IL-6 as a predictor of radiation pneumonitis. Int J Radiat Oncol Biol Phys 49:641–648
22. Chen Y, Williams J, Ding I (2002) Radiation pneumonitis and early circulatory cytokine markers. Semin Radiat Oncol 12:26–33
23. Common Terminology Criteria for Adverse Events (CTCAE) (2003) Version 3.0. US Department of Health and Human Services. National Institutes of Health, National Cancer Institute
24. Cooper JA, Zitnik R, Matthay RA (1988) Mechanisms of drug-induced pulmonary disease. Ann Rev Med 39:395–404
25. Cooper JAD, White DA. Matthay RA (1986) Drug induced pulmonary disease, part I. Cyto-toxic drugs. Am Rev Respir Dis 133:321–340
26. Couderc LJ, Stelianides S, Frachon I, Stern M, Epardeau B, Baumelou E, Caubarrere I, Hermine O (1999) Pulmonary toxicity of chemotherapy and G/GM-CSF: a report of five cases. Resp Med 93:65–68
27. Davidson DE, Grenan MM, Sweeney TR (1980) Biological characteristics of some improved radioprotectors. In: Brady LW (ed) Radiation sensitizers. Masson, New York, pp 309–320
28. DeLana M, Guzzon A, Monfardini S (1972) Clinical radiologic and histopathologic studies on pulmonary toxicity induced by treatment with bleomycin. Cancer Chemother Rep 56:343–355
29. Dent RG (1982) Fatal pulmonary toxic effects of lomustine. Thorax 37:627–629

30. Doll DC, Ringenberg Q, Yarbo JW (1986) Vascular toxicity associated with antineoplastic agents. J Clin Oncol 4:1405–1417
31. Donat SM, Levy DA (1998) Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? J Urol 160:1347–1352
32. Einhom L, Krause M, Homback N (1976) Enhanced pulmonary toxicity with bleomycin and radiotherapy in oat cell lung cancer. Cancer 37:2414–2416
33. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B/ Solin LJ, Wesson M (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21:109–122
34. Emmons K, Li FP, Whitton J, Mertens AC, Hutchinson R, Diller L, Robison LL (2002) Predictors of smoking initiation and cessation among childhood cancer survivors: a report from the childhood cancer survivor study. J Clin Oncol 20:1608–1616
35. Emmons KM, Butterfield RM, Puleo E, Park ER, Mertens A, Gritz ER, Lahti M, Li FP (2003) Smoking among participants in the childhood cancer survivors cohort: the Partnership for Health Study. J Clin Oncol 21:189–196
36. Engelstad RB (1940) Pulmonary lesions after roentgen and radium irradiation. Am J Roentgenol 43:676–681
37. Evans RF, Sagerman RH, Ringrose TL (1974) Pulmonary function following mantle field irradiation for Hodgkin's disease. Radiology 111:729–731
38. Fontán JP, Haddad GG (2004) St Louis respiratory pathophysiology. In: Behrman RE, Kliegman RM, Jenson H (eds) Nelson textbook of pediatrics. Elsevier, Amsterdam, pp 1362–1370
39. Fryer CJ, Hutchinson RJ, Krailo M (1990) Efficacy and toxicity of 12 courses of ABVD chemotherapy followed by low-dose regional radiation in advanced Hodgkin's disease in children: a report from the children cancer study group. J Clin Oncol 8:1971–1980
40. Fryer CJH, Fitzpatrick PJ, Rider WD (1978) Radiation pneumonitis: experience following a large single dose of radiation. Int J Radiat Oncol Biol Phys 4:931–936
41. Germon PA, Brady LW (1968) Physiologic changes before and after radiation treatment for carcinoma of the lung. JAMA 206:809–814
42. Gilson AJ, Sahn SA (1985) Reactivation of bleomycin lung toxicity following oxygen administration. Chest 88:304–306
43. Glazer HS, Lee JKT, Levitt RG (1985) Radiation fibrosis: differentiation from recurrent tumor by MR imaging. Radiology 156:721–726
44. Graham MV, Burdy JA, Emami B (1999) Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 45:323–329
45. Gross NJ (1977) Pulmonary effects of radiation therapy. Ann Intern Med 86:81–92
46. Gross NJ (1980) Experimental radiation pneumonitis IV. Leakage of circulatory proteins onto the alveolar surface. J Lab Clin Med 95:19–31
47. Gross NJ (1981) The pathogenesis of radiation-induced lung damage. Lung 159:115–125
48. Gunstream SR, Seidenfeld JJ, Sobonya RE (1983) Mitomycin associated lung disease. Cancer Treat Rep 67:301–304
49. Hakenjos L, Bamberg M, Rodemann HP (2000) TGF-β1-mediated alterations of rat lung fibroblast differentiation resulting in the radiation -induced fibrotic phenoty. Int J Radiat Biol 76:503–509
50. Hale GA, Marina NM, Jones-Wallace D, Greenwald CA (1999) Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol 21:115–122
51. Hallahan DF, Virudachlam S (1997) Intercellular adhesion molecule –1 knockout abrogates radiation induced pulmonary inflammation. Proc Natl Acad Sci USA 94:6432–6437
52. Haupt HM, Hutchins GM, Moore GW (1981) Ara-C lung: non-cardiogenic pulmonary edema complicating cytosine-arabinoside therapy of leukemia. Am J Med 70:256–261
53. Hay J, Shahriar S, Laurent G (1991) Mechanisms of bleomycin-induced lung damage. Arch Toxicol 65:81–94
54. Hernando ML, Marks LB, Bentel GC (2001) Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 51:650–659
55. Higa GM, AlKhouri N, Auber ML (1997) Elevation of the erythrocyte sedimentation rate precedes exacerbation of bleomycin pulmonary toxicity: report of two cases and review of literature. Pharmacotherapy 17:1315–1321
56. Hirsch A, Vander Els N, Straus DJ, Gomez EG, Leung D, Portlock CS, Yahalom J (1996) Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease. J Clin Oncol 14:1297–1305
57. Hodson WA (1977) Development of the lung. Dekker, New York
58. Hoyt DG, Lazo JS (1992) Murine strain differences in acute lung injury and activation of poly(ADP-ribose) polymerase by in vitro exposure of lung slices to bleomycin. Am J Respir Ces Mol Biol 7:645–651
59. Inoue A, Kunitoh H, Sekine I (2001) Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 49:649–655
60. Ishii Y, Kitamura S (1999) Soluble intercellular adhesion molecule-1 as an early detection marker for radiation pneumonitis. Eur Respir J 13:733–738
61. Johnston CJ, Wright TW, Rubin P, Finkelstein JN (1998) Alterations in the expression of chemokine mRNA levels in fibrosis-resistant and -sensitive mice after thoracic irradiation. Exp Lung Res 4:321–337

62. Kaplan E, Sklar C, Wilmott R, Michaels S, Ghavimi F (1996) Pulmonary function in children treated for rhabdomyosarcoma. Med Pediatr Oncol 27:79–84
63. Kataoka M, Kawamura M, Itoh H (1992) Ga-67 citrate scintigraphy for the early detection of radiation pneumonitis. Clin Nucl Med 17:27–31
64. Kawana A, Shioya S, Katoh H, Tsuji C, Tsuda M, Ohta Y (1997) Expression of intercellular adhesion molecule-1 on alveolar macrophages in the acute stage of radiation -induced lung injury in rats. Radiat Res 147:431–436
65. Keane TJ, van Dyk J, Rider WD (1981) Idiopathic interstitial pneumonia following bone marrow transplantation: the relationship with total body irradiation. Int J Radiat Oncol Bio Phys 7:1365–1370
66. Kharasch VS, Lipsitz S, Santis W, Hallowell JA, Goorin A (1996) Long-term pulmonary toxicity of multiagent chemotherapy including bleomycin and cyclophosphamide in osteosarcoma survivors. Med Pediatr 27:85–91
67. Komaki R, Lee JS, Kaplan B (2002) Randomized phase III study of chemoradiation with or without amifostine for patients with favorable performance status inoperable stage II-III non-small cell lung cancer: preliminary results. Semin Radiat Oncol 12:46–49
68. Kwa SLS, Lebesque JV, Theuws JCM (1998) Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 42:1–9
69. Lazo JS, Merrill WW, Pham ET (1984) Bleomycin hydrolase activity in pulmonary cells. J Pharmacol Exp Ther 231:583–588
70. Lehne G, Lote K (1990) Pulmonary toxicity of cytotoxic and immunosuppressive agents. A review. Ada Oncol 29:113–124
71. Leroy EP, Liebner EJ, Jensick RJ (1966) The ultrastructure of canine alveoli after supervoltage irradiation of the thorax. Lab Invest 15:1544–1558
72. Libshitz HI, Shuman LS (1984) Radiation induced pulmonary change: CT findings. J Comput Assist Tomogr 8: 15–19
73. Libura J, Bettens F, Radkowski A, Tiercy JM, Piguet PF (2002) Risk of chemotherapy-induced pulmonary fibrosis is associated with polymorphic tumour necrosis factor-a2 gene. Eur Respir J 19:912–918
74. Littman P, Meadows AT, Polgar G (1976) Pulmonary function in survivors of Wilms' tumor: patterns of impairment. Cancer 37:2773–2776
75. Maasilta P, Hallman M, Taskinen E (1993) Bronchoalveolar lavage fluid findings following radiotherapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 26:117–123
76. Mah K, Poon PY, van Dyk J (1986) Assessment of acute radiation-induced pulmonary changes using computed tomography. J Comput Assist Tomogr 10:736–743
77. Mah K, van Dyk J, Keane T (1987) Acute radiation-induced pulmonary damage: a clinical study on the response to fractionated radiation therapy. Int J Radiat Oncol Biol Phys 13:179–188
78. Maisin JR (1974) The influence of radiation on blood vessels and circulation. HI. Ultrastructure of the vessel wall. Curr Top Radiat Res Q 10:29–57
79. Makipemaa A, Heino M, Laitnen L (1989) Lung function following treatment of malignant tumors with surgery, radiotherapy, or cyclophosphamide in childhood. Cancer 63:625–630
80. Marruchella A, Franco C, Garavaldi G, Uccelli M, Bottrighi P (2002) Bleomycin-induced upper lobe fibrosis: a case report. Tumori 88:414–416
81. McCrea ES, Diaconis JJN, Wade C (1981) Bleomycin toxicity simulating metastatic nodules to the lungs. Cancer 48: 1096–1100
82. McDonald S, Rubin P, Phillips TL, Marks LB (1995) Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. J Radiat Oncol Biol Phys 31:1187–1203
83. McGaughey DS, Nikcevich DA, Long GD, Vredenburgh JJ (2001) Inhaled steroids as prophylaxis for delayed pulmonary toxicity syndrome in breast cancer patients undergoing high-dose chemotherapy and autologous stem cell transplantation. Biol Blood Marrow Transplant 7:274–278
84. Mertens AC, Yasua Y, Liu Y, Stovall M (2002) Pulmonary complications in survivors of childhood and adolescent cancer. A report from the childhood cancer survivor study. Cancer 95:2431–2441
85. Miller RW, Fusner JE, Fink R (1986) Pulmonary function abnormalities in long term survivors of childhood cancer. Med Pediatr Oncol 14:202–207
86. Mosher RB, McCarthy BJ (1998) Late effects in survivors of bone tumors. J Pediatr Oncol Nurs 15:72–84
87. Moss WT, Haddy FJ, Sweany SK (1960) Some factors altering the severity of acute radiation pneumonitis: variation with cortisone, heparin and antibiotics. Radiology 75:50–54
88. Nadel J (2000) General principles and diagnostic approach. In: Murray JF, Nadel JA (eds) Textbook of respiratory medicine. Saunders, St Louis, pp 1173–1182
89. Nakayama Y, Makino S, Fukuda Y (1996) Activation of lavage lymphocytes in lung injuries caused by radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 34:459–467
90. Neve V, Foot AB, Michon J, Fourquet A, Zucker JM, Boule M (1999) Longitudinal clinical and functional pulmonary follow-up after megatherapy, fractionated total body irradiation, and autologous bone marrow transplantation for metastatic neuroblastoma. Med Pediatr Oncol 32:170–176
91. Nysom K, Holm K, Olsen JH, Hertz H, Hesse B (1998) Pulmonary function after treatment for acute lymphoblastic leukaemia in childhood. Br J Can 78:21–27
92. O'Driscoll BR, Hasleton PS, Taylor PM (1990) Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. N Engl J Med 323:378–382
93. O'Driscoll BR, Kalra S, Gattamaneni HR, Woodcock AA (1995) Late carmustine fibrosis. Age ate treatment may influence severity and survival. Chest 107:1355–1357

94. Ortiz LA, Lasky JA, Hamilton R (1998) Expression of TNF and the necessity for TNF receptors in bleomycin-induced lung injury in mice. Exp Lung Res 24:721–743
95. Osanto S, Bukman A, van Hoek F (1992) Long term effects of chemotherapy in patients with testicular cancer. J Clin Oncol 10:574–579
96. Parish JM, Muhm JR, Leslie KO (2003) Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. Mayo Clin Proc 78:630–634
97. Penney DP, Rubin P (1977) Specific early fine structural changes in the lung following irradiation. Int J Radiat Oncol Biol Phys 2:1123–1132
98. Penney DP, Shapiro DL, Rubin P (1981) Effects of radiation on the mouse lung and potential induction of radiation pneumonitis. Virchows Arch B Cell Pathol 37:327–336
99. Penney DP, Siemann DW, Rubin P (1982) Morphologic changes reflecting early and late effects of irradiation of the distal lung of the mouse review. Scanning Microsc 1:413–4255
100. Perry DJ, Weiss RB, Taylor HG (1982) Enhanced bleomycin toxicity during acute renal failure. Cancer Treat Rep 66: 592–593
101. Phillips T (1981) Pulmonary section-cardiorespiratory workshops. Cancer Clin Trial 4 [Suppl]:45–52
102. Phillips TL, Margolis L (1972) Radiation pathology and the clinical response of lung and esophagus. Front Radiat Ther Oncol 6:254–273
103. Phillips TL, Wharam MD, Margolis LW (1975) Modification of radiation injury to normal/tissues by chemotherapeutic agents. Cancer 35:1678–1684
104. Phillips TL, Wyatt JP (1980) Radiation fibrosis. In: Fishman AP (ed) Pulmonary diseases and disorders, vol 1. McGraw-Hill, New York
105. Post M, Copland I (2002) Overview of lung development. Acta Pharmacol Sin 23 [Suppl]:4–7
106. Prato FS, Kurdyak R, Saibil EA (1977) Physiological and radiographic assessment during the development of pulmonary radiation fibrosis. Radiology 122:389–397
107. Prato FS, Kurdyak R, Saibil EA (1977) Regional and total lung function in patients following pulmonary irradiation. Invest Radio 12:224–237
108. Rabinowiiz M, Souhami L, Gil RA (1990) Increased pulmonary toxicity with bleomycin and cisplatin chemotherapy combinations. Am J Clin Oncol 13:132–138
109. Reckzeh B, Merte H, Pflluger K-H (1996) Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small cell lung cancer. J Clin Oncol 14:1071–1076
110. Roach M, Gandara D, You H-S (1995) Radiation pneumonitis following combined modality therapy for lung cancer: analysis of prognostic factors. J Clin Oncol 13: 2606–2612
111. Roberts CM, Foulcher E, Zaunders JJ (1993) Radiation pneumonitis: a possible lymphocyte-mediated hypersensitivity reaction. Ann Intern Med 118:696–700
112. Robnett TJ, Machtay M, Vines EF (2000) Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 48:89–94
113. Rubin P (1977) Radiation toxicity: quantitative radiation pathology for predicting effects. Cancer 39 [Suppl 2]:729–736
114. Rubin P (1984) The Franz Busche lecture: late effects of chemotherapy and radiation therapy: a new 7 hypothesis. Int J Radiat Oncol Biol Phys 10:5–34
115. Rubin P, Finkelstein J, McDonald S (1991) The identification of new early molecular mechanisms in the pathogenesis of radiation induced pulmonary fibrosis. Int J Radiat Oncol Biol Phys 21 [Suppl I]:163 (abstract)
116. Rubin P, Finkelstien J, Shapiro D (1992) Molecular biology mechanisms in the radiation induction of pulmonary injury syndromes: interrelationship between the alveolar macrophage and the septal fibroblast. Int J Radiat Oncol Biol Phys 24:93–101
117. Rubin P, Johnston CJ, Williams JP (1995) A perpetual cascade of cytokines post-irradiation leads to pulmonary fibrosis. Int J Radiat Oncol Biol Phys 33:99–109
118. Rubin P, Shapiro DL, Finklestein JN (1980) The early release of surfactant following lung irradiation of alveolar type II cells. Int J Radiat Oncol Biol Phys 6:75–77
119. Rubin P, Siemann DW, Shapiro DL (1983) Surfactant release as an early measure of radiation pneumonitis. Int J Radiat Oncol Biol Phys 9:1669–1673
120. Samuels ML, Douglas EJ, Holoye PV (1976) Large dose bleomycin therapy and pulmonary toxicity. JAMA 235: 1117–1120
121. Schuchter L, Glick J (1993) The current status of WR-2721 (amifostine): a chemotherapy and radiation therapy protector. Biol Ther Cancer Update 1:1–10
122. Schwarz MI, King TE, Cherniack RM (2000) Principles of and approach to the patient with interstitial lung disease. In: Murray JF, Nadel JA (eds) Textbook of respiratory medicine. Saunders, St Louis, pp 1649–1670
123. Segawa Y, Takigawa N, Kataoka M (1997) Risk factors for development of radiation pneumonitis following radiation therapy with or without chemotherapy for lung cancer. Int J Radiat Oncol Biol Phys 39:91–98
124. Selker RG, Jacobs SA, Moore PB (1980) 1,3-Bis (2-chloroethyl)-l-nitrosourea (BCNU)-induced pulmonary fibrosis. Neurosurgery 7:560–565
125. Shaw NJ, Tweeddale PM, Eden OB (1989) Pulmonary function in childhood leukemia survivors. Med Pediatr Oncol 17:149–154
126. Shrivastava PN, Hans L, Concannon JP (1974) Changes in pulmonary compliance and production of fibrosis in x-irradiated lungs of rats. Radiology 112:439–440

127. Siemann DW, Hill RP, Penney DP (1982) Early and late pulmonary toxicity in mice evaluated 180 and 420 days following localized lung irradiation. Radiat Res 89:396–407
128. Siemann DW, Rubin P, Penney DP (1986) Pulmonary toxicity following multi-fraction radiotherapy. Br J Cancer 53:365–367
129. Simon G, Reiol L, Tanner SM (1972) Growth of radiobiologically determined heart diameter, lung width and lung lengths from 5–(19 years with standard for clinical use. Arch Dis Child 47:373–382
130. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH (1996) Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. Eur J Cancer 32A:550–552
131. Sostman HD, Matthay RA, Puinam CE (1976) Methotrexate induced pneumonitis. Medicine 55:371–389
132. Spector I, Zimbler H, Ross S (1979) Early-onset cyclophosphamide induced interstitial pneumonitis. JAMA 242: 2852–2854
133. Stewart P, Buckner CD, Thomas ED (1983) Intensive chemotherapy with autologous marrow transplantation for small cell carcinoma of the lung. Cancer Treat Rep 7:1055–1059
134. Theise ND, Henegariu O, Grove J, Jagirdar J, Kao PN, Crawford JM, Badve S, Saxena R, Krause DS (2002) Radiation pneumonitis in mice: a severe injury model for pneumocyte engraftment from bone marrow. Exp Hematol 30: 1333–1338
135. Thurlbeck WM (1975) Postnatal growth and development of the lung. Am Rev Respir Dis 111:803–843
136. Thurlbeck WM (1988) In: Murray JF, Nadel JA (eds) Textbook of respiratory medicine. Saunders, Philadelphia
137. Travis EL (1980) Early indicators of radiation injury on the lung: are they useful predictors for late changes? Int J Radiat Oncol Biol Phys 6:1267–1269
138. Travis EL, Hanley RA, Fenn JO (1977) Pathologic changes in the lung following single and multi-fraction irradiation. Int J Radiat Oncol Biol Phys 2:475–490
139. Tyc VL, Rai SN, Lensing S, Klosky JL, Stewart DB, Gattuso J (2003) Intervention to reduce intentions to use tobacco among pediatric cancer survivors. J Clin Oncol 21:1366–1372
140. Van Barneveld PWC, Veenstra G, Sleifer DT (1985) Changes in pulmonary function during and after bleomycin treatment in patients with testicular carcinoma. Cancer Chemother Pharmacol 14:168–171
141. Van Dyk J, Hill RP (1983) Postirradiation lung density changes measured by computerized tomography. Int J Radiat Oncol Biol Phys 9:847–852
142. Verschoore J, Lagrange JL, Boublil JL (1987) Pulmonary toxicity of a combination of low-dose doxorubicin and irradiation for inoperable lung cancer. Radiother Oncol 9:281–288
143. Vieras F, Bradley EW, Alderson PO (1983) Regional pulmonary function after irradiation of the canine lung: radionuclide evaluation. Radiology 147:839–844
144. Vujaskovic Z, Anscher MS, Feng QF, Rabbani ZN, Amin K, Samulski TS, Dewhirst MW, Haroon ZA (2001) Radiation-induced hypoxia may perpetuate late normal tissue injury. Int J Radiat Oncol Biol Phys 50:851–855
145. Wall MA, Wohl MEB, Jaffe N (1979) Lung function in adolescents receiving high dose methotrexate. Pediatrics 63: 741–746
146. Wara WM, Phillips TL, Margolis LW (1973) Radiation pneumonitis: a new approach to the derivation of time-dose factors. Cancer 32:547–552
147. Ward WT, Molteni A, Solliday SH (1985) The relationship between endothelial dysfunction and collagen accumulation in irradiated rat lung. Int J Radiat Oncol Biol Phys 11:1985–1990
148. Wasserman TH, Phillips TL, Ross G (1981) Differential protection against cytotoxic chemotherapeutic effects on bone marrow CFUs by WR-2721. Cancer Clin Trials 4:3–6
149. Weichselbaum RR, Awan AM (1987) Principles of radiation oncology. In: Bitran JD et al. (eds) Lung cancer-a comprehensive treatise. Grune and Stratton, Orlando
150. Weinstein AS, Diener-West M, Nelson DF (1986) Pulmonary toxicity of carmustine in patients treated for malignant glioma. Cancer Treat Rep 70:943–946
151. White DA, Stover DE (1984) Severe bleomycin induced pneumonitis. Clinical features and response to corticosteroids 86:723–728
152. Whitneld AGW, Bond WH, Kunkler PB (1963) Radiation damage to thoracic tissues. Thorax 18:371–380
153. Wohl ME, Griscom NT, Traggis DG, Jaffe N (1975) Effects of therapeutic irradiation delivered in early childhood upon subsequent lung function. Pediatrics 55:507–516
154. Yuhas JM, Spellman JM, Jordan SW (1980) Treatment of tumours with the combination of WR-2721 and cis-dichlorodiammineplatinum(II) or cyclophosphamide. Br J Cancer 42:574–585

Late Gastrointestinal and Hepatic Effects

M. M. Hudson

Contents

12.1 Introduction

Radiation and specific chemotherapeutic agents may produce gastrointestinal (GI) or hepatic toxicity that is acute and transient in the majority of patients, but may be delayed and persistent. It should be noted, however, that these relatively uncommon late gastrointestinal and hepatic complications are potentially life threatening and capable of severely compromising quality of life. Although the most common malignancies that can be complicated by GI and hepatic injury are abdominal sarcomas (rhabdomyosarcoma and other soft tissue sarcomas), a limited number of reports describe GI complications observed in pediatric patients with genitourinary solid tumors or in those with lymphoma who underwent staging laparotomy [1–8]. Not surprisingly, the severity of GI tract and hepatic toxicity is related to the specific treatment modality and intensity employed; multimodal therapy confers additive risks. Other comorbid conditions, for example, transfusion-acquired hepatitis or graft versus host disease (GVHD), may enhance risk [9–17]. Many reports describe complications resulting from now outdated treatment modalities. As a result, the current paucity of literature about long-term gastrointestinal outcomes may be due to the low frequency of these complications after contemporary therapy. However, long-term outcomes after veno-occlusive disease, chronic graft-versus-host disease and transfusion-acquired hepatitis remain to be established, as these conditions have been associated with subclinical liver dysfunction that may predispose aging childhood cancer survivors to clinically significant liver disease [11, 16–20].

This chapter will summarize complications involving the GI tract and hepatobiliary tree observed following treatment for childhood cancer in the context of normal organ pathophysiology. These sequelae may develop after a variety of therapeutic interventions, for example, radiation, chemotherapy, surgery or bone marrow transplantation, or they may result from supportive therapies such as blood product transfusion. Guidelines for monitoring predisposed childhood cancer survivors and recommendations for health-protective, risk-reducing counseling will also be provided.

12.2 Pathophysiology

12.2.1 Upper and Lower Gastrointestinal Tract

12.2.1.1 Normal Anatomy and Physiology

The upper GI tract extends from the oropharynx to the ileocecal valve and includes the esophagus, stomach and small intestine. The esophagus is a distensible tube lined by an inner mucosa of squamous epithelium, surrounded by a submucosa, a muscularis externa (composed of both striated and smooth muscle) and an outermost connective tissue layer. The neurovascular supply and mucous glands, which are located primarily in submucosa, open into the lumen of the esophagus. The lower esophageal sphincter prevents esophageal injury from reflux of gastric contents, while the epithelium and mucous glands protect against peptic injury. Salivation and esophageal peristalsis also protect the esophageal mucosa by facilitating acid clearance.

Located inferior to the left hemidiaphragm, the stomach is anatomically divided into the cardia, fundus, body and antrum. A thick, muscular-walled pylorus forms a sphincter that connects the gastric antrum to the duodenum. The stomach is lined by an inner mucosa of columnar epithelium that is surrounded by a submucosa and an outer muscularis comprised of longitudinal and circular smooth muscle. Gastric mucosal glands secrete mucus, hydrochloric acid or hormones that regulate gastric secretions and motility. The gastric fundus mucosa secretes an intrinsic factor required for the absorption of vitamin B_{12} by the small intestine.

The small intestine contains mucosal, submucosal and muscularis layers similar to that of the stomach. The mucosal layer of the small intestine is composed of rapidly proliferating epithelium arranged in villi, which increase the absorptive and digestive surface area. The columnar cells forming the villi are arranged in microvilli and form the brush border of the small intestine luminal surface. The digestive enzymes (disaccharidases and peptidases) are located on the surface of the microvilli. Several ligaments fix the duodenum into a C-shaped configuration in the retroperitoneum. The head of the pancreas is situated in the concavity. Suspended by mesentery, the jejunum and most of the ileum are usually freely mobile within the abdominal cavity. The ileocecal valve functions as a sphincter that prevents bacterial contamination of the small bowel.

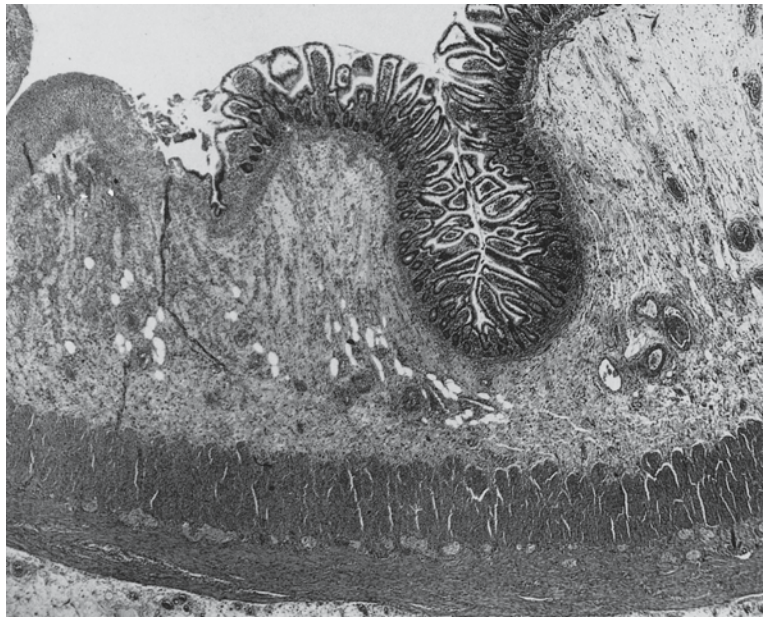
Originating in the right lower quadrant, the colon ascends to the hepatic flexure, traverses the abdomen to the splenic flexure, and then descends in a tortuous fashion to the anus. The splenic flexure and rectosigmoid region comprise two "watershed" areas of arterial blood flow to the colon and are predisposed to ischemic injury. Similar to the small bowel, the colon is lined with columnar epithelium, but there are no villi. The transport of electrolytes and water occurs in the microvilli located on the luminal surface of the epithelial cells. Copious goblet cells secrete mucus onto the luminal surface of the colon.

12.2.1.2 Organ Damage Induced by Cytotoxic Therapy

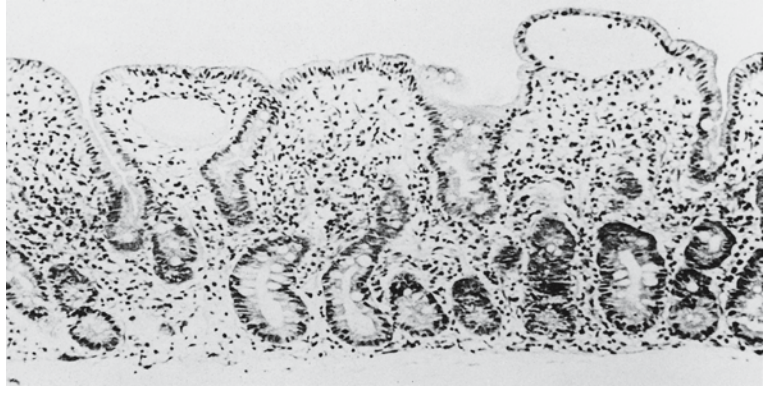
Acute GI toxicity develops frequently following radiation and a variety of chemotherapeutic agents and is characterized by recovery without sequelae in the majority of individuals. The most common gastrointestinal tract complications observed in long-term childhood cancer survivors typically result from chronic mucosal inflammation that interferes with the digestion and absorption of nutrients (enteritis) or predisposes patients to scarring (fibrosis) of the intra-abdominal tissues. Persistent or chronic GI effects are most often observed in long-term sur-

Figure 12.1 a, b

Top: Delayed radiation injury in wall of ileum. Note chronic ulceration (left third), extensive fibrosis of submucosa, and subserosa. Villous atrophy is slight in this case. Approximately 10 years after exposure to undetermined (kilorad) dose of external radiation for adjacent intraabdominal neoplasm. (Hematoxylin-eosin stain; ×21) From [21]. *Bottom*: Histologic picture of the small bowel at the time of obstruction, demonstrating severe villous blunting, distended lymphatics, and an abnormally dense mucosal round cell infiltrate. The normal columnar epithelium is lost, with only low cuboidal cells present. Villi are shortened. (Hematoxylin-eosin stain; ×10). From [1]



a



b

vivors treated with radiation, although specific chemotherapeutic agents may enhance the risk of chronic injury. Combined modality therapy and other treatment complications may have additive adverse effects. For example, chronic infections or graft-versus-host disease (GVHD) may exacerbate radiation-induced enterocolitis. Similarly, extensive bowel resection may contribute to the malabsorption associated with chronic enteritis.

Complications related to fibrosis are the most commonly observed late GI effects in childhood cancer survivors. Fibrosis may involve any site within the GI tract, as well as the extraintestinal structures. Pathologically, fibrosis developing within the wall of the upper GI tract may produce thickening of the serosa, muscularis and submucosa (Fig. 12.1 a), leading to an increased risk of stricture formation. Because of its rapid cell turnover, the submucosa is especially prone to the development of fibrosis. Fibrosis of extraintestinal tissues predisposes patients to the formation of adhesions [1, 21]. Enteritis, or inflammation of the mucosa or lamina propria, ulceration and villous atrophy may occur in association with, or independent of, fibrosis (Fig. 12.1 b). Focal vascular

changes associated with chronic ischemia in the submucosa and mesentery may be responsible for these lesions. Chronic GVHD involving the GI tract of survivors treated with bone marrow transplantation is characterized by mononuclear infiltration of the lamina propria, mucosal ulceration and reepithelialization [22]. Less commonly observed GI tract sequelae are related to the anatomic revisions undertaken during intra-abdominal exenteration and bowel resections, GI tract dysmotility associated with neuronal toxicity [5] and esophageal varices from portal hypertension. Secondary malignancies have been observed with increasing frequency in aging, long-term childhood cancer survivors. Radiation has been implicated as the primary contributor to GI tract carcinogenesis; however, alkylating agent chemotherapy appears to enhance this risk [23–25]. The reader should refer to Chapter 18 for a more detailed description of secondary malignancy after childhood cancer.

12.3 Clinical Manifestations

Clinical signs and symptoms of GI tract toxicity are related to the severity of tissue injury and the specific tissues involved. Mild injury to GI tract tissues may be asymptomatic and noted as an incidental finding at the time of a diagnostic imaging procedure, surgery or autopsy. More severe injury produces chronic or persistent symptoms associated with inflammation and fibrosis of specific tissues. The most common clinical sequelae of fibrosis include partial or complete bowel obstruction resulting from strictures or adhesions. Chronic enteritis and bowel resection may result in malabsorption, bowel ulceration/perforation or fistula formation.

Common constitutional symptoms referable to the GI tract include dysphagia, odynophagia, vomiting, abdominal pain (which may be focal or generalized), colic, constipation/obstipation, diarrhea and GI bleeding, with or without anemia. Non-specific symptoms of anorexia, fatigue and wasting may also be observed. Individuals with chronic hyperchloremic metabolic acidosis resulting from excess GI bicarbonate loss may present with obtundation and confusion. This complication may on rare occasion develop following ureterosigmoidostomy, ileal or jejunal loop procedures. A young child with upper GI tract obstruction and reflux may present with aspiration pneumonia.

12.3.1 Radiation

Radiation injury of the GI tract has been the most extensively studied cause of fibrosis and enteritis. According to data from cohorts of adults treated with radiation for abdominopelvic tumors, radiation complications typically develop within five years after treatment in individuals who experienced acute GI toxicity [26]. However, primary presentations of strictures or inflammatory lesions may occur as late as 20 years after radiation [26–28]. The risk of radiation injury to the GI tract is related to the cumulative radiation dose, daily fraction dose and extent of treatment volume [26]. Fixed loops of the duodenum and terminal ileum are more prone to radiation injury than the esophagus or other intestinal sites [7, 27]. The incidence of small bowel fibrosis is about 5% after 40–50 Gy and rises to 40% when doses exceed 60 Gy [21, 29]. Chronic GI tract injury is uncommon after treatment doses below 42 Gy, given over 4–4.5 weeks.

Limited studies are available describing the chronic effects of GI radiation therapy in children [1, 3, 4, 8]. Donaldson et al. comprehensively evaluated intestinal symptoms in 44 children with cancer treated with whole abdominal (10–40 Gy) and involved field (25–40 Gy) radiation at the Institute Gustave-Roussy [1]. Additional interventions predisposing to GI tract toxicity in the group included abdominal laparotomy in 43 (98%) and chemotherapy in 25 (57%). Late small bowel obstruction was observed in 36% of patients surviving 19 months to 7 years, and this was uniformly preceded by small bowel toxicity during therapy. Infants and children younger than two years appeared to experience more acute and chronic GI toxicity following intensive radiation or combined modality therapy, compared with older children.

Several reports document GI toxicity in long-term survivors of genitourinary rhabdomyosarcoma [3, 4, 8]. Overall, abnormalities of the irradiated bowel

have been observed infrequently. Investigators from the Intergroup Rhabdomyosarcoma Study evaluated the late effects in long-term survivors of paratesticular and bladder/prostate rhabdomyosarcoma [3, 8]. Radiation-related complications occurred in approximately 10% of patients and included intraperitoneal adhesions with bowel obstruction, chronic diarrhea and stricture or enteric fistula formation. Similar findings were observed in another small cohort of survivors of paratesticular rhabdomyosarcoma, treated at a single institution [4]. The small number of patients and GI events reported in these studies precluded any correlation of host and treatment factors predicting GI toxicity.

Radiation would be expected to enhance the risk of late post-surgical small bowel obstruction in long-term childhood survivors, but this complication has been rarely observed. Donaldson reported only one case of late bowel obstruction in 79 surgically-staged pediatric patients treated with radiation (35–44 Gy) [30]. Children irradiated at lower doses for Wilms' tumor also uncommonly develop chronic GI toxicity [31]. However, definitive radiation for Hodgkin's disease in adolescents and young adults has been associated with a one-percent incidence of late-onset, nonspecific abdominal pain attributable to retroperitoneal fibrosis involving the genitourinary tract, rather than the GI tract [2].

Thoracic radiation, particularly when administered to young children at high cumulative doses (40 Gy or more), predisposes to the development of esophageal strictures [6]. The frequency of stricture formation after mediastinal radiation has been reported at 17–42% in older series [32–34]. This complication is uncommon following contemporary treatment for pediatric tumors, which has reduced or eliminated radiation in many frontline therapies. The development of acute radiation esophagitis during radiation administration is likely the nidus for stricture formation; fungal esophagitis may also enhance the risk of this complication [35, 36]. Subacute or chronic candidal esophagitis may predispose to stricture formation that (usually) involves the upper third of the esophagus [35, 36]. Strictures developing in individuals with chronic candidal esophagitis have been seen in association with intramucosal pseudodiverticulitis, an inflammatory disorder characterized by digitation of the excretory ducts of the submucosal glands. Another characteristic histopathological event includes the development of mucosal bridges that may result in webs. Similarly, the administration of radiation-enhancing chemotherapeutic agents (such as doxorubicin) may augment the risk of stricture formation by inducing recurrent episodes of esophagitis through a "recall" phenomenon (Fig. 12.2). This speculation concurs with the increased frequency of strictures observed in patients treated with combined modality therapy, including radiation and radiomimetics chemotherapy [37–40].

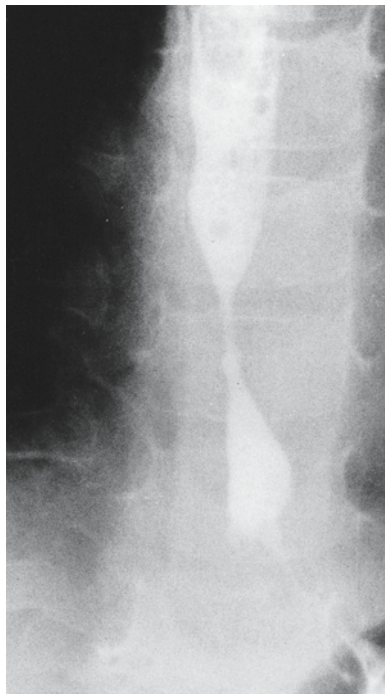


Figure 12.2

Barium study of 5-year-old girl previously treated for ALL showing distal esophageal stricture. The distal location of the stricture and its endoscopic appearance suggest that gastroesophageal reflux and chronic esophagitis may have played a role in the pathogenesis of the stricture. (Courtesy of Dr. S. Kocoshis)

12.3.2 Chemotherapy

In general, chemotherapy plays a less prominent role in the development of chronic enteritis. Multiple chemotherapeutic agents produce acute GI toxicity, which typically manifests as mucositis; however, complete resolution of symptoms after completion of therapy is the usual clinical course. The anthracyclines, in addition to dactinomycin, have potent radiomimetic effects that enhance acute GI toxicity and likely contribute to late onset radiation-related GI toxicity [30, 38, 40, 41]. Rapid chemotherapy-induced tumor lysis has been associated with intestinal necrosis and fistula formation [42].

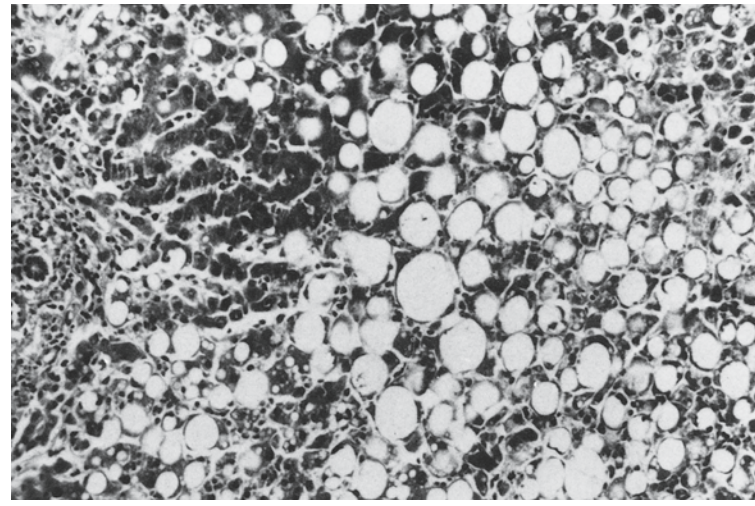
12.3.3 Surgery

Abdominal surgery is associated with a life-long risk of developing adhesive and obstructive complications involving the GI tract. Numerous pediatric studies describe adhesive or obstructive complications, which usually develop within the acute or subacute postoperative period [1, 43–54]. In contrast, information about very late onset adhesive and obstructive complications in childhood cancer survivors is more likely to be found in manuscripts describing global, long-term outcome after pediatric sarcomas, in which the incidence of complications related to adhesions and obstructions is approximately 10% [3, 4, 8]. Besides laparotomy, risk factors for post-operative complications include intensive combination chemotherapy that comprises either radiomimetic agents or radiation therapy. Investigators from the National Wilms' Tumor Study Group observed small bowel obstruction in 7% of patients; however, the incidence of late onset obstruction (more than one year from laparotomy) occurred in fewer than 2% of patients, with events rarely reported more than five years postoperatively [44]. Jockovich et al. evaluated long-term complications of laparotomy in a cohort of 133 pediatric and adult patients who had undergone staging laparotomy with splenectomy before treatment of Hodgkin's disease [45]. At a median follow-up of 15.7 years (range: 2.5–28 years) after laparotomy, the most frequent surgical complication was small bowel obstruction, which occurred in 9.8% and required surgical intervention in 6.8%. Patients younger than 15 years of age at the time of laparotomy had a higher risk of small bowel obstruction, compared with older patients. This increased risk may be related to the increased intensity of the pediatric surgical staging protocols. An increased frequency of obstructive complications is also anticipated in survivors who have undergone multiple laparotomies for staging and assessment of tumor response [1, 41].

A temporary or permanent enterostomy may be required for the management of cancer-related GI toxicity on rare occasion – for example, after resection of ischemic bowel, for a refractory GI tract stricture or fistula or for chronic fecal incontinence. Affected survivors must cope with physical and psychological issues related to stoma maintenance. Finally, excess gastrointestinal bicarbonate loss associated with ureterosigmoidostomy or ileal or jejunal loop procedures predisposes patients to hyperchloremic metabolic acidosis [55]. These individuals are also at increased risk for developing adenocarcinoma of the large bowel [56, 57].

12.3.4 Bone Marrow Transplant

The incidence and the severity of delayed GI tract toxicity following allogeneic hematopoietic stem cell transplantation are related to the cumulative radiation dose used in the conditioning regimen, the presence of GVHD, or, a combination of both. Whereas GI tract toxicity is frequent in the acute transplant setting, chronic late problems affecting GI tissues are relatively uncommon. Xerostomia may result from sclerodermatous changes of the mucous membranes and salivary glands and predispose to accelerated tooth decay and periodontal disease [9]. Esophageal stricture formation is the most common form of delayed GI toxicity and may require dilation procedures to maintain satisfactory oral intake [58, 59]. Affected tissues show characteristic web-like intraluminal membranes that form strictures; some patients also demonstrate perimuscular fibrosis similar to that seen in scleroderma [58, 59]. GVHD of the small bowel may result in chronic diarrhea from malabsorption (Fig. 12.3). Steatorrhea and diarrhea may


a

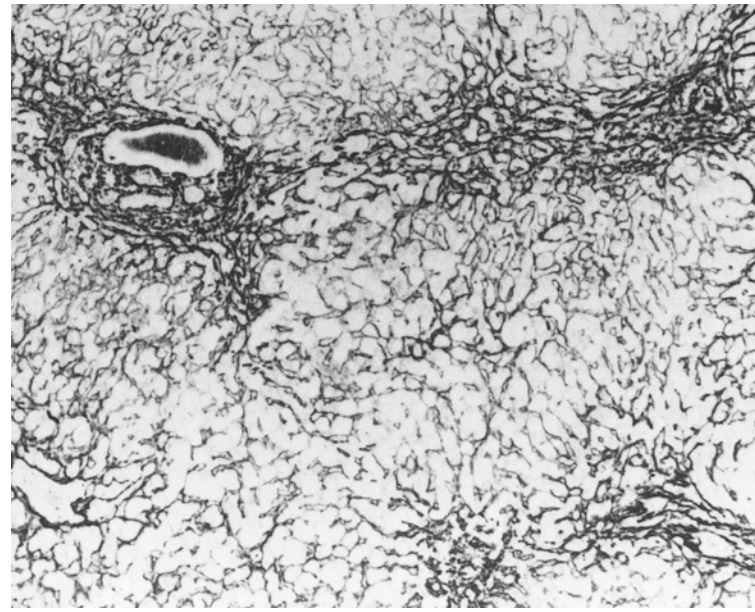

b

Figure 12.3 a, b

Colonic mucosa in graft versus host disease. Two glands show architectural disruption with infiltration of lymphocytes accompanied by epithelial cell necrosis and dropout. Hematoxylin & eosin stain; 20× original magnification. (Courtesy of Dr. J. Jenkins)

also signal the presence of bacterial overgrowth with stasis syndrome. As a result, many individuals with chronic GVHD involving the GI tract are anorexic and undernourished. Endoscopic evaluation with biopsy is generally required to identify the specific GI pathology and provide appropriate therapeutic interventions.

12.4 Detection and Screening

Assessment of cancer-related GI tract sequelae should begin with a thorough history with close attention to symptoms attributable to GI tract pathology, including dysphagia, odynophagia, vomiting, chronic abdominal pain, chronic constipation or diarrhea and hematochezia (Table 12.1). Anorexia,

Table 12.1. GI and Hepatitic Late Effects and Screening Recommendations

Therapeutic Agent	Potential Late Effects	Risk Factors	Periodic Evaluation	Minimum Recommended Frequency
Dactinomycin	**No known late effects** Dactinomycin has been associated with acute veno-occlusive disease, from which the majority of patients recover without sequelae	**Treatment factors** Hepatic radiation	Physical exam ALT, AST, Bilirubin	Yearly Baseline at entry into long-term follow-up
Mercaptopurine **Thioguanine**	**Hepatic dysfunction** **Veno-occlusive disease** Acute toxicities predominate from which the majority of patients recover without sequelae	**Medical conditions** Viral hepatitis	Physical exam ALT, AST, Bilirubin	Yearly Baseline at entry into long-term follow-up
Methotrexate (PO, IV, IM)	**Hepatic dysfunction** Acute toxicities predominate from which the majority of patients recover without sequelae.	**Treatment factors** Abdominal radiation, especially before 1970 **Medical conditions** Viral hepatitis	Physical exam ALT, AST, Bilirubin	Yearly Baseline at entry into long-term follow-up
Laparotomy	**Adhesive/obstructive complications**	**Treatment factors** Combined with radiation	Physical exam	When symptomatic
Total body Irradiation **All abdominal and pelvic fields** **Spinal ≥ 20 Gy**	**Bowel obstruction** **Clinician Info Link** Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery	**Treatment factors** Higher radiation dose to bowel, especially dose ≥ 45 Gy Abdominal surgery	Physical exam KUB	With clinical symptoms of obstruction
	Chronic enterocolitis **Fistula, Strictures**	**Treatment factors** Higher radiation dose to bowel, especially dose ≥ 45 Gy Abdominal surgery	History Serum protein, albumin	Yearly Yearly in patients with chronic diarrhea or fistula
Total Body Irradiation **All abdominal and pelvic fields ≥ 25 Gy** **Spine ≥ 25 Gy**	**Gastrointestinal Malignancy** **Clinician Information Link:** Screening should begin 15 years after radiation or at age 35 years (whichever occurs later). Monitor more frequently indicated	**Treatment factors** Higher radiation dose to bowel, especially dose ≥ 25 Gy Higher daily fraction dose Combine with chemotherapy (especially alkylators)	Fecal occult blood (minimum 3 cards) – and – Flexible sigmoidoscopy – or – Double contrast if clinically barium enema – or – Colonoscopy	Yearly Every 5 years Every 5 years Every 10 years

Table 12.1. Continued

Therapeutic Agent	Potential Late Effects	Risk Factors	Periodic Evaluation	Minimum Recommended Frequency
Total Body Irradiation **Whole abdomen** **Hepatic**	**Hepatic fibrosis** **Cirrhosis**	**Treatment factors** Higher radiation dose to liver, especially dose > 40 Gy to at least 1/3 of liver volume or 20–30 Gy to entire liver **Medical conditions** Chronic hepatitis **Health behaviors** Alcohol use	Physical exam ALT, AST Bilirubin	Yearly Baseline at entry into long-term follow-up
	Hepatocellular carcinoma	**Medical conditions** Chronic hepatitis B, C Cirrhosis **Treatment factors** Higher radiation dose to liver **Health behaviors** Alcohol use	AFP Liver ultrasound	Yearly in patients with chronic hepatitis Yearly in patients with cirrhosis
Hematopoietic Stem Cell Transplantation	**Chronic hepatitis** **Cirrhosis** **Iron overload**	**Treatment factors** History of multiple transfusions Radiation to the liver **Medical conditions** Chronic GVHD Viral hepatitis **Health behaviors** Alcohol use	ALT, AST, Bilirubin Ferritin	Baseline at entry into long-term follow-up
Transfusion Consider any blood or serum product including: Packed red cells Whole blood White cells Platelets Fresh frozen plasma Cryoprecipitate Allogeneic marrow or stem cells Immunoglobulin Preparations: IVIG, VZIG Clotting factor Concentrates	**Chronic Hepatitis B**	**Host factors** Living in hyperendemic area Chronic immuno-suppression **Treatment factors** Transfusion before 1972 Health behaviors IV drug use Unprotected sex Multiple partners High-risk sexual behavior Sexually transmitted diseases Tattoos, body piercing	Hepatitis B surface antigen (HBsAg) – and – Hepatitis B core antibody (anti HBc or HBcAb)	Once in patients who received any blood or serum product prior to 1972

Table 12.1. Continued

Therapeutic Agent	Potential Late Effects	Risk Factors	Periodic Evaluation	Minimum Recommended Frequency
Transfusion	**Chronic Hepatitis C**	**Host factors** Living in hyperendemic area **Treatment factors** Transfusion before 1993 **Health behaviors** IV drug use Unprotected sex Multiple partners High-risk sexual behavior Sexually transmitted diseases Tattoos, body piercing	Hepatitis C antibody PCR to establish chronic infection	Once in patients who received any blood or serum product prior to 1993 Once in patients with positive hepatitis C antibody
	Complications related to chronic hepatitis: **Cirrhosis** **Hepatic failure** **Hepatocellular carcinoma**	**Treatment factors** Stem cell transplantation **Medical conditions** Chronic hepatitis B, C or co-infection with hepatotoxic viruses **Health behaviors** Alcohol use	Physical exam ALT, AST, AFP, bilirubin, prothrombin time Liver ultrasound	Yearly in patient with chronic hepatitis Yearly in patients with cirrhosis

fatigue and wasting may be secondary nonspecific complaints. Physical examination should assess nutritional status, which can be inferred by height and weight, and abdominal findings suggestive of GI pathology, such as distension and pain. Although not routinely used in pediatric assessments, a digital rectal exam and fecal occult blood test should be performed on children presenting with signs and symptoms of GI tract pathology.

Aside from screening levels of vitamin B_{12} and folate, laboratory studies are important to assess secondary effects of GI tract pathology. Anemia and microcytosis may reflect iron deficiency from GI tract blood loss. Macrocytic anemia may result from vitamin B_{12} or folate deficiency associated with chronic malabsorption or resection of the terminal ileum. Albumin and serum protein provide useful assessments of protein stores in patients with chronic diarrhea or fistulas and should be monitored periodically in individuals with chronic malabsorption. A hemoglobin and hematocrit provides useful information in patients who present with hematochezia, but further radiographic and endoscopic evaluation is typically needed to identify the site and specific pathological lesion. Gastroenterology or surgical consultation may be required to establish the diagnosis or provide remedial interventions.

The preferred screening evaluations for GI tract malignancies are the same as for the general population: beginning at age 50, patients should be tested annually for fecal occult blood; and a flexible sigmoidoscopy should be performed every 5 years [60, 61]. Several studies have described an excess risk of gastrointestinal malignancies in childhood cancer survivors treated with abdominal/pelvic radiation [23–25]. As a result, although the median age of onset for this complication has not been established, the Children's Oncology Group Guideline recommends that the process of monitoring predisposed childhood cancer survivors for occult GI malignancies

begin earlier, either 15 years after radiation or at age 35 years (whichever occurs last) [62]. While the efficacy of this approach has not been established in longitudinal trials, this represents a conservative strategy that would increase the likelihood of early detection of an occult GI malignancy.

12.5 Management of Established Problems

Optimal management of cancer-related GI complications requires cooperation between the survivor's primary physician, gastroenterologist and surgeon. Conditions most often requiring intervention usually result from primary or secondary consequences of chronic inflammation or fibrosis of GI tissues. Esophagitis and gastritis are usually easily managed with a variety of pharmacologic agents, including H_2 antagonists and proton pump inhibitors, which eliminate or reduce acid production by the parietal cells. Prokinetic agents are also helpful if acid reflux is contributing to chronic esophagitis. Adjunctive agents such as carafate, which binds to the proteins of denuded mucosa, may also be used as a physical barrier to mucosal irritation.

Dysphagia resulting from abnormal motility associated with neuronal injury can be identified through manometric studies; treatment with calcium channel blockers may ameliorate symptoms. Chronic constipation and obstipation may be predisposed by more severe motility abnormalities. Aggressive treatment with laxatives and enemas are required for individuals who develop stool impaction. Regular treatment with stool softeners and peristaltic stimulants reduces the risk of this complication.

Chronic enteritis may be associated with malabsorption. Affected patients present with chronic diarrhea, abdominal distension, failure to thrive and other signs of protein deficiency. In cases with malabsorption, contrast studies are used to determine the site of pathology, and small bowel biopsies are used to define the histologic features. Individual tests of absorption are used to define the defect. These include the D-xylose absorption test, lactose breath hydrogen test, 72-hour fecal fat determinations, serum B_{12} and folate levels and measurement of stool pH and reducing substances, as well as the Schilling test. Bacterial contamination of the small bowel may also predispose to malabsorption; strictures and blind loops can also contribute to this complication. Intubation and quantitative bacterial cultures of the small bowel may be required to confirm the diagnosis, especially in the absence of the ileocecal valve or in the presence of small bowel stasis. Bacterial overgrowth responds to appropriate antimicrobial therapy, such as tetracycline or metronidazole. Chronic diarrhea associated with bile salt malabsorption after ileal resection may improve with cholestyramine. Refractory malabsorption associated with villous atrophy may require enteral or parenteral nutritional support.

While the management of acute GI bleeding is generally easily accomplished in the primary care setting, the evaluation and treatment of chronic GI blood loss associated with chronic enterocolitis usually requires the expertise of subspecialists who can localize the site of bleeding. Following contrast diagnostic imaging studies, endoscopic evaluation is used to confirm inflammation and ulceration. Biopsy will determine the etiology of mucosal lesions. Only rarely are more aggressive interventions – for example, enterolysis, tagged red-cell study or exploratory laparotomy – needed to localize the site of GI tract bleeding.

Upper GI tract strictures are best evaluated by barium swallow followed by endoscopy. Repeated endoscopy and dilation procedures may be required for long-term management of esophageal strictures. Concurrent evaluation and treatment of peptic esophagitis is important in order to reduce the risk of further mucosal injury. Surgical procedures that reduce or prevent reflux may also be undertaken to minimize the risk of recurrent stricture formation. Patients presenting with signs and symptoms of bowel obstruction should be promptly evaluated with abdominal radiographs, decompression (if clinically indicated) and the appropriate contrast imaging. Chronic or refractory intestinal obstruction associated with strictures or adhesions may eventually require surgical intervention for definitive correction.

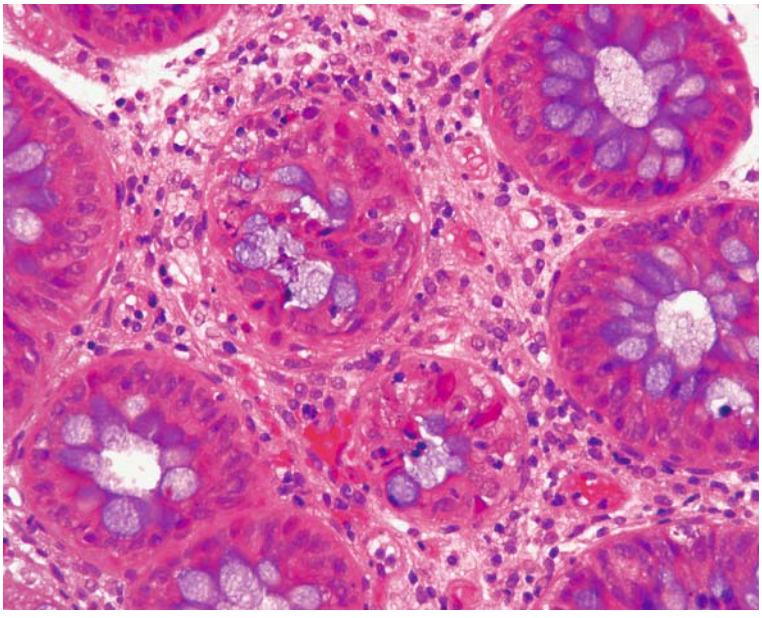


Figure 12.4

Chronic methotrexate liver damage. There is fatty change together with chronic portal inflammation and fibrosis. Hematoxylin-eosin stain; ×180. (From [63]; reprinted with the kind permission of Dr. R.S. Patrick and Chapman Hall, Ltd.)

12.3 Hepatobiliary Tree

12.3.1 Pathophysiology

12.3.1.1 Normal Anatomy and Physiology

The liver is the largest organ in the body and consists of right and left lobes joined posteroinferiorly at the porta hepatis. The gall bladder lies under the visceral surface of the liver. The hepatic lobule, which contains a central vein that is a tributary of the hepatic vein, is the basic ultrastructural unit of the liver. The central vein of each hepatic lobule drains into the inferior vena cava. Columns of hepatocytes radiate from the center of each lobule and are separated by sinusoids. Hepatic sinusoids are lined with reticuloendothelial or Kupffer's cells. The hepatic lobule is divided into three functional zones that each receives blood of varying nutrient and oxygen content. Zone 3, which receives the least oxygen and nutrients, is the most vulnerable to injury. Hepatic arterioles, portal vein radicles, and branches of the left and right hepatic ducts are located in portal triads between the hepatic lobules. The left and right hepatic ducts fuse at the porta hepatitis to form the common hepatic duct. The cystic duct, which drains the gallbladder, joins the hepatic duct to form the common bile duct that drains into the duodenum.

Liver function is diverse and includes the synthesis of enzymes albumin, coagulation proteins, urea and steroids (such as cholesterol and primary bile acids); the conjugation of bilirubin, the detoxification of drugs and storage of fat-soluble vitamins. Hepatocytes are also responsible for gluconeogenesis and glycolysis. The Kupffer cells, which engage in phagocytosis and secrete cytokines, play a role in immune regulation.

12.3.1.2 Changes Induced by Cytotoxic Therapy

Fibrosis, which is generally periportal and concentric (Fig. 12.4), is the most frequently described complication of antineoplastic therapy observed in the liver [63]. Hepatic fibrosis may be associated with fatty infiltration, focal necrosis and nodular regeneration of cirrhosis, as well as portal hypertension. Chronic hepatitis, regardless of its etiology, is characterized by portal-periportal lymphoplasmacytic infiltration with varying degrees of fibrosis and piecemeal necro-

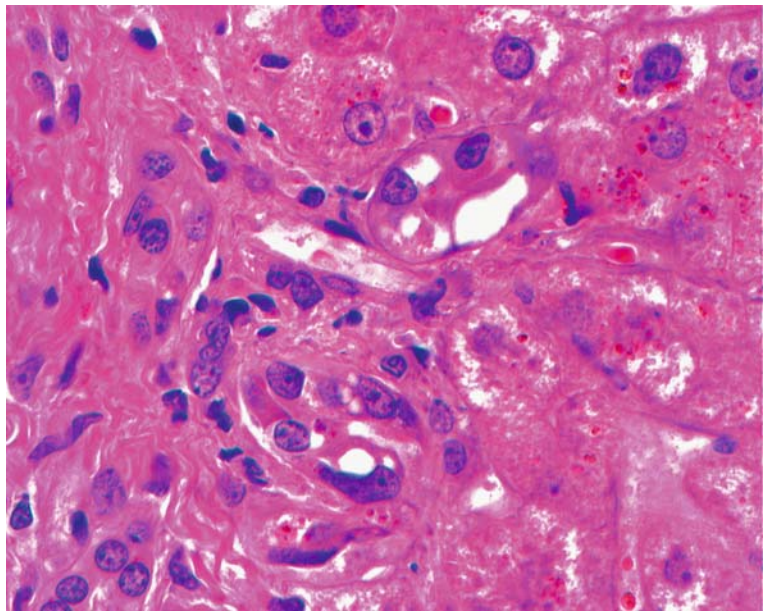


Figure 12.5

Hepatic portal triad in graft versus host disease. Bile ducts show epithelial damage in the form of irregular cellular and nuclear size and spacing around the duct lumen with some epithelial cells completely missing. Epithelial cell cytoplasm is vacuolated and shows variable eosinophilia. In this example a paucity of lymphocytes is noted. Hematoxylin & eosin stain; 60× original magnification. (Courtesy of Dr. J. Jenkins)

sis. The histopathology of veno-occlusive disease demonstrates endothelial injury with fibrin deposition; if progressive, fibrous obliteration of central veins ensues. GVHD is associated with hepatocellular necroinflammatory changes suggestive of chronic active hepatitis, a paucity of interlobular bile ducts and intrahepatic cholestasis (Fig. 12.5) [22, 64]. Cell-mediated immune dysregulation is implicated in the pathophysiology of chronic GVHD in most studies. However, findings of deposits of immunoglobulin and complement along the dermal-epidermal junction in 85% of individuals with chronic GVHD suggest that a humoral mechanism may play a role as well [65]. Hepatocellular carcinoma has been reported only rarely, and either in patients treated with chemotherapy and radiation therapy for Wilms' tumor or in long-term survivors of childhood leukemia with chronic hepatitis-C infection [17, 66].

12.3.2 Clinical Manifestations

Liver injury related to the treatment for childhood cancer is most often subclinical and may develop without a history of prior acute toxicity. Asymptomatic abnormalities of serum transaminases (alanine aminotransferase and aspartate aminotransferase) are most commonly observed. In the setting of chronic GVHD, alkaline phosphatase and bilirubin may also be elevated. However, bilirubin elevation is variable and does not correlate with clinical outcome. Patients with chronic liver dysfunction frequently report constitutional complaints such as pruritus, fatigue and weight loss. In contrast, hepatic veno-occlusive disease is characterized by the acute onset of jaundice, upper quadrant pain on the right side, hepatomegaly, ascites, liver dysfunction and thrombocytopenia. The clinical course of VOD varies from mild and reversible to life-threatening, with progressive hepatic failure. The impact of acute VOD on long-term hepatic function has not been established. Chronic progressive hepatic fibrosis associated with cirrhosis may cause portal hypertension and resulting sequelae, such as hypersplenism and variceal bleeding. If cirrhosis leads to liver decompensation, clinical signs and symptoms of hepatic synthetic dysfunction appear, including ascites and coagulopathy. As hepatic failure ensues, affected individuals manifest progressive metabolic derangements and encephalopathy.

12.3.2.1 Radiation

The majority of reports describing acute radiation hepatopathy in pediatric patients involve obsolete radiation technology and treatment approaches. Persistent or late-onset radiation hepatopathy after contemporary treatment is uncommon in the absence of other predisposing conditions, for example, viral hepatitis. The low frequency of hepatopathy after contemporary radiation suggests complete resolution of acute hepatic injury, but this has not been confirmed in prospective studies.

The liver generally has good tolerance to radiation doses up to 30–35 Gy, which is delivered using conventional fractionation [29, 67]. The risk of hepatic injury increases significantly with doses exceeding 35 Gy, but smaller volumes of the liver can be safely irradiated at higher doses. Jirtle et al., in correlating hepatic tolerance to radiation dose and volume, estimated that the whole liver could tolerate 20 Gy, while one-third to one-half of the liver could be irradiated to 40 Gy without complications [68]. Contemporary three-dimensional planning permits more accurate delivery of high-dose radiation to liver tumors with normal liver sparing. However, the long-term outcomes of liver function using this technology are not available.

Radiation-induced hepatic injury has been studied in children with Wilms' tumor, neuroblastoma and hepatoblastoma [29, 31, 67, 69–74]. An increasing risk of radiation injury was observed with increasing radiation dose and hepatic volume, younger age at treatment, prior partial hepatectomy and concomitant use of radiomimetic chemotherapy, such as dactinomycin and doxorubicin [31]. Radiation-induced hepatotoxicity typically presents subacutely in the first 12 weeks after completion of radiation. Delayed and chronic hepatic toxicity after radiation has been rarely reported [75].

12.3.2.2 Chemotherapy

Several chemotherapeutic agents used in the treatment of pediatric malignancies are associated with hepatotoxicity [76]. Unless there is an exacerbating condition like chronic hepatitis or GVHD, most children usually recover completely from acute hepatic injury related to chemotherapy [77–80]. The clinical features of acute methotrexate-induced hepatotoxicity are well described, but limited information is available about long-term liver outcomes [81–83]. Information about other commonly used hepatotoxins, such as 6-mercaptopurine and dactinomycin, is restricted to descriptions of acute toxicity [84–86]. The relative dearth of publications about long-term chemotherapy-associated hepatotoxicity may be related to the low incidence of clinically significant liver disease, or to the fact that the latency for the manifestation of liver toxicity has not been reached.

Methotrexate-induced hepatic injury is characterized by transient elevations of serum transaminases, alkaline phosphatase or lactate dehydrogenase; biochemical changes do not consistently correlate with the severity of hepatic injury [87–89]. The risk of hepatotoxicity following treatment with oral methotrexate increases with duration of continuous therapy and cumulative dose [76]. The risk of fibrosis or cirrhosis after daily oral methotrexate is more than two-fold the incidence observed after intermittent parenteral administration [90, 91]. Early studies of methotrexate described the development of hepatic fibrosis in up to 80% of children with acute lymphoblastic leukemia, treated with oral low-dose methotrexate (2.5–10 mg daily) over 2.5 to 5 years. The risk of hepatic fibrosis reported in later investigations using intermediate-dose parenteral administration was less than 5%. Studies evaluating hepatic histology in children treated with methotrexate demonstrated mild structural changes and a low incidence of portal fibrosis [87–89]. These findings suggest that methotrexate-induced fibrosis regresses or stabilizes after discontinuation of the agent and rarely produces end-stage liver disease [87, 89, 92].

12.3.2.3 Hepatic Veno-Occlusive Disease

Hepatic radiation and a variety of chemotherapeutic agents have been implicated in the causation of veno-occlusive disease (VOD). Initially, VOD was attributed to the concomitant administration of hepatic radiation and radiosensitizing drugs like dactinomycin and doxorubicin [31, 71, 73]. Subsequent in-

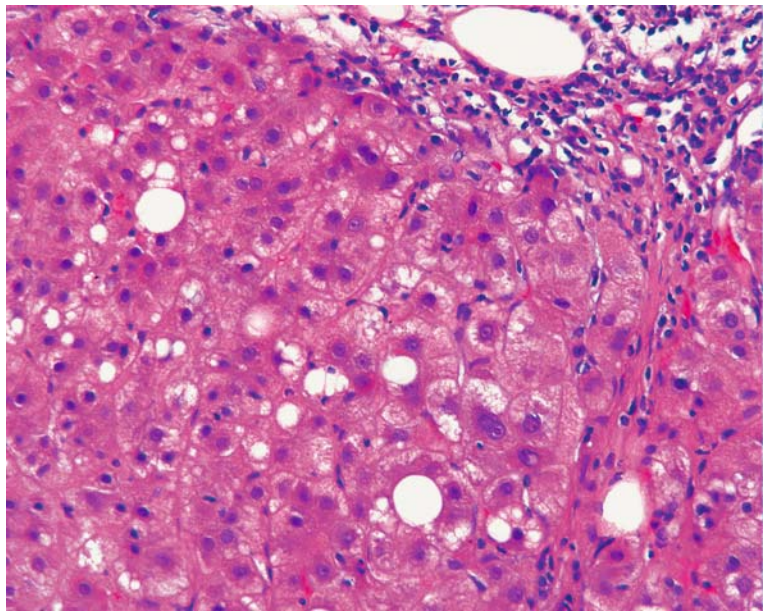


Figure 12.6

Regenerative liver nodule and portal triad in hepatitis C disease. Narrow bands of connective tissue separate small nodules of regenerative liver which shows fatty metamorphosis of some individual hepatocytes. The portal triad contains a dense lymphocytic infiltrate that in some cases may contain germinal centers. Hematoxylin & eosin stain; 20× original magnification. (Courtesy of Dr. J. Jenkins)

vestigations demonstrated that treatment with dactinomycin and vincristine chemotherapy alone could produce VOD [74, 85, 86]. In fact, several chemotherapeutic agents used in conventional dosing regimens have been associated with the development of VOD, including dactinomycin, cytosine arabinoside, dacarbazine and 6-mercaptopurine. Myeloablative chemotherapy used in conditioning regimens before hematopoietic stem cell transplantation may also cause VOD. The most common agents in this setting are cyclophosphamide, carmustine and busulfan. Whatever the cause, the clinical course described in most series is consistent with full recovery for the majority of children. Information is lacking about long-term complications related to VOD.

12.3.2.4 Bone Marrow Transplant

Liver disease in long-term survivors of childhood cancer treated with bone marrow transplantation may result from chronic GVHD, chronic infection, nodular regenerative hyperplasia from cytoreductive therapy and drug-related liver injury [93, 94]. Chronic GVHD is the most frequent late complication after allogeneic hematopoietic stem cell transplantation and represents a major cause of transplant-related morbidity and mortality [95]. Approximately 80 % of individuals with chronic GVHD have liver involvement [10, 96]. Drug toxicity from immunosuppressive agents, antibiotics, antifungal and antiviral drugs, sedatives, antiemetics and antipyretics may exacerbate chronic GVHD [22]. Chronic infections, most commonly hepatitis-C, may also accelerate the course of liver injury. Severe chronic liver disease with cirrhosis represents an important late complication of hematopoietic stem cell transplantation that, in most cases, is due to chronic hepatitis-C (Fig. 12.6) [16, 19, 20]. Reports documenting deaths from cirrhosis and hepatic failure suggest that chronic liver disease may predispose to early mortality in long-term survivors treated with allogeneic bone marrow transplantation [11, 16, 19].

12.3.2.5 Transfusion-Acquired Chronic Hepatitis

Childhood cancer survivors transfused before the introduction of effective screening measures for hepatitis-B and -C represent a significant population at risk for transfusion-acquired hepatitis. Hepatitis-B

screening was implemented in 1971 in the United States. Hepatitis-C screening by the first generation enzyme immunoassay (EIA) was initiated in 1990; a more sensitive, second generation EIA became available in 1992. Hence, transfusion-acquired viral hepatitis should be considered in long-term survivors presenting with chronic hepatic dysfunction who received transfusions before donor screening was available. Hepatitis-B is characterized by a more aggressive acute clinical course and a lower rate of chronic infection (≤ 10 %). In contrast, acute infection with hepatitis-C is often mild or asymptomatic, but the rate of chronic infection is high (approximately 80 %). Regardless of the etiology, survivors with chronic hepatitis experience significant morbidity and mortality related to cirrhosis, end-stage liver disease and hepatocellular carcinoma [15, 17, 18, 97–100]. Co-infection with hepatitis-B and -C appears to accelerate the progression of liver disease, as does the immunosuppression or hepatotoxicity associated with allogeneic hematopoietic stem cell marrow transplantation [15, 17, 87].

Numerous reports provide descriptive information about preliminary outcomes in childhood cancer survivors with chronic hepatitis C [12–15, 17, 18, 77, 99, 99, 101–114]. The prevalence of HCV infection (positive EIA or PCR) ranges from 5 % to almost 50 %, depending on the geographic location of the center. Among these cases, chronic infection is common, as evidenced by the prevalence of PCR detection of viral RNA (in the range of 70–100 % in the cohorts studied) [18, 98, 99, 101, 103]. Most patients are asymptomatic, but laboratory evaluations of ALT are abnormal in 29–79 % of the cases. Early studies of chronically infected childhood cancer survivors suggest that fibrosis develops more slowly in patients who acquire the infection at age 20 years or younger [108, 110, 115]. However, in a recent report describing the histologic outcomes of chronically infected survivors after a more prolonged follow-up (median: 19 years), the progressive fibrosis and end-stage liver disease rates were similar to those seen both in larger adult cohorts with transfusion-associated hepatitis, and in hemophiliacs coinfected with HIV and hepatitis B [18, 116–118]. More aggressive chronic infection has also been observed in survivors coinfected with hepatitis-B and in those treated with hematopoietic stem cell transplantation [15, 17]. Further longitudinal follow-up is required to accurately define the long-term sequelae of transfusion-associated hepatitis-C acquired during treatment of childhood cancer.

12.3.2.6 Other Late Hepatobiliary Complications

Less commonly reported hepatobiliary complications include cholelithiasis, focal nodular hyperplasia, nodular regenerative hyperplasia and hepatic microvesicular fatty change and siderosis. In a single-institution study including 6,050 childhood cancer patients, Mahmoud et al. reported a higher risk of biliary calculi in childhood cancer patients (median age: 12.4 years) who did not have underlying chronic hemolytic anemia or a history of gallstones before treatment, compared with rates observed in the general population [119]. The cumulative risk for cholelithiasis was 0.42 % at 10 years, and 1.03 % at 18 years, after diagnosis. Treatment factors significantly associated with an increased risk of cholelithiasis included a history of ileal conduit (RR 61.6; 27.9–135.9), parenteral nutrition (RR 23.0; 9.8–54.1), abdominal surgery (RR 15.1; 7.1–32.2) and abdominal radiation (RR 7.4; 3.2–17.0). The frequency of conventional predisposing factors like family history, obesity, oral contraceptive use and pregnancy was not higher among study patients, compared with rates observed in the general population.

Focal nodular hyperplasia (FNH) is an uncommon hepatic tumor that has been reported anecdotally in childhood cancer survivors [120]. The pathogenesis of FNH is poorly understood, but the most widely accepted theory is that the lesion is a reaction to a localized vascular anomaly. Others have speculated that FNH results from vascular injuries such as thrombosis, intimal hyperplasia, high sinusoidal pressures or increased flow [121, 122]. FNH is most commonly discovered as an incidental finding on abdominal imaging. High doses of alkylating agents (e.g. busulfan or melphalan), veno-occlusive disease and hepatic radiation may produce vascular injury and the subsequent localized circulatory distur-

bances [123]. The lesion is characterized by infrequent complications and the absence of malignant transformation; hence, only close follow-up is recommended.

Nodular regenerative hyperplasia (NRH) is a rare condition that is characterized by the development of multiple monoacinar, regenerative hepatic nodules. The presence of mild fibrosis distinguishes NRH from FNH and cirrhosis. Like FNH, the pathogenesis of NRH is not well established, but may represent a non-specific tissue adaptation to heterogeneous hepatic blood flow [121]. NRH has rarely been observed in survivors of childhood cancer treated with chemotherapy, with or without liver radiotherapy [120, 124]. Biopsy may be required to distinguish NRH from metastatic cancer.

In a recent study, Finnish investigators described the results of liver biopsy in 27 patients who had recently completed intensified therapy for acute lymphoblastic leukemia [125]. Fatty infiltration was detected in 93% and siderosis in 70% of patients; 52% exhibited both histologic abnormalities. Fibrosis developed in 11% and was associated with higher levels of serum LDL-cholesterol. Prospective studies are needed to show whether 1) acute post-therapy liver fatty change after childhood leukemia contributes to the development of steatohepatitis or the metabolic syndrome characterized by obesity, glucose intolerance and dyslipidemia, and 2) whether siderosis predisposes to more severe liver histopathology.

12.3.3 Detection and Screening

Screening of childhood cancer survivors treated with hepatotoxic chemotherapy and radiation therapy should begin with a thorough physical examination (Table 12.1). Physical findings suggesting liver dysfunction, e.g. spider angioma, palmar erythema, hepatomegaly, splenomegaly, icterus or ascites, may be observed in individuals with long-standing liver dysfunction associated with significant hepatitic fibrosis. Patients transfused with any blood product before implementation of blood donor testing for hepatitis-B (1971) or -C (1992) should been screened for viral hepatitis; PCR can establish the diagnosis of chronic infection. Since most childhood cancer survivors with hepatic dysfunction are asymptomatic, baseline screening of liver function with ALT, AST and bilirubin should be performed beginning at two years after completion of therapy. Persistent liver dysfunction should prompt referral for GI/hepatic evaluation, with liver biopsy. Individuals with abnormal screening should undergo annual (or more frequent, if clinically indicated) evaluations of hepatic synthetic function with a prothrombin time. Albumin and INR also provide good indications of liver function in patients with established, chronic liver disease. Anemia and thrombocytopenia may be associated with complications related to portal hypertension, including hypersplenism and variceal bleeding. To screen for varices in individuals with chronic liver dysfunction, esophagogastroduodenoscopy is recommended. A yearly serum alpha-fetoprotein level and hepatic ultrasound should be obtained in patients with established cirrhosis to monitor for neoplastic complications, such as adenoma and hepatocellular carcinoma.

12.3.4 Management

It is imperative to preserve residual hepatocyte function, given that therapy is not available to reverse hepatic fibrosis induced by antineoplastic therapy or chronic viral infection. Childhood cancer survivors treated with hepatotoxic therapy should be counseled regarding behaviors to prevent further hepatic injury. Standard recommendations include abstinence from alcohol use and immunization against hepatitis-A and -B in patients who have not established immunity to these hepatotrophic viruses. Survivors should also receive counseling about precautions to reduce viral transmission to household and sexual contacts. Patients with persistent liver dysfunction associated with chronic viral hepatitis may benefit from antiviral therapy. Consultation with GI/hepatology subspecialists will facilitate access to optimal antiviral therapies. Treatment, as a rule, is preceded by a liver biopsy to define the etiology and histopathological features of the liver injury.

Once established, treatment of fibrosis is largely symptomatic. Patients with cirrhosis may remain asymptomatic for many years. Portal hypertension

and GI bleeding from varices may herald the onset of decompensated cirrhosis. Treatment with beta-blockers may significantly reduce the incidence of variceal bleeding [126, 127]. Eventually, hepatic failure manifests as jaundice, hepatic encephalopathy, hypoproteinemia, progressive ascites and coagulopathy. Supportive care in end-stage liver disease includes a low-protein diet with lactulose and neomycin to minimize urea production, blood and plasma products to replete albumin and coagulation proteins, salt restriction and diuretics to prevent ascites formation and, lastly, sclerotherapy or vascular shunting to reduce portal pressure and prohibit variceal bleeding. Liver transplantation is the only definite and lifesaving treatment for patients presenting with decompensated cirrhosis.

References

1. Donaldson SS, Jundt S, Ricour C, Sarrazin D, Lemerle J, Schweisguth O (1975) Radiation enteritis in children. A retrospective review, clinicopathologic correlation, and dietary management. Cancer 351167–1178
2. Chao N, Levine J, Horning SJ (1987) Retroperitoneal fibrosis following treatment for Hodgkin's disease. J Clin Oncol 5:231–232
3. Heyn R, Raney RB, Jr., Hays DM et al. (1992) Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. J Clin Oncol 10:614–623
4. Hughes LL, Baruzzi MJ, Ribeiro RC et al. (1994) Paratesticular rhabdomyosarcoma: delayed effects of multimodality therapy and implications for current management. Cancer 73:476–482
5. Kaplinsky C, Kornreich L, Tiomny E, Cohen IJ, Loven D, Zaizov R (1991) Esophageal obstruction 14 years after treatment for Hodgkin's disease. Cancer 68:903–905
6. Mahboubi S, Silber JH (1997) Radiation-induced esophageal strictures in children with cancer. Eur Radiol 7:119–122
7. Papazian A, Capron JP, Ducroix JP, Dupas JL, Quenum C, Besson P (1983) Mucosal bridges of the upper esophagus after radiotherapy for Hodgkin's disease. Gastroenterology 84:1028–1031
8. Raney B Jr, Heyn R, Hays DM et al. (1993) Sequelae of treatment in 109 patients followed for 5 to 15 years after diagnosis of sarcoma of the bladder and prostate. A report from the Intergroup Rhabdomyosarcoma Study Committee. Cancer 71:2387–2394
9. Deeg HJ, Storb R, Thomas ED (1984) Bone marrow transplantation: a review of delayed complications. Br J Haematol 57:185–208
10. Fisher VL (1999) Long-term follow-up in hematopoietic stem-cell transplant patients. Pediatr Transplant 3 [Suppl 1]:122–129
11. Knapp AB CJ, Rappeport JM, Gollan JL (1987) Cirrhosis as a consequence of graft versus host disease. Gastroenterology 92:513–519
12. Locasciulli A, Bacigalupo A, van Lint MT et al. (1990) Hepatitis B virus (HBV) infection and liver disease after allogeneic bone marrow transplantation: a report of 30 cases. Bone Marrow Transplant 6:25–29
13. Locasciulli A, Gornati G, Tagger A et al. (1991) Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. Blood 78:1619–1622
14. Locasciulli A, Testa M, Valsecchi MG et al. (1997) Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: a 10-year prospective study. Blood 90:3799–3805
15. Paul IM, Sanders J, Ruggiero F, Andrews T, Ungar D, Eyster ME (1999) Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. Blood 93:3672–3677
16. Socie G, Stone JV, Wingard JR et al. (1999) Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med 341:14–21
17. Strickland DK, Jenkins JJ, Hudson MM (2001) Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. J Pediatr Hematol Oncol 23:527–529
18. Castellino S, Lensing S, Riely CA et al. (2004) The epidemiology of chronic hepatitis C infection in survivors of childhood cancer – an update of the St. Jude Children's Research Hospital hepatitis C seropositive cohort. Blood 103:2460–2466
19. Yau JC, Zander AR, Srigley JR et al. (1986) Chronic graft-versus-host disease complicated by micronodular cirrhosis and esophageal varices. Transplantation 41:129–130
20. Strasser SI, Sullivan KM, Myerson D et al. (1999) Cirrhosis of the liver in long-term marrow transplant survivors. Blood 93:3259–3266
21. Fajardo L (1989) Radiation-induced pathology of the alimentary tract. In: Whitehead R (ed) Gastrointestinal and oesophageal pathology. Churchill Livingstone, Edinburgh
22. Shulman H (1990) Pathology of chronic graft-vs.-host disease. In: Burakoff S (ed) Graft-vs-host disease immunology, pathophysiology and treatment. Dekker, New York
23. Bhatia S, et al. (2003) High risk of second malignant neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. J Clin Oncol (in press)

24. Metayer C, Lynch CF, Clarke EA et al. (2000) Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 18:2435–2443
25. Swerdlow AJ, Barber JA, Hudson GV et al. (2000) Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol 18:498–509
26. Roswit B (1974) Complications of radiation therapy: the alimentary tract. Semin Roentgenol 9:51–63
27. Berthrong M, Fajardo LF (1981) Radiation injury in surgical pathology. Part II. Alimentary tract. Am J Surg Pathol 5:153–178
28. Localio SA, Stone A, Friedman M (1969) Surgical aspects of radiation enteritis. Surg Gynecol Obstet 129:1163–1172
29. Emami B, Lyman J, Brown A et al. (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21:109–122
30. Donaldson SS, Glatstein E, Rosenberg SA, Kaplan HS (1976) Pediatric Hodgkin's disease. II. Results of therapy. Cancer 37:2436–2447
31. Tefft M (1977) Radiation related toxicities in National Wilms' Tumor Study Number 1. Int J Radiat Oncol Biol Phys 2:455–463
32. Seaman WB, Ackerman LV (1957) The effect of radiation on the esophagus; a clinical and histologic study of the effects produced by the betatron. Radiology 68:534–541
33. Lepke RA, Libshitz HI (1983) Radiation-induced injury of the esophagus. Radiology 148:375–378
34. Goldstein HM, Rogers LF, Fletcher GH, Dodd GD (1975) Radiological manifestations of radiation-induced injury to the normal upper gastrointestinal tract. Radiology 117: 135–140
35. Orringer MB, Sloan H (1978) Monilial esophagitis: an increasingly frequent cause of esophageal stenosis? Ann Thorac Surg 26:364–374
36. Simson JN, Kinder RB, Isaacs PE, Jourdan MH (1985) Mucosal bridges of the oesophagus in Candida oesophagitis. Br J Surg 72:209–210
37. Horwich A, Lokich JJ, Bloomer WD (1975) Doxorubicin, radiotherapy, and oesophageal stricture. Lancet 2:561–562
38. Newburger PE, Cassady JR, Jaffe N (1978) Esophagitis due to adriamycin and radiation therapy for childhood malignancy. Cancer 42:417–423
39. Phillips TL, Fu KK (1976) Quantification of combined radiation therapy and chemotherapy effects on critical normal tissues. Cancer 37 [Suppl 2]:1186–1200
40. Boal DK, Newburger PE, Teele RL (1979) Esophagitis induced by combined radiation and adriamycin. AJR Am J Roentgenol 132:567–570
41. Tefft M, Lattin PB, Jereb B et al. (1976) Acute and late effects on normal tissues following combined chemo- and radiotherapy for childhood rhabdomyosarcoma and Ewing's sarcoma. Cancer 37 [Suppl 2]:1201–1217
42. Meyers PA, Potter VP, Wollner N, Exelby P (1985) Bowel perforation during initial treatment for childhood non-Hodgkin's lymphoma. Cancer 56:259–261
43. Wobbes T, Verschueren RC, Lubbers EJ, Jansen W, Paping RH (1984) Surgical aspects of radiation enteritis of the small bowel. Dis Colon Rectum 27:89–92
44. Ritchey ML, Kelalis PP, Breslow N et al. (1992) Surgical complications after nephrectomy for Wilms' tumor. Surg Gynecol Obstet 175:507–514
45. Jockovich M, Mendenhall NP, Sombeck MD, Talbert JL, Copeland EM 3rd, Bland KI (1994) Long-term complications of laparotomy in Hodgkin's disease. Ann Surg 219: 615–621; discussion 621–614
46. Hays DM, Ternberg JL, Chen TT et al. (1986) Postsplenectomy sepsis and other complications following staging laparotomy for Hodgkin's disease in childhood. J Pediatr Surg 21:628–632
47. Hays DM, Ternberg JL, Chen TT et al. (1984) Complications related to 234 staging laparotomies performed in the Intergroup Hodgkin's Disease in Childhood study. Surgery 96: 471–478
48. Kaiser CW (1981) Complications from staging laparotomy for Hodgkin disease. J Surg Oncol 16:319–325
49. Smith IE, Peckham MJ, McElwain TJ, Gazet JC, Austin DE (1977) Hodgkin's disease in children. Br J Cancer 36:120–129
50. Green DM, Ghoorah J, Douglass HO Jr et al. (1983) Staging laparotomy with splenectomy in children and adolescents with Hodgkin's disease. Cancer Treat Rev 10:23–38
51. Lanzkowsky P, Shende A, Karayalcin G, Aral I (1976) Staging laparotomy and splenectomy: treatment and complications of Hodgkin's disease in children. Am J Hematol 1:393–404
52. Filler RM, Jaffe N, Cassady JR, Traggis DG, Vawter GF (1975) Experience with clinical and operative staging of Hodgkin's disease in children. J Pediatr Surg 10:321–328
53. Cohen IT, Higgins GR, Powars DR, Hays DM (1977) Staging laparotomy for Hodgkin's disease in children. Evaluation of the technique. Arch Surg 112:948–951
54. Bell MJ, Land VJ, Ternberg JL (1977) Staging laparotomy for Hodgkin's disease in children. Am J Surg 133:582–583
55. Zinchke H, Segura JW (1975) Ureterosigmoidostomy: critical review of 173 cases. J Urol 113:324–327
56. Bristol JB, Williamson RC (1981) Ureterosigmoidostomy and colon carcinogenesis. Science 214:351
57. Gittes RF (1986) Carcinogenesis in ureterosigmoidostomy. Urol Clin North Am 13:201–205
58. McDonald GB, Sullivan KM, Schuffler MD, Shulman HM, Thomas ED (1981) Esophageal abnormalities in chronic graft-versus-host disease in humans. Gastroenterology 80:914–921
59. McDonald GB, Sullivan KM, Plumley TF (1984) Radiographic features of esophageal involvement in chronic graft-vs.-host disease. AJR Am J Roentgenol 142:501–506

60. Screening for colorectal cancer (2004). United States Preventive Services Task Force. Available at: http://www.ahrq.gov/clinic/uspstfix.htm. Acessed September 28
61. Smith RA, Cokkinides V, Eyre HJ (Jan–Feb 2004) American Cancer Society guidelines for the early detection of cancer, 2004. CA Cancer J Clin 54 (1): 41–52
62. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. CureSearch Children's Oncology Group. March 2004
63. Patrick RS, McGee JOD (1980) Biopsy pathology of the liver. Chapman Hall, London
64. Shulman HM, Sullivan KM, Weiden PL et al. (1980) Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 69: 204–217
65. Tsoi MS, Storb R, Jones E et al. (1978) Deposition of IgM and complement at the dermoepidermal junction in acute and chronic cutaneous graft-vs-host disease in man. J Immunol 120:1485–1492
66. Blatt J, Olshan A, Gula MJ, Dickman PS, Zaranek B (1992) Second malignancies in very-long-term survivors of childhood cancer. Am J Med 93:57–60
67. Ingold JA RG, Kaplan HS, Bagshaw MA (1965) Radiation hepatitis. Am J Roentgenol 93:200–208
68. Jirtle RL, Alati T (1990) Radiation sensitivity of the liver. Adv Radiat Biol 14:269–311
69. Tefft M, Jaffe MA (1971) Irradiation of the liver in children: acute effects enhanced by concomitant chemotherapeutic administration. Am J Roentgenol Rad Ther Nucl Med 111: 165–173
70. Tefft M MA, Das L, Vawter GF, Filler RM (1970) Irradiation of the liver in children: review of the experience in the acute and chronic phases, and in the intact normal and partially resected. Am J Roentgenol Rad Ther Nucl Med 108:365–385
71. Kun LE, Camitta BM (1978) Hepatopathy following irradiation and adriamycin. Cancer 42:81–84
72. Bhanot P, Cushing B, Philippart A, Das L, Farooki Z (1979) Hepatic irradiation and adriamycin cardiotoxicity. J Pediatr 95:561–563
73. Johnson FL (1982) Hepatopathy following irradiation and chemotherapy for Wilms' tumor. Am J Pediatr Hematol Oncol 4:217–221
74. Flentje M, Weirich A, Potter R, Ludwig R (1994) Hepatotoxicity in irradiated nephroblastoma patients during postoperative treatment according to SIOP9/GPOH. Radiother Oncol 31:222–228
75. Barnard JA MG, Neblett WW, Gray G, Ghishan FK (1986) Noncirrhotic portal fibrosis after Wilms' tumor therapy. Gastroenterology 90:1054–1056
76. Perry M (1992) Chemotherapeutic agents and hepatotoxicity. Semin Oncol 19:551–565
77. Locasciulli A, Vergani GM, Uderzo C et al. (1983) Chronic liver disease in children with leukemia in long-term remission. Cancer 52:1080–1087
78. Weber BL, Tanyer G, Poplack DG et al. (1987) Transient acute hepatotoxicity of high-dose methotrexate therapy during childhood. NCI Monogr 5:207–212
79. Bessho F, Kinumaki H, Yokota S, Hayashi Y, Kobayashi M, Kamoshita S (1994) Liver function studies in children with acute lymphocytic leukemia after cessation of therapy. Med Pediatr Oncol 23:111–115
80. Ballauff A, Krahe J, Jansen B, Ross RS, Roggendorf H, Havers W (1999) Chronic liver disease after treatment of malignancies in children. Klin Pediatr 211:49–52
81. Lascari AD, Givler RL, Soper RT, Hill LF (1968) Portal hypertension in a case of acute leukemia treated with antimetabolites for ten years. N Engl J Med 279:303–306
82. Ruymann FB, Mosijczuk AD, Sayers RJ (1977) Hepatoma in a child with methotrexate-induced hepatic fibrosis. JAMA 238:2631–2633
83. Nesbit M, Krivit W, Heyn R, Sharp H (1976) Acute and chronic effects of methotrexate on hepatic, pulmonary, and skeletal systems. Cancer 37 [Suppl 2]:1048–1057
84. Einhorn M DI (1964) Hepatotoxicity of mercaptopurine. JAMA 188:102–106
85. Green DM, Norkool P, Breslow NE, Finklestein JZ, D'Angio GJ (1990) Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: a report from the National Wilms' Tumor Study. J Clin Oncol 8:1525–1530
86. Raine J, Bowman A, Wallendszus K, Pritchard J (1991) Hepatopathy-thrombocytopenia syndrome – a complication of dactinomycin therapy for Wilms' tumor: a report from the United Kingdom Childrens Cancer Study Group. J Clin Oncol 9:268–273
87. Parker D, Bate CM, Craft AW, Graham-Pole J, Malpas JS, Stansfeld AG (1980) Liver damage in children with acute leukaemia and non-Hodgkin's lymphoma on oral maintenance chemotherapy. Cancer Chemother Pharmacol 4:121–127
88. McIntosh S DD, O'Brien RT, Pearson HA (1977) Methotrexate hepatotoxicity in children with leukemia. J Pediatr 90:1019–1021
89. Topley JM, Squier MV, Chessells JM (1979) Hepatotoxicity in the treatment of acute lymphoblastic leukemia. Med Pediatr Oncol 7:393–399
90. Hutter RVP, Tan CTC, Murphy ML, Chowdhury M (1960) Hepatic fibrosis in children with acute leukemia: a complication of therapy. Cancer 13:288–307
91. Colsky J, Warren TN (1955) Hepatic fibrosis in children with acute leukemia after therapy with folic acid antagonists. Arch Pathol Lab Med 59:198–206
92. Hersh EM WV, Henderson ES, Freireich E (1966) Hepatotoxic effects of methotrexate. Cancer 19:600–606

93. Farthing MJG, Sloane JP (1982) Liver disease after bone marrow transplantation. Gut 23:465–474
94. Shulman HM, McDonald DB (1984) Liver disease after marrow transplantation. In: Sale GE, Shulman HM (eds) The pathology of bone marrow transplantation. Year Book Medical Publishers, Chicago, pp 104–135
95. Zecca M, Prete A, Rondelli R et al. (2002) Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. Blood 100:1192–1200
96. Sullivan KM, Agura E, Anasetti C et al. (1991) Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol 28:250–259
97. Seeff LB, Koff RS (1986) Evolving concepts of the clinical and serologic consequences of hepatitis B virus infection. Semin Liver Dis 6:11–22
98. Strickland DK, Riely CA, Patrick CC et al. (2000) Hepatitis C infection among survivors of childhood cancer. Blood 95:3065–3070
99. Fink FM, Hocker-Schulz S, Mor W et al. (1993) Association of hepatitis C virus infection with chronic liver disease in paediatric cancer patients. Eur J Pediatr 152:490–492
100. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL (1999) Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology 29:908–914
101. Arico M, Maggiore G, Silini E et al. (1994) Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. Blood 84:2919–2922
102. Cesaro S, Rossetti F, de Moliner L, Crivellaro C, Zanesco L, Bortolotti F (1994) Interferon for chronic hepatitis C in patients cured of malignancy. Eur J Pediatr 153:659–662
103. Cesaro S, Petris MG, Rossetti F et al. (1997) Chronic hepatitis C virus infection after treatment for pediatric malignancy. Blood 90:1315–1320
104. Locasciulli A, Alberti A, Barbieri R et al. (1983) Evidence of non-A, non-B hepatitis in children with acute leukemia and chronic liver disease. Am J Dis Child 137:354–356
105. Locasciulli A, Bacigalupo A, Vanlint MT et al. (1991) Hepatitis C virus infection in patients undergoing allogeneic bone marrow transplantation. Transplantation 52:315–318
106. Locasciulli A, Cavalletto D, Pontisso P et al. (1993) Hepatitis C virus serum markers and liver disease in children with leukemia during and after chemotherapy. Blood 82:2564–2567
107. Locasciulli A, Pontisso P, Cavalletto D et al. (1994) Evidence against the role of hepatitis C virus in severe liver damage occurring early in the course of acute leukemia in children. Leuk Lymph 13:119–122
108. Locasciulli A, Testa M, Pontisso P et al. (1997) Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. Blood 90:4628–4633
109. Locasciulli A, Testa M, Pontisso P et al. (1997) Hepatitis C virus genotypes and liver disease in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant 19:237–240
110. Lucidarme D DF, Arpurt J et al. (1997) Natural history of hepatitis C: age at the time of transfusion might be an important predictive factor of progression to cirrhosis. Gastroenterology 112:A361
111. Swilley S SD, Davila R, Levstik M, Ribeiro R, Hudson MM (2002) Hepatitis C infection during treatment for childhood cancer: pitfalls in diagnosis and management. Med Pediatr Oncol 39:58–59
112. Vogt M, Lang T, Frosner G et al. (1999) Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med 341:866–870
113. Neilson JR, Harrison P, Skidmore SJ, King JA, Collingham KE, Milligan DW (1996) Chronic hepatitis C in long term survivors of haematological malignancy treated in a single centre. J Clin Pathol 49:230–232
114. Gigliotti AR, Fioredda F, Giacchino R (2003) Hepatitis B and C infection in children undergoing chemotherapy or bone marrow transplantation. J Pediatr Hematol Oncol 25:184–192
115. Poynard T, Bedossa P, Opolon P (1997) Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 349:825–832
116. Goedert JJ, Eyster ME, Lederman MM et al. (2002) End-stage liver disease in persons with hemophilia and transfusion-associated infections. Blood 100:1584–1589
117. Franchini M, Rossetti G, Tagliaferri A et al. (2001) The natural history of chronic hepatitis C in a cohort of HIV-negative Italian patients with hereditary bleeding disorders. Blood 98:1836–1841
118. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH (2000) Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med 132:296–305
119. Mahmoud H, Schell M, Pui CH (1991) Cholelithiasis after treatment for childhood cancer. Cancer 67:1439–1442
120. Chu WC, Roebuck DJ (2003) Nodular regenerative hyperplasia of the liver simulating metastases following treatment for bilateral Wilms tumor. Med Pediatr Oncol 41: 85–87
121. Wanless IR (1990) Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 11:787–797
122. Kumagai H, Masuda T, Oikawa H, Endo K, Endo M, Takano T (2000) Focal nodular hyperplasia of the liver: direct evidence of circulatory disturbances. J Gastroenterol Hepatol 15:1344–1347

123. Bouyn CI, Leclere J, Raimondo G et al. (2003) Hepatic focal nodular hyperplasia in children previously treated for a solid tumor. Incidence, risk factors, and outcome. Cancer 97:3107–3113
124. Brisse H, Servois V, Bouche B et al. (2000) Hepatic regenerating nodules: a mimic of recurrent cancer in children. Pediatr Radiol 30:386–393
125. Halonen P, Mattila J, Ruuska T, Salo MK, Makipernaa A (2003) Liver histology after current intensified therapy for childhood acute lymphoblastic leukemia: microvesicular fatty change and siderosis are the main findings. Med Pediatr Oncol 40:148–154
126. Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T (1997) Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. J Hepatol 26:312–324
127. Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T (1997) Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. Hepatology 25:63–70

The Ovary

Debra L. Friedman

Contents

13.1 Pathophysiology

13.1.1 Normal Organ Development

Hormonal function and potential for fertility are synchronous in females, as the ovary both produces oocytes and secretes steroid hormones. Prepubertal females possess their lifetime supply of oocytes with no new oogonia formed after birth. Active mitosis of oogonia occurs during fetal life, reaching a peak of 6–7 million by 20 weeks of gestation, and then rapidly declining to 1–2 million at birth. At the onset of puberty, only 300,000 remain [1]. The cortices of the ovaries harbor the follicles within connective tissue. These follicles arise from the germinal epithelium, which covers the free surface of the ovary. Through involution, atresia and, to a much lesser extent, ovulation, the follicles disappear entirely at menopause.

At initiation of puberty, there is a surge in the production of gonadotropin-releasing hormone (GnRH) by the hypothalamus. GnRH then stimulates release of the gonadotropins by the pituitary gland: follicle-stimulating hormone (FSH), responsible for follicular maturation, and luteinizing hormone (LH), responsible for ovarian luteinization. With menarche, the menstrual cycle occurs approximately every 28 days. Each cycle is marked by an estrogen-dependent mid-cycle surge of FSH and LH. After ovulation, the corpus luteum forms and produces progesterone, estradiol and 17- hydroxyprogesterone, as well as the endometrial changes required for implantation of a fetus. In the absence of fertilization, there is no chorionic gonadotropin from a conceptus; the corpus luteum becomes exhausted and progesterone and estrogen falls. At this time, FSH increases and the endometrium sloughs, resulting in menstruation.

The normal pre-menopausal ovary contains degenerating ova and follicles in varying stages of maturity.

Ovarian hormones also have critical physiologic effects on other organs and bodily processes, including the stimulation of libido, the maturation and function of the breasts and vagina, bone mineralization and the integrity of the cardiovascular system. With depletion of oocytes by radiotherapy, chemotherapy or normal senescence, the ovaries undergo atresia. As a result, menstruation and estrogen production cease, and menopause ensues.

13.1.2 Organ Damage Induced by Cytotoxic Therapy

Radiotherapy and chemotherapy each may cause transitory or permanent effects on hormonal function, reproductive capacity and sexual function. Primary ovarian failure, impaired development of secondary sexual characteristics, menstrual irregularities, including oligomenorrhea and amenorrhea, or premature menopause may occur. The menopausal state, when it occurs prematurely, is associated with the same physical symptoms as are seen with normal aging, including hot flashes, loss of libido and osteoporosis [2, 3]. Such effects are not simply physically bothersome to survivors, but adversely impact their quality of life [4]. The specific effects are dependent on the ovarian dose of radiation and the chemotherapeutic agents and their doses. They also depend on the developmental status of the patient at the age of treatment.

13.1.3 Cytotoxic Effects of Radiotherapy

Radiation causes a decrease in the number of ovarian follicles, impaired follicular maturation, cortical fibrosis and atrophy, generalized hypoplasia and hyalinization of the capsule. Females treated prior to puberty have a greater number of ova than do older women. Thus, ovarian function is more likely to be preserved after radiotherapy in prepubertal females, compared with post-pubertal females [5]. The dose of radiation that will ablate ovarian function depends on the patient's age and, by implication, stage of sexual development. Several investigators have provided information regarding the dose of radiotherapy that results in sterility in women of varying ages. Wallace and colleagues reported on 19 adult females treated in childhood with whole abdominal radiotherapy to a total dose of 30 Gy. Using the assumption that the number of oocytes within the ovary declines exponentially by atresia from approximately 2,000,000 at birth to approximately 2000 at menopause, they were able to estimate that the LD_{50} (radiation causing ablation in 50% of patients) for the human oocyte is not greater than 4 Gy [6]. Ash's summary of clinical information on radiation to the human ovary is shown in Table 13.1. Menopause was induced by a dose of 12 to 15 Gy in women under 40 years of age, whereas women over 40 years of age required only 4 to 7 Gy for the same clinical effect. Permanent sterility occurred in 60% of females 15–40 years of age receiving 5 to 6 Gy [7]. When one considers doses to the ovary after single fractions, temporary sterility can occur with ovarian doses of 1.7–6.4 Gy, and permanent sterility after doses of

Table 13.1. Effect of fractionated Ovarian X-irradiation on ovarian function in women of reproductive age irradiated for malignant or nonmalignant disease[a]

Minimum ovarian dose (Gy)	Effect
0.6	None.
1.5	No deleterious effect in most young women. Some risk of sterilization especially in women aged >40.
2.5–5.0	Variable. Aged 15–40 years: about 60% sterilized permanently, some with temporary amenorrhea. Aged >40: usually 100% permanently sterile.
5–8	Variable. Aged 15–40 years: about 70% sterilized permanently; of the remainder, some temporary amenorrhea.
>8	100% permanently sterilized.

[a] No attempt has been made to allow for variation in mode of fractionation. Modified from [7].

3.2–10 Gy [8]. Whole abdomen doses of 20–30 Gy are associated with primary or premature secondary ovarian failure in young females [6, 9].

13.1.4 Cytotoxic Effects of Chemotherapy

The effects of chemotherapy on ovarian function are both agent and dose-dependent, and this effect may be additive to that resulting from abdominopelvic radiotherapy. Alkylating agents affect the resting oocyte in a dose-dependent, cell cycle-independent manner. Thecal cells and ova are depleted, as are the primordial follicles, resulting in arrest of follicular maturation and decreased estrogen secretion. Again, as was the case with radiotherapy, the effects are more pronounced in post-pubertal as compared with prepubertal females, due to the fact that post-pubertal females have fewer remaining viable oocytes. The effects worsen with age, as the normal aging process is accompanied by an ongoing depletion of oocytes. Risks of menstrual irregularity, ovarian failure and infertility increase with age at treatments. Conversely, younger females can tolerate higher doses of alkylating agents without impairment of fertility, compared with adult females [10–15].

13.2 Clinical Manifestations

13.2.1 Effects of Radiotherapy on Ovarian Function

The clinical relationship between ovarian failure and the dose of radiation to the ovary is well illustrated by Stillman's study of 182 girls treated at less than 17 years of age with 12–15 Gy of abdominal radiotherapy. Overall, primary ovarian failure occurred in 22 girls (12%). However, ovarian failure was noted in 68% of the girls whose ovaries received the full irradiation dose, but in only 14% of those who had at least one ovary at the edge of the abdominal treatment volume (estimated dose 0.9–10 Gy, with a mean of 2.9 Gy). Conversely, none of 34 girls who received an estimated ovarian dose of 0.5–1.5 Gy (mean: 0.54 Gy) to at least one ovary outside the direct treatment volume had ovarian failure. Covariate and multivariate analyses revealed that the location of the ovaries relative to radiation treatment fields was the only risk factor for ovarian failure [16].

In considering the risk of ovarian failure related to radiotherapy, other fields than the abdomen and pelvis must be considered. Direct or scattered irradiation from the spinal component of craniospinal radiotherapy may also produce ovarian damage [6, 17]. With the expanded use of hematopoietic stem cell transplantation in pediatric oncology, it is important to recall that total body irradiation (TBI) utilized in the conditioning regimen is commonly associated with primary ovarian failure or premature menopause, with prevalence rates as high as 90–100% [18–22].

13.2.2 Effects of Chemotherapy on Ovarian Function

The dose–response relationship of alkylating agents, and the effect of age, is a recurring theme in studies of fertility following chemotherapy. Amenorrhea and ovarian failure occur more commonly in adult women treated with cyclophosphamide and other alkylating agents than with adolescents, with prepubertal females tolerating cumulative cyclophosphamide doses as high as 25 gm/m^2 [11, 23]. In examining protocols with common chemotherapy, 86% of women >24–30 years have been shown to have ovarian failure, compared with 28–31% of younger women [2, 23].

Due to improved survivorship from childhood cancer noted as early as the 1970s to 1980s, large cohorts of female survivors have reached the 3rd and 4th decades of life, where the risk for infertility and premature menopause has been examined. Two large studies of these survivors demonstrated elevated risks for infertility and premature menopause [9, 24]. A study of 2,498 female survivors, treated between 1945 and 1975, showed a 7% deficit in fertility, compared with siblings. Between ages 21 and 25 years, survivors had a risk of premature menopause four times greater than that of siblings. Treatment-related risk factors included radiotherapy alone (RR = 3.7), alkylating agents alone (RR = 9.2) or a combination of both (RR = 27). By age 31, 42% of these women had reached menopause, compared with 5% of siblings

[9]. In a study of 719 survivors treated between 1964 and 1988, 15.5% of women were unable to conceive. Women treated with abdominopelvic radiotherapy alone had a fertility deficit of 23%, compared with those treated with surgery. As with the previous study, the risk of infertility and premature menopause increased with increasing dose of abdominopelvic radiotherapy and amount of alkylating agent [24].

It is clear that the sterilizing effects of all alkylating agents are not equal. Mechlorethamine and procarbazine together are perhaps the most damaging of the alkylating agents. Newer risk-adapted protocols in pediatric oncology have been developed to avoid mechlorethamine or procarbazine and to limit cumulative doses of alkylating agents, without negatively impacting the efficacy of the chemotherapy regimens. This is best illustrated by the development of risk-adapted protocols in Hodgkin disease, where avoidance of long-term toxicities is a primary study goal [25–27]. The substitution of cyclophosphamide for mechlorethamine and total dose reductions appear to have significantly reduced the risk of ovarian dysfunction [28–30].

However, the full impact of these risk-adapted protocols is yet to be felt, with respect to long-term ovarian function. Females treated with cyclophosphamide with or without other alkylating agents are just now reaching the age where premature menopause was noted in earlier patient cohorts treated with mechlorethamine and procarbazine (in the 1960 s–80 s). Investigators are now starting to collect data on premature menopause in this group of women.

In recent years, ifosfamide, a congener of cyclophosphamide, has been used for a variety of solid tumors and lymphoma. The effects of ifosfamide on reproductive function are only beginning to be evaluated. An Italian study compared the residual ovarian function and fertility of two groups of female patients treated for osteosarcoma during different time periods with the same chemotherapy (ifosfamide, methotrexate, doxorubicin, cisplatin) at the same institution. Between 1997 and 2000, a group of 31 females treated with this chemotherapy, together with an oral contraceptive (OC), was compared with a group of 90 patients treated between 1974 and 1995 with the same drugs, but without any attempt to protect ovarian function. No protective effect on ovarian function was noted with the addition of the oral contraceptives [31]. Data is now being collected on female patients treated with ifosfamide, with or without cyclophosphamide, during childhood and adolescence in North America during the 1980s and 1990s. It remains to be seen whether the gonadal toxicity of ifosfamide is similar to that already well documented with cyclophosphamide, and whether, and to what extent, the toxicity is additive in regimens where both agents are administered.

Similar to what has been done with conventional chemoradiotherapy protocols, transplant conditioning protocols without TBI are being utilized to avoid some of the associated adverse long-term sequelae. The use of high dose cyclophosphamide without TBI or other alkylating agents is associated with a lower risk of ovarian failure than conditioning regimens with TBI or multiple alkylating agents. In a study by Sanders, 100% of women (n = 15) younger than age 26 and three of nine older than age 26 who were treated with 200 mg/kg cyclophosphamide recovered normal gonadotropin levels and menstruation post-transplantation [32]. However, many transplant protocols use high doses of alkylating agents together, most commonly busulfan and cyclophosphamide, which are associated with similar degrees of ovarian failure in females as protocols containing TBI [19, 33, 34].

13.2.3 Effects of Radiotherapy and Chemotherapy on Reproductive Outcomes

Many survivors of childhood cancer previously treated with cytotoxic therapy will remain fertile, and, therefore, pregnancy outcomes and the risk of cancer or genetic disease in offspring must be addressed. Young women who have been exposed to radiotherapy below the diaphragm are also at risk of impaired uterine development, which can adversely affect pregnancy outcomes, often resulting in premature labor and low birth-weight infants. The magnitude of the risk is related to the radiotherapy field, total dose and fractionation schedule. Female long-term sur-

vivors treated with total body irradiation and marrow transplantation are at risk for impaired uterine growth and blood flow, and, if pregnancy is achieved, for early pregnancy loss and premature labor. Despite standard hormone replacement, the uterus of the childhood cancer survivor may be impaired in its development and measure only 40% of normal adult size, the ultimate uterine volume correlating with the age at which radiotherapy was received [18, 34–36].

With more childhood cancer survivors retaining fertility, pregnancy outcome data is now available. Of 4,029 pregnancies occurring among 1,915 women followed in the Childhood Cancer Survivor Study (CCSS), there were 63% live births, 1% stillbirths, 15% miscarriages, 17% abortions and 3% unknown or in gestation. Risk of miscarriage was 3.6-fold higher in women treated with craniospinal radiotherapy and 1.7-fold higher in those treated with pelvic radiotherapy. Chemotherapy exposure alone did not increase the risk of miscarriage. Compared with siblings, however, survivors were less likely to have live births and more likely to have medical abortions and low birth-weight babies [35].

In the National Wilms Tumor Study, records were obtained for 427 pregnancies of >20 weeks duration. In this group, there were 409 single and 12 twin live births. Early or threatened labor, malposition of the fetus, lower birth-weight (<2500 g) and premature delivery (<36 weeks) were more frequent among women who had received flank radiotherapy, in a dose-dependent manner [36].

Preservation of fertility and successful pregnancies may occur following HSCT. Sanders and colleagues evaluated pregnancy outcomes in a group of females treated with bone marrow transplant. Among 116 treated before puberty and 23 treated after the onset of puberty who retained ovarian function, 32 (28%) and 9 (30%), respectively, became pregnant. Of the 32 pregnancies in those treated with TBI 50% (16) resulted in early termination, compared with a 21% prevalence of early termination in those treated with cyclophosphamide alone. There were no pregnancies among the women treated with busulfan and cyclophosphamide [34].

For childhood cancer survivors who have offspring, there is the concern about congenital anomalies, genetic disease or risk of cancer in the offspring. In the report from the National Wilms Tumor Group, congenital anomalies were marginally increased in the offspring of females who had received flank radiotherapy [36]. However, this risk was not observed in a study of 247 offspring of 148 cancer survivors treated at a single institution [37], or in several larger cohort studies. In a study that compared a group of 2,198 offspring from adult survivors treated for childhood cancer between 1945 and 1975 with a group of 4,544 offspring from sibling controls, there were no differences in the proportion of offspring with cytogenetic syndromes, single-gene defects or simple malformations. Nor was there an effect with respect to the type of childhood cancer treatment used and the occurrence of genetic disease in the offspring [38]. Similar results were reported in a study of 5,847 offspring of survivors of childhood cancers treated in five Scandinavian countries. In the absence of a hereditary cancer syndrome (such as hereditary retinoblastoma), there was no increased risk of cancer [39]. Further follow-ups are needed to determine whether patterns of cancer or genetic disease in offspring change with changes in cancer treatments, further elapsed time and studies of greater numbers of offspring.

13.3 Detection and Screening

All prepubertal females who are treated with potentially gonadal toxic radiotherapy or chemotherapy should be rigorously assessed for appropriate progression through puberty. The average age for menarche is 12.7 years ± 1.0 year [40]. An evaluation should include a complete history, a physical examination that includes an assessment of sexual development and pubertal milestones (Tables 13.3 and 13.4) and selected laboratory studies (Table 13.5), as summarized in Table 13.2. In conjunction with the evaluation of gonadal effects, attention must be paid to growth. Cranial radiotherapy confers significant risk for growth hormone deficiency. Once patients have reached full sexual maturity, linear growth will stop. Linear and sexual development must, therefore, be monitored simultaneously (see the chapter on Neuro-

Table 13.2. Pertinent history and physical examination

History	Physical examination
Doses and types of chemotherapy agents received	Height, weight and height velocity
Doses and fields of radiotherapy	Complete examination of all organ systems, with particular attention to pubertal status and thyroid gland
Surgical history, especially for patients with CNS and GU tumors	Gynecologic examination in postpubertal females as indicated by treatment history, sexual activity and overall developmental status
Patient and maternal history of menarche and thelarche	
Menstrual periods – timing and tempo	
Symptoms of estrogen deficiency (hot flashes, dry skin, leg cramps, reduced libido)	
Parental heights	
Family history of infertility, pregnancy, labor complications, assisted fertilization	

Table 13.3. Tanner staging (pubertal milestones) for breast development [40]

Stage	Age (mean ± SD, years)
I: Preadolescent. Only papilla is elevated.	
II: Breast and papilla are elevated as small mound. Areolar diameter is enlarged.	10.0 ± 1.0
III: Areola and papilla project to form a secondary mound above the level of the breast.	11.9 ± 1.0
IV: There is projection only of papilla because of recession of the areola to the general contour of the breast.	12.9 ± 1.2

Table 13.4. Tanner staging (pubertal milestones) for pubic hair growth [40]

Stage	Age (mean ± SD, years)
I: Preadolescent vellus over pubis is no further developed than that over anterior abdominal wall (i.e. no pubic hair).	
II: There is sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia.	11.2 ± 1.1
III: Hair is considerably darker, coarser and more curled. Hair spreads sparsely over pubic junction.	11.9 ± 1.1
IV: Hair is now adult in type but area covered by it is still considerably smaller than in most adults. There is no spread to medial surface of the thighs.	12.6 ± 1.1

Table 13.5. Laboratory assessment for ovarian function[a]

Testing	Treatment exposure	Time and frequency of evaluations
LH, FSH, estradiol	Alkylating agents Abdominopelvic, cranial or total body radiotherapy	Baseline at 11 years of age or older, and then yearly. Assessment also of whether the following are present: delayed puberty, irregular menses or amenorrhea, clinical signs or symptoms of estrogen deficiency
Free T4, TSH	Neck, cranial or total body radiotherapy	Yearly Assessment also of presence of signs or symptoms of thyroid dysfunction

[a] Also see Chapter 13.2

endocrine late effects for further details). Patients who received radiotherapy to the central nervous system or the neck are also at risk for thyroid dysfunction that can negatively impact gonadal function and linear growth. Even after successful progression through puberty, it is important to monitor the frequency and characteristics of menstrual periods, due to risk for premature menopause.

Females with ovarian failure, either primary or secondary, should undergo assessments for impaired bone mineral density. Calcium intake, weight-bearing exercise, a history of fractures and a family history of osteopenia/osteoporosis should be evaluated. The determination of bone mineral density, using dual-energy X-ray absorptiometry (DEXA) scan, and comparison of results with the well-established adult normative values, is indicated for all adult females. Screening in children is less defined. Several different measurement techniques and standards have been applied, but none has been well validated in large pediatric populations (much less in pediatric oncology patients). However, some monitoring is indicated, and trends over time may be of greater value than a single DEXA scan.

Pediatric endocrinologists and reproductive endocrinologists/gynecologists are essential consultants in the monitoring, prevention and management of ovarian late effects in childhood cancer survivors.

13.4 Management of Established Problems

13.4.1 Prevention Strategies

Reduction in the dose or use of alkylating agents and abdominopelvic radiotherapy is the most effective means of preserving ovarian function and promoting positive reproductive outcomes. This has been done for pediatric Hodgkin disease, where cooperative group and consortium studies conducted in the mid-1980s through the present have utilized low-dose involved field radiotherapy, or no radiotherapy, in those with a complete response to chemotherapy; these studies have also reduced the number, type and dose of alkylating agents [25–27, 30, 41–44]. There are, however, many instances where cytotoxic and gonadal toxic chemotherapy and radiotherapy are still required for long-term cure. As a result, additional strategies need to be employed to minimize adverse long-term outcomes. To shield the ovaries from direct irradiation during abdominal or pelvic radiotherapy, an oophoropexy may be performed. Typically, with whole abdominal radiotherapy, the ovaries are moved to a midline position in front of or behind the uterus. For pelvic radiotherapy, they may be moved laterally to the iliac wings. This may also be helpful for young girls or adolescents undergoing cranial spinal radiotherapy for brain tumors. The ovaries should be marked by the surgeon with clips that can later by identified by a simulator film. Central pelvic blocking at the time of "inverted Y" field will prevent direct irradiation, although scatter dose

and transmitted dose will be inevitable. Medial or lateral transposition of the ovaries results in ovarian doses of 8–10 % and 4– 5 %, respectively, of the pelvic dose [45, 46]. For most patients, this will be compatible with the preservation of fertility, although there may be temporary amenorrhea.

Because dividing cells are more sensitive to the cytotoxic effects of alkylating agents than are cells at rest, it has been hypothesized that inhibition of the pituitary–gonadal axis by gonadotropin-releasing hormone (GnRH) agonists may protect the ovarian germinal epithelium from the cytotoxic effects of chemotherapy. In a mixed teenage and young adult group of women treated for lymphoma, leukemia or autoimmune disease, Blumenfeld and colleagues [47, 48] reported a significant benefit in the concomitant use of GnRH agonist treatment with cytotoxic chemotherapy. Pereya and colleagues evaluated the role of GnRH analogs with respect to the prevention of early onset ovarian insufficiency following chemotherapy in adolescent females. Their study compared prepubertal females treated with GnRH analogs prior to chemotherapy with a control group of prepubertal patients who were not given GnRH analogs. Pereya and colleagues found that GnRH analog treatment before and during chemotherapy might enhance ovarian function and preserve adolescent fertility [49].

Progress in reproductive endocrinology has resulted in the availability of several potential options for preserving or permitting fertility in females about to receive potentially toxic chemotherapy or radiotherapy. In pre- and post-pubertal females, cryopreservation of ovarian cortical tissue and enzymatically-extracted follicles, with the in vitro maturation of prenatal follicles, is of potential clinical use. To date, most of the studies involving this technology have been performed in laboratory animals [50–52]. Another option available to the post-pubertal female is the stimulation of ovaries with exogenous gonadotropins and the retrieval of mature oocytes for cryopreservation. Only a few oocytes, however, can be harvested after stimulation of the ovaries [51]. In vitro fertilization and subsequent embryo cryopreservation have also been successful. These interventions, however, may not be readily available to the pediatric and adolescent patient, and the necessary delay in cancer therapy for ovarian stimulation or in vitro fertilization cycles often renders them impractical [52]. All such approaches harbor the risk that malignant cells will be present in the specimen and reintroduced in the patient at a later date. Those with hematologic or gonadal tumors would be at greatest risk for this eventuality [51, 52]. Standards for best practice in the cryopreservation of gonadal tissue remain to be defined. Should offspring result as a consequence of these assisted fertility techniques, it would be imperative to evaluate the risk of chromosomal and other congenital disorders, which have been reported following intracytoplasmic sperm injection [53–57].

A critical component to prevention is health counseling for females at risk. For females treated during the prepubertal period, parents should be counseled regarding the risk of primary ovarian failure. Normal gonadal development should be reviewed with recommendations for monitoring of growth and development. Reproductive counseling should be made cautiously and preferably, in conjunction with a specialist in reproductive endocrinology. The effects on the female gonadal system from radiotherapy and chemotherapy may demonstrate significant inter-individual variation, even with identical exposures at identical ages. Post-pubertal females who have normal menstrual function should be counseled about appropriate contraception should they currently not wish to conceive a child, and they should also be made aware of their potential risk for premature menopause. Not inconsequential for young adults is the impact of ovarian failure or impending failure in sexual drive or libido, an effect that may be treatable if addressed. Risks for osteopenia and osteoporosis also must be addressed. Appropriate calcium intake, avoidance of substances that interfere with bone deposition and appropriate weight-bearing exercise should be encouraged to maintain skeletal health.

13.4.2 Management of Delayed Puberty

Female patients exposed to gonadal toxic therapies during the prepubertal period and who are not progressing appropriately through puberty should be

promptly referred to a pediatric endocrinologist for further evaluation and treatment. The use of hormonal replacement therapy for induction and progression of puberty must be closely monitored together with skeletal growth, as the two processes are closely linked. Generally, the recommendation will be to initiate a regimen of hormone replacement such as estrogen, which is now available in a variety of doses and modes of administration. Gonadotropins, gonadotropin agonists or antagonists, progesterone and growth hormone may also be part of the treatment regimen.

13.4.3 Management of Infertility

Post-pubertal patients at risk for infertility should be referred to a reproductive endocrinologist to discuss assisted fertility techniques that may be appropriate. These specialists can also monitor fertility status and assist survivors with reproductive decisions.

13.4.4 Management of Pregnancy and Delivery

While many childhood cancer survivors may have no prenatal or perinatal complications, others may be at risk and should be managed appropriately by obstetricians and perinatologists. Patients treated with abdominopelvic radiotherapy are at risk for spontaneous abortion, premature labor and delivery and, compared with controls, small for gestational stage neonates. Those treated with anthracyclines at doses >300 mg/m^2 or at lower doses, when combined with thoracic radiotherapy, or those women treated with high doses of thoracic radiotherapy (>35 Gy) without anthracyclines, may be at risk for cardiac complications, which may manifest during pregnancy (especially during the third trimester and during delivery). Similarly, women previously treated with bleomycin, carmustine or busulfan, with higher doses of thoracic radiotherapy, may be at risk for pulmonary fibrosis or decreased diffusing capacity, and this may result in complications during pregnancy and delivery (see the chapters on Heart and Lung late effects for further details).

13.4.5 Management of Premature Menopause

Female survivors who develop premature menopause should be referred to a gynecologist for management and consideration for hormone replacement therapy. The decision to proceed with hormone replacement therapy, and the form that it should take, involves a careful evaluation of many competing healthcare factors, a subject that is beyond the scope of this chapter. However, it is imperative that patients be managed by a team of physicians who are well versed in this area and can assist in carefully weighing the risks and benefits of various hormonal replacement strategies.

13.5 Summary

Both chemotherapy and radiotherapy can affect ovarian function in female survivors of childhood cancer. The effects are varied and dependent on the chemotherapeutic agents and doses, radiotherapy doses, techniques, volumes and fields and the age and pubertal status of the female. There is also considerable individual variation, the reasons for which remain largely unknown. Problems may include primary ovarian failure, reduced libido, pregnancy complications and premature menopause. Preventive strategies remain limited. Avoidance or reduction in the dose of gonadal toxic therapies should be attempted where possible. Where this is not possible, advances in reproductive medicine may ultimately allow for ovarian cryopreservation and similar techniques. Survivors should receive health counseling about risks, annual physical examinations with attention paid to endocrine and reproductive function, close monitoring of gonadal function and referral to pediatric endocrinologists, reproductive endocrinologists, gynecologists and perinatologists as indicated. In survivors who do become pregnant, the majority will have favorable pregnancy outcomes with healthy offspring, and it does not appear that the offspring will have an increased risk of cancer (in the absence of a known heritable syndrome or congenital anomalies).

Much of what we have learned about gonadal function in female childhood cancer survivors is based on patients treated in the 1960s through the middle 1980s. During the past 20 years, there has been increased awareness of the adverse gonadal effects, and, where possible, therapies have been altered to limit these effects. This period has also resulted in the increased use of more dose-intensive chemotherapy regimens and greater use of myeloablative hematopoietic stem cell transplants. Survivorship has increased and, as a result, there are now large cohorts of adult young women treated with more contemporary therapy who will require close follow-up of their gonadal status. It is only with continued follow-up that we will be able to fully appreciate the impact of relatively recent changes in therapy. Challenges still face young females being treated for cancer today with respect to gonadal function. Therefore, it is incumbent upon pediatric oncologists and reproductive specialists to develop better preventive strategies. In addition, there is more to be learned about the inter-individual differences in gonadal effects that are seen, despite very similar treatment exposures. The role of genetic predisposition and inherent chemotherapy (or radiotherapy) sensitivity has yet to be studied with respect to most adverse long-term outcomes (including ovarian function) for childhood cancer survivors.

References

1. Palter S, Olive D (2002) Reproductive physiology. In: Berek J, Adams Hillard P, Adashi E (eds) Novak's gynecology. Lippincott Williams and Wilkins, Philadelphia, pp 163–164
2. Chapman RM, Sutcliffe SB, Malpas JS (1979) Cytotoxic induced ovarian failure in women with Hodgkin's disease. JAMA 242:1877–1881
3. Shalet SM (1996) Endocrine sequelae of cancer therapy. Eur J Endocrinol 135:135–143
4. Syrjala KL, Roth-Roemer SL, Abrams JR, Scanlan JM, Chapko MK, Visser S, Sanders JE (1998) Prevalence and predictors of sexual dysfunction in long-term survivors of marrow transplantation. J Clin Oncol 16:3148–3157
5. Constine LS (1991) Late effects of radiation therapy. Pediatrician 18:37–48
6. Wallace WH, Shalet SM, Hendry JH, Morris-Jones PH, Gattamaneni HR (1989) Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. Br J Radiol 62:995–998
7. Ash P (1980) The influence of radiation on fertility in man. Br J Radiol 53:271–278
8. Lushbaugh CC, Casarett GW (1976) The effects of gonadal irradiation in clinical radiation therapy: a review. Cancer 37 [Suppl 2]:1111–1125
9. Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K (1987) Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 317:1315–1321
10. Nicosia SV, Matus-Ridley M, Meadows AT (1985) Gonadal effects of cancer therapy in girls. Cancer 55:2364–2372
11. Damewood MD, Grochow LB (1986) Prospects for fertility after chemotherapy or radiation for neoplastic disease. Fertil Steril 45:443–459
12. Bath LE, Hamish W, Wallace B, Critchley HO (2002) Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. BJOG: an Int J Obstet Gynaecol 109:107–114
13. Hill M, Milan S, Cunningham D, Mansi J, Smith I, Catovsky D, Gore M, Zulian G, Selby P, Horwich A et al. (1995) Evaluation of the efficacy of the VEEP regimen in adult Hodgkin's disease with assessment of gonadal and cardiac toxicity (see comments). Comment in: J Clin Oncol 1995, 13:1283–1284. J Clin Oncol 13:387–395
14. Mayer EI, Dopfer RE, Klingebiel T, Scheel-Walter H, Ranke MB, Niethammer D (1999) Longitudinal gonadal function after bone marrow transplantation for acute lymphoblastic leukemia during childhood. Pediatric Transplant 3:38–44
15. Thomson AB, Critchley HO, Kelnar CJ, Wallace WH (2002) Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. Best Pract Res Clin Endocrinol Metab 16:311–334
16. Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, Jaffe N, Li FP (1981) Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol 139:62–66
17. Halperin EC (1993) Concerning the inferior portion of the spinal radiotherapy field for malignancies that disseminate via the cerebrospinal fluid. Int J Radiat Oncol Biol Phys 26:357–362
18. Critchley HO, Bath LE, Wallace WH (2002) Radiation damage to the uterus – review of the effects of treatment of childhood cancer. Hum Fertil (Camb) 5:61–66
19. Sklar C, Boulad F, Small T, Kernan N (2001) Endocrine complications of pediatric stem cell transplantation. Front Biosci 6:G17–G22
20. Ogilvy-Stuart AL, Clark DJ, Wallace WH, Gibson BE, Stevens RF, Shalet SM, Donaldson MD (1992) Endocrine deficit after fractionated total body irradiation. Arch Dis Child 67:1107–1110
21. Sklar CA (1991) Growth and pubertal development in survivors of childhood cancer. Pediatrician 18:53–60

22. Howell S, Shalet S (1998) Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Am 27:927–943
23. Kreuser ED, Xiros N, Hetzel WD, Heimpel H (1987) Reproductive and endocrine gonadal capacity in patients treated with COPP chemotherapy for Hodgkin's disease. J Cancer Res Clin Oncol 113:260–266
24. Chiarelli AM, Marrett LD, Darlington G (1999) Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964–1988 in Ontario, Canada. Am J Epidemiol 150:245–254
25. Hudson MM (2002) Pediatric Hodgkin's therapy: time for a paradigm shift. J Clin Oncol 20:3755–3757
26. Linch DC, Gosden RG, Tulandi T, Tan SL, Hancock SL (2000) Hodgkin's lymphoma: choice of therapy and late complications. Hematology (Am Soc Hematol Educ Program) 205–221
27. Schwartz CL (2003) The management of Hodgkin disease in the young child. Curr Opin Pediatr 15:10–16
28. Santoro A, Valagussa P (1992) Advances in the treatment of Hodgkin's disease. Curr Opin Oncol 4:821–828
29. Hamilton VM, Norris C, Bunin N, Goldwein JW, Bunin GR, Lange B, Meadows AT (2001) Cyclophosphamide-based, seven-drug hybrid and low-dose involved field radiation for the treatment of childhood and adolescent Hodgkin disease. J Pediatr Hematol Oncol 23:84–88
30. Hudson MM, Greenwald C, Thompson E, Wilimas J, Marina N, Fairclough D, Kauffman W, Bozeman P, Mackert PW, Abromowitch M et al. (1993) Efficacy and toxicity of multiagent chemotherapy and low-dose involved-field radiotherapy in children and adolescents with Hodgkin's disease. J Clin Oncol 11:100–108
31. Longhi A, Pignotti E, Versari M, Asta S, Bacci G (2003) Effect of oral contraceptive on ovarian function in young females undergoing neoadjuvant chemotherapy treatment for osteosarcoma. Oncol Rep 10:151–155
32. Sanders JE, Buckner CD, Leonard JM, Sullivan KM, Witherspoon RP, Deeg HJ, Storb R, Thomas ED (1983) Late effects on gonadal function of cyclophosphamide, total-body irradiation, and marrow transplantation. Transplantation 36: 252–255
33. Teinturier C, Hartmann O, Valteau-Couanet D, Benhamou E, Bougneres PF (1998) Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. Bone Marrow Transplant 22:989–994
34. Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, Doney K, Storb R, Sullivan K, Witherspoon R, Appelbaum FR (1996) Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 87:3045–3052
35. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, Pendergrass TW, Robison LL (2002) Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 187:1070–1080
36. Green DM, Peabody EM, Nan B, Peterson S, Kalapurakal JA, Breslow NE (2002) Pregnancy outcome after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 20:2506–2513
37. Green DM, Fiorello A, Zevon MA, Hall B, Seigelstein N (1997) Birth defects and childhood cancer in offspring of survivors of childhood cancer. Arch Pediatr Adolesc Med 151:379–383
38. Byrne J, Rasmussen SA, Steinhorn SC, Connelly RR, Myers MH, Lynch CF, Flannery J, Austin DF, Holmes FF, Holmes GE, Strong LC, Mulvihill JJ (1998) Genetic disease in offspring of long-term survivors of childhood and adolescent cancer (comment). Am J Hum Genet 62:45–52
39. Sankila R, Olsen JH, Anderson H, Garwicz S, Glattre E, Hertz H, Langmark F, Lanning M, Moller T, Tulinius H (1998) Risk of cancer among offspring of childhood-cancer survivors. Association of the Nordic Cancer Registries and the Nordic Society of Paediatric Haematology and Oncology (comment). N Engl J Med 338:1339–1344
40. Rosenfield RL (2002) Puberty in the female. In: Sperling MA (ed) Pediatric endocrinology. Saunders, Philadelphia
41. Hudson MM, Donaldson SS (1999) Treatment of pediatric Hodgkin's lymphoma. Semin Hematol 36:313–323
42. Kelly KM, Hutchinson RJ, Sposto R, Weiner MA, Lones MA, Perkins SL, Massey V (2002) Feasibility of upfront dose-intensive chemotherapy in children with advanced-stage Hodgkin's lymphoma: preliminary results from the Children's Cancer Group Study CCG-59704. Ann Oncol 13 [Suppl 1]:107–111
43. Donaldson SS, Hudson MM, Lamborn KR, Link MP, Kun L, Billett AL, Marcus KC, Hurwitz CA, Young JA, Tarbell NJ, Weinstein HJ (2002) VAMP and low-dose, involved-field radiation for children and adolescents with favorable, early-stage Hodgkin's disease: results of a prospective clinical trial. J Clin Oncol 20:3081–3087
44. Nachman JB, Sposto R, Herzog P, Gilchrist GS, Wolden SL, Thomson J, Kadin ME, Pattengale P, Davis PC, Hutchinson RJ, White K (2002) Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 20:3765–3771
45. Ortin TT, Shostak CA, Donaldson SS (1990) Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: the Stanford experience (see comments). Int J Radiat Oncol Biol Phys 19:873–880
46. Haie-Meder C, Mlika-Cabanne N, Michel G, Briot E, Gerbaulet A, Lhomme C, Cosset JM, Sarrazin D, Flamant F, Hayat M (1993) Radiotherapy after ovarian transposition: ovarian function and fertility preservation. Int J Radiat Oncol Biol Phys 25:419–424

47. Blumenfeld Z, Dann E, Avivi I, Epelbaum R, Rowe JM (2002) Fertility after treatment for Hodgkin's disease. Ann Oncol 13 [Suppl 1]:138–147
48. Blumenfeld Z, Avivi I, Linn S, Epelbaum R, Ben-Shahar M, Haim N (1996) Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy. Hum Reprod 11:1620–1626
49. Pereyra Pacheco B, Mendez Ribas JM, Milone G, Fernandez I, Kvicala R, Mila T, di Noto A, Contreras Ortiz O, Pavlovsky S (2001) Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. Gynecol Oncol 81:391–397
50. Bahadur G, Steele S (1996) Ovarian tissue cryopreservation for patients. Hum Reprod 11:2215–2216
51. Donnez J, Godin P, Qu J, Nisolle M (2000) Gonadal cryopreservation in the young patient with gynaecological malignancy. Curr Opin Obstet Gynecol 12:1–9
52. Newton H (1998) The cryopreservation of ovarian tissue as a strategy for preserving the fertility of cancer patients. Hum Reprod Update 4:237–247
53. Ericson A, Kallen B (2001) Congenital malformations in infants born after IVF: a population-based study. Hum Reprod 16:504–509
54. Bonduelle M, Liebaers I, Deketelaere V, Derde MP, Camus M, Devroey P, van Steirteghem A (2002) Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995 infants born after IVF (1983–1999). Hum Reprod 17: 671–694
55. Hansen M, Kurinczuk JJ, Bower C, Webb S (2002) The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. N Engl J Med 346:725–730
56. Serafini P (2001) Outcome and follow-up of children born after IVF-surrogacy. Hum Reprod Update 7:23–27
57. Simpson JL, Lamb DJ (2001) Genetic effects of intracytoplasmic sperm injection. Semin Reprod Med 19:239–249

The Testes

Jill P. Ginsberg · Amit Maity

Contents

14.1 Introduction

Chemotherapy, radiation and surgery all may affect the testes, exerting a profound effect on future reproductive function. The differential sensitivity of spermatozoa-producing Sertoli cells, in contrast to testosterone-producing Leydig cells, results in more significant effects on reproductive capacity than on sexual function. Since the testes are more sensitive than the ovary to cytotoxic therapies, ensuing injuries from identical treatment regimens are more damaging to male fertility than to females. A comparison of fertility in treated men versus women revealed a 0.76 adjusted relative fertility [11]. In this chapter, we review the pathophysiology of the testes and the clinical manifestations of testicular injury in response to gonado-toxic therapies. We also outline methods for screening males for gonadotoxicity and suggest potential preventative measures for consideration.

14.2 Pathophysiology

14.2.1 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 [51]. 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 [51]. 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 [51]; the medulla differentiates into a testis and the cortex regresses. The gonads can be recognized as testes 7–9 weeks post-fertilization.

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 pre-spermatogonia, 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 [83]. After the 8th week of fetal life, the Leydig cell of the fetal testis secretes testosterone. Luteinizing hormone (LH) release is suppressed, and masculinization of the external genitalia and urogenital sinus of the fetus results. By the third month, the penis and prostate form [17]. Normal testes descend by the seventh month of gestation with little likelihood of continuing spontaneous descent after 9 months [19].

14.2.2 Anatomy of Normal Testis

The adult testis is an oblong organ, approximately 4.5 cm in length and weighing 34–45 grams [82]. 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 [76]. Seminiferous tubules, the sites of spermatogenesis, are formed by germ cells and Sertoli cells. The Leydig cells that are responsible for the production of testosterone lie near the basal compartment of the seminiferous tubules, enabling them to deliver the high concentrations of testosterone necessary for normal spermatogenesis and male secondary sexual characteristics [52, 76].

The seminiferous tubules are embedded in a connective tissue matrix containing interspersed Leydig cells, blood vessels and lymphatics, and they 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. The haploid cells (the spermatids) that are formed develop into flagellate motile spermatozoa. This process requires up to 74 days [79]. 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.

14.2.3 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. 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 [52]. 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 [52, 76]. Testosterone is transported from the Leydig cells to the seminiferous tubules, where it acts to enhance spermatogenesis [76]. Testosterone is also a prohormone 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 [78]. Testosterone controls pituitary LH secretion by a negative feedback mechanism; LH levels rise when the Leydig cells are unable to produce testosterone.

Table 14.1. Genital development stages [50, 55]

Stage	Description	Mean age at onset (years), range 95%
1	Preadolescent. Testes, scrotum and penis are about the same size and proportion as in early childhood.	
2	Scrotum and testes have enlarged; there is a change in texture and some reddening of the scrotal skin. Testicular length is greater than 2cm, but less than 3.2 cm.	11.6 (9.5–13.8)
3	Growth of penis has occurred, at first this is mainly in length, some increase in breadth; further growth of testes and scrotum. Testicular length is greater than3.3cm, but less than 4.0 cm.	12.9 (10.8–14.9)
4	Penis is further enlarged in length and breadth, with development of glans. Testes and scrotum are further enlarged. Scrotal skin has darkened. Testicular length is greater than 4.1cm but less than 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 is greater than 5 cm.	14.9 (12.7–17.1)

Sertoli cells are the only cells of the testis that possess FSH receptors [76]. 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 cells, where it mediates the synthesis of a variety of proteins and enzymes, including the inhibins [52]. Inhibin is a major feedback regulator of FSH and may thus be useful as a marker of spermatogenesis [30, 71]. 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 spermiogenesis. Thereafter, spermatogenesis proceeds 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.

14.2.4 Normal Developmental Stages

A neonatal surge in testosterone secretion is caused by high LH and FSH concentrations 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 [76]. At the onset of puberty, pulsatile secretion of LH (and, to a lesser extent, FSH) occurs during sleep and is associated with increased nighttime plasma concentrations of testosterone [76]. As puberty progresses, the increased pulsatile release of gonadotropins and the high concentrations of testosterone are maintained throughout the day and night [76].

In a normal male, the first sign of puberty is growth of the testis to larger than 2.5 cm [83]. 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 is 9–14 years of age. Boys complete pubertal development in 2–4.5 years (mean 3.2 years) [83]. The stages corresponding to the development of the external genitalia and pubic hair have been described by Marshall and Tanner and are shown in Tables 14.1 and 14.2 [50]. The first appearance of spermatozoa in early morning urinary specimens (spermarche) occurs at a mean age of 13.4 years during gonadal stages 3 and 4 (pubic hair stages 2–4), simultaneously with the pubertal growth spurt.

Table 14.2. Pubic hair developmental stages [50, 55]

Stage	Description	Mean age at onset (years), range 95%
1	Preadolescent. No pubic hair.	
2	Sparse growth of long, slightly pigmented downy hair, either straight or only slightly curled, appearing chiefly at the 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 the area it covers is still smaller than in most adults. There is no spread to the 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)

14.3 Cytotoxic Effects of Therapy

14.3.1 Cytotoxic Effects of 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. In 1948, azoospermia after an alkylating agent (nitrogen mustard) was described in 27 of 30 men treated for lymphoma [81]. Subsequently, it became apparent that all alkylating agents are gonadotoxic [31, 49, 59], while antimetabolite therapy (with, e.g. methotrexate or mercaptopurine) does not have a long-term impact on male fertility. Cisplatin-based regimens, including vinblastine, bleomycin and etoposide, result in temporary impairment of spermatogenesis in all patients, but a significant percentage recovers [27]. The agents most commonly gonadotoxic in males are listed in Table 14.3.

Table 14.3. Gonadotoxic chemotherapeutic agents

- Alkylating agents
  - Cyclophosphamide
  - Ifosfamide
  - Nitrosoureas, e.g. BCNU and CCNU
  - Chlorambucil
  - Melphalan
  - Busulfan
  - Procarbazine (non-classic alkylator)
- Vinca alkaloids
  - Vinblastine
- Antimetabolites
  - Cytarabine
- Other
  - Cisplatin

Initial reports, based upon histological studies and normal basal FSH levels from small numbers of patients, suggested that the immature testis was relatively resistant to chemotherapy [75]. More recently, however, it has become apparent that both the prepubertal and pubertal testes are vulnerable to cytotoxic drugs [5, 7, 33]. Impairment of spermatogenesis may be irreversible in the months to years following chemotherapy, although late recovery of spermatogenesis (up to 14 years following chemotherapy) has been reported on rare occasion [10, 88]. 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 [20, 34, 63, 88].

Compared with the germinal epithelium, Leydig cells are relatively resistant to the effects of chemotherapy [73, 85]. However, with more intensive gonadotoxic regimens, reductions in testosterone concentrations have been noted that may be clinically relevant.

Table 14.4. Impairment of spermatogenesis and Leydig cell function after fractionated radiotherapy [4]

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. 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 in most boys to ensure pubertal changes.

14.3.2 Cytotoxic Effects of Testicular Irradiation

Soon after the discovery of X-rays by Roentgen, investigators noted that spermatogenesis was exquisitely sensitive to radiation [2, 65]. The testes are directly irradiated in situations such as the testicular relapse of acute lymphoblastic leukemia (ALL). Although the testes are usually not directly in the radiation field, they can still receive radiation 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 [40]. 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 may become an issue when treating a field that extends into the pelvis. Small children, because of their short trunk length, can be at greater risk from scattered radiation than larger individuals.

Some effect on spermatogenesis will be seen at doses of 10 cGy, with permanent sterilization occurring at doses as low as 100 cGy (Table 14.4) [4]. Data in mammals indicate that the total radiation dose required to induce permanent azoospermia is lower with fractionated regimens than with single-dose therapy [80]. The radiation doses used in these experiments cannot be directly extrapolated to humans since germ cell radiosensitivity differs between species. However, the general conclusion does appear to be true in humans, a finding attributable to the fact that non-proliferating spermatogonia are radioresistant and unlikely to be killed with a single, large dose of radiation. However, fractionated radiation increases the chance that such cells will enter the proliferating compartment and be susceptible to radiation-induced killing. Spermatogonia are thus most affected by regimens in which each fraction is maximally efficient in causing death in proliferating spermatogonia and in which there are a sufficient number of fractions such that all the spermatogonia are eventually

irradiated while in a proliferative, radiosensitive state.

More attention has been focused on the effects of radiation on spermatogenesis than on its effects on Leydig cell function. The available data indicate that chemical changes in Leydig cell function are observable following direct testicular irradiation, particularly after higher doses (e.g. 2,400 cGy vs 1,200 cGy) [77]. This effect is more severe in the younger the patient [12].

14.4 Clinical Manifestations

14.4.1 Effects of Chemotherapy

The extent and reversibility of cytotoxic damage generally depends on the agent and cumulative dose received, although significant individual variation has been observed. The effects of alkylating agents on testicular function have been studied extensively.

Cyclophosphamide, either alone or in combination with other agents, is known to damage the germinal epithelium. In a meta-analysis of 30 studies that examined gonadal function following various chemotherapy regimens, gonadal dysfunction correlated with the total cumulative dose of cyclophosphamide; more than 300 mg/kg was associated with >80% risk of gonadal dysfunction [66]. A study of men treated for pediatric solid tumors reported permanent azoospermia in 90% of men treated with cyclophosphamide doses >7.5 g/m^2 [84]. Other studies have also found that 7.5–9 g/m^2 of cyclophosphamide is associated with a significant risk of testicular injury [5, 39].

Although tumor cytotoxicity data indicates that 1.1 g/m^2 cyclophosphamide is approximately equivalent to 3.8 g/m^2 ifosfamide [16], the relative gonadotoxic effect is not well known. In a recent series of male childhood survivors of osteosarcoma 4–17 years after therapy (median: 9 years), the incidence of azoospermia related to ifosfamide therapy (median 42 g/m^2), versus no ifosfamide, was statistically significant (P=0.005). Six patients were normospermic: five had received no ifosfamide and one had received low-dose ifosfamide (24 g/m^2). Azoospermia occurred in 15 of the 19 patients who received ifosfamide. Infertility in the others may have been related to cisplatin (560–630 mg/m^2). One patient had oligospermia [48].

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 with boys who had received OPPA/COPP (including procarbazine). This again, points out that procarbazine is a potent gonadotoxic agent [29]. The treatment of Hodgkin's disease with combination chemotherapy regimens, such as ChlVPP (chlorambucil, vinblastine, procarbazine and prednisolone) or COPP (cyclophosphamide, vincristine, procarbazine and prednisolone), has also been reported (in several studies) to result in permanent azoospermia in 99–100% of patients treated with 6–8 courses of these regimens [15, 49]. After ChlVPP, both FSH and LH were elevated (by 89% and 24%, respectively), and azoospermia occurred in all seven patients tested. Charak and coworkers 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 [15]. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP-like regimens, such as those 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) [54, 64]. Azoospermia occurring on therapy for NHL is likely to recover within the following year [63]. Efforts to reduce the risk of sterility after Hodgkin's disease include, among other related regimens, the use of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine). This is an effective combination that does not contain the alkylating agents, chlorambucil

or procarbazine [43, 86]. Viviani and co-workers showed that, while recovery of spermatogenesis after MOPP was rare, all who experienced oligospermia after ABVD recovered completely by 18 months [86]. Hybrid regimens (i.e. alternating cycles of ABVD with ChlVPP or MOPP) are also less gonadotoxic than MOPP, ChlVPP or COPP given alone.

Nitrosoureas, used in the treatment of brain tumors in childhood, may also cause gonadal damage in boys [1, 47, 71]. In nine children treated for medulloblastoma with craniospinal radiation and a nitrosourea (carmustine or lomustine, plus vincristine in four boys 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 chemotherapy. The authors concluded that nitrosoureas were responsible for the gonadal damage, with procarbazine also contributing in the three children who received this drug.

PVB (cisplatin, vinblastine and bleomycin), which is used in patients with germ cell tumors, is a standard chemotherapy and results in minimal effects on long-term testicular function. 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 whether patients were treated with orchiectomy, or with orchiectomy plus PVB, sperm production 1.5 years after treatment was similar. Approximately half in each group had sperm counts below the normal control reference level [28]. Lampe et al. analyzed the data on 170 patients with testicular germ cell cancers who had undergone treatment with either cisplatin or carboplatin-based chemotherapy [44]. After median of 30 months from the completion of chemotherapy, they discovered that azoospermia occurred in 54 (32%) of the patients and oligospermia occurred in 43 (25%). The probability of recovery to a normal sperm count was higher in men who: a) had a normal pretreatment sperm count, b) had received carboplatin rather than cisplatin-based therapy and c) had undergone a treatment with fewer than 5 cycles of chemotherapy. Recovery continued for more than two years, with the calculated chance of spermatogenesis at two years being 48%, and the calculated chance of spermatogenesis at five years being 80% [34, 44].

Heyn and colleagues described the late effects of therapy on testicular function in patients between the ages of 10 months and 19 years afflicted with paratesticular rhabdomyosarcoma as a result of cyclophosphamide, radiation and retroperitoneal lymph node dissection. Tanner staging was normal in 45 patients for whom it was recorded. However, eight had loss of normal ejaculatory function. The available data showed that elevated FSH values and/or azoospermia occurred in greater than half the patients. Testicular size was decreased in those who received either cyclophosphamide or testicular irradiation [32].

The importance of alkylating agents in the induction of gonadal toxicity is noted by contrasting the above outcomes to those of children with acute lymphoblastic leukemia (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 [87]. 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 [87]. Thus, it may be inferred that, in contrast to alkylating agents, the classic anti-metabolites used in the treatment of childhood ALL are not associated with long-term gonadal toxicity. Although both vincristine and corticosteroids can cause immediate inhibition of spermatogenesis, following the cessation of these agents, spermatogenesis recovery occurs [42].

14.4.1.1 Treatment-Induced Leydig Cell Failure from Chemotherapy

Leydig cells are much less vulnerable to damage from cancer therapy than germ cells. This is likely due to their slow rate of turnover [73]. 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. In fact, 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 the failure to develop secondary sexual characteristics [76]. If the insult follows completion of normal pubertal development, observed symptoms include loss of libido, erectile dysfunction, decreased bone density and decreased muscle mass [76]. 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 level should be considered for androgen replacement therapy.

14.4.2 Effects of Radiation

The data for gonadal function following fractionated radiotherapy in humans comes from a) patients with cancers who have been treated with either fields near the testes in which there is scatter dose or b) patients with diseases such as testicular cancers or ALL in which the testes are thought to be at risk of harboring disease and therefore irradiated directly. One of the potentially confounding issues is that some of these cancers may themselves be associated with decreased gonadal function independent of irradiation. For example, Hodgkin's disease is well documented to cause oligospermia in some patients (reviewed in [35]). Patients with testicular tumors may have preexisting gonadal dysfunction [35, 70, 90]. In ALL, the leukemic cells may infiltrate the interstitium of the testis and conceivably affect Leydig cell function.

Ash et al. summarized data from several older studies [25, 67, 80] 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 [4] (see Table 14.4). They found that oligospermia occurred at doses as low as 10 cGy and that azoospermia, which was generally reversible, occurred at doses as low as 35 cGy. However, doses of 200–300 cGy could result in azoospermia that did not reverse even years after irradiation.

These results are 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, FSH levels remained normal in patients who received <20 cGy [41]. Those receiving ≥ 20 cGy had a dose-dependent increase in serum FSH levels, with a maximum difference seen at six months following radiation. In all patients, the FSH normalized within 12–24 months. Eight patients had normal pretreatment sperm counts. Most of the 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 who had received 23 cGy or less went on to father children. Ortin et al. reported on children treated for Hodgkin's disease [57]. 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) [74]. These patients were estimated to have received between 1–2500 cGy (median dose 80 cGy) of scatter dose to the testes. Patients who received 50 cGy or more 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. In the former group, 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 [26]. The scatter dose to the remaining testicle in these 14 patients ranged from

32–114 cGy (median 82 cGy). Ten patients who received ≥70 cGy to the testes developed azoospermia 10–30 weeks following radiation. All patients, except two, had recovery of spermatogenesis; and the recovery time from azoospermia was dose-dependent. Centola et al., in a study of males with seminoma, also showed that the recovery time from oligospermia/azoospermia was dose-dependent [13].

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 [77]. All the patients had received identical chemotherapy; however, the RT fields varied significantly and included: 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 seven years after diagnosis of ALL, gonadal function abnormalities occurred in 55%, 17% and 0% of patients in groups 1, 2, and 3, respectively. Because, at the time of testing, many of the patients were adolescents, when evaluation of germ cell function can be difficult, this study probably underestimated the incidence of the problem. Castillo et al. examined 15 boys with ALL who were 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 [12]. Semen analyses, performed at least nine 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.

14.4.2.1 Leydig Cell Function Following Radiotherapy

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 [41]. In the study of men treated for sarcomas by Shapiro et al. discussed above [74], maximal increases in LH levels relative to baseline were seen at six 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 cGy or <50 cGy. For those receiving >200cGy, 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 [24]. 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 [35, 70, 90]. 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 [61]. Out of 42 men for whom data was available, 18 received hormonal supplementation therapy because of symptoms of androgen insufficiency. All patients underwent 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 in boys following radiation comes primarily from studies of boys who received direct testicular irradiation for ALL. In the analysis by Sklar et al. mentioned previously, only one out of 53 boys tested for gonadotropins had increased LH levels, and only two out of 50 patients tested had a reduced testosterone level [77]. 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, and both 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 [9]. 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 [8]. All seven had elevated FSH levels. Four of these boys had documented bilateral testicular disease, and three showed delayed sexual maturation with low testosterone levels.

There are data that suggest that the prepubertal testis is more susceptible to Leydig cell injury that the adult testis. Shalet et al. [73] examined Leydig cell function in three groups of patients: 1) 16 adults who underwent unilateral orchiectomy for testicular teratoma and did not receive post-operative 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 1–4 years for various pediatric malignancies [73]. The median LH level was lower in group 1 than in group 2 (6 IU 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. Brauner et al. also found that younger children were more vulnerable than older ones to Leydig cell dysfunction following testicular radiation for ALL. 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 cell failure and require androgen replacement therapy [45, 72].

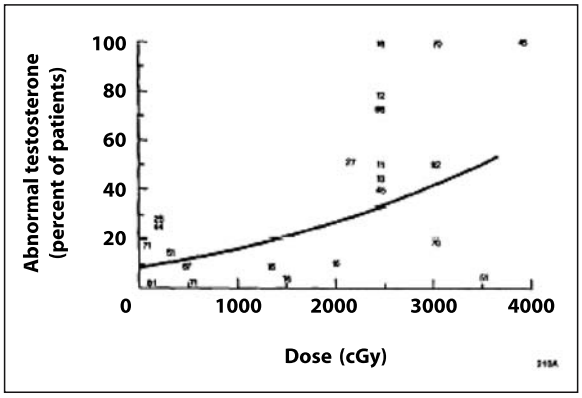


Figure 14.1

Based on a review of the literature, this graph shows the percentage of patients with an abnormal testosterone value in relation to the stated dose of radiation to the testes. A curve showing best fit was extrapolated from the values by log-rank regression. Taken from Izard [36].

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 in the same percentage of men (see Fig. 14.1) [36]. 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 [76].

14.4.2.2 Testicular Function Following Total Body Irradiation

There are data on germ cell function following total body irradiation (TBI) as part of transplant conditioning. Sarafoglou et al. followed 17 boys who had received cyclophosphamide and TBI (either 1375 cGy

or 1500 cGy in 125 cGy t.i.d. fractionation) prior to puberty as part of a transplantation regimen for leukemia [69]. 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.

Costo-Silva followed 29 boys who received TBI for different malignancies in association with a variety of chemotherapy regimens [18]. 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 [6]. Transplantation included cyclophosphamide and TBI (single doses of 500 cGy, 750 cGy or 800 cGy, or 1200 cGy in six fractions). Nineteen boys who had not received the 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 [46, 56] 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. In contrast to this, Sanders [68], reporting on the Seattle Marrow Transplant Team's experience, found a higher incidence of pubertal developmental delay in boys undergoing transplantation for leukemia using cyclophosphamide and TBI (900–1,000 cGy in a single fraction or 1,200–1,575 cGy in 200–225 cGy daily fractions over 6–7 days). There were 31 boys who were prepubertal at the time of transplantation. They were between the ages of 13 and 22 at the time of the study. Twenty-one out of 31 of these patients were delayed in their development of secondary sexual characteristics. Serum gonadotropins were obtained in 25 of the 31 boys and showed elevated LH levels in 10, normal levels in 12 and prepubertal levels in three. It is not clear why this particular report showed such a high incidence of pubertal developmental delay compared to other studies, but it is possible that some of these boys had received prior testicular irradiation. Alternatively, the differences could be due to variations in exposure to alkylating agents or in the total dose/fractionation schedule.

14.4.2.3 Summary

The spermatogenic capacity of the testes can be suppressed by extraordinarily low doses of radiation. As little as 10–20 cGy of scattered radiation in a fractionated regimen 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. In contrast, the doses used for testicular ALL, which are an order of magnitude larger (1200–2400 cGy), are expected to lead to permanent azoospermia in virtually all patients.

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. 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. With respect to irradiation doses between 1200– 2000 cGy, the data are less clear-cut. Some studies show normal sexual maturation in prepubertal boys who received

Table 14.5. Evaluation of hypothalamic–pituitary axis

Disease	Testosterone	FSH	LH	Response to	
				GnRH	HCG
Primary Leydig cell disease	Normal/low	High	High		Low
Primary disease of germinal epithelium	Normal	High	Normal		
Hypothalamic disease	Normal/low	Normal/low	Normal/low	Normal	
Pituitary disease	Normal/low	Normal/low	Normal/low	Low	

these doses [12, 69], but others show decreases in testosterone levels and a subsequent requirement for androgen supplementation [61, 68]. 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 respect to differences in the underlying diseases. Some diseases (e.g. testicular carcinoma or testicular ALL) might themselves affect Leydig cell function. Other variables could be the age of the patients at the time of irradiation, the use of alkylating agents, especially in transplantation studies and, lastly, the frequency and timing of the subsequent laboratory investigations to identify Leydig cell dysfunction.

14.5 Detection and Screening

14.5.1 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 these testicular functions (i.e. the production of hormones and the production of semen). The development of normal secondary sexual characteristics suggests intact Leydig cell function, with normal steroidogenesis, and 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 (Table 14.5). In prepubertal children, however, 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 are indicative of Leydig cell dysfunction, while elevated FSH and diminished inhibin B suggest germ cell failure. HCG may be given to confirm the diagnosis of end organ failure as a cause of hypogonadism. An abnormal response to HCG is suggestive of disturbed Leydig cell function. Patients with hypogonadotrophic hypogonadism should have a brisk response, while those with decreased Leydig cell function will have little or no response. GnRH may be administered to determine whether the primary defect is in the hypothalamus or in the pituitary. If it's in the hypothalamus, the pituitary and testicles themselves should respond normally to exogenous GnRH. Alternatively, if the primary defect is in the pituitary, there will be an inadequate response. An exaggerated response of FSH and LH to GnRH suggests a "failing" testis; hence, this test may be useful in detecting early testicular failure. Depressed gonadotropins may also be found in patients after the administration of exogenous androgen. The determination of elevated FSH, along with small testicular size, may offer the most practical approach for predicting subsequent testicular damage in boys with malignancies.

Recently, 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 devel-

oped enzyme-linked immunosorbent assay [3]. It has been postulated that inhibin B is produced by the Sertoli cells and germ cells of the testes and reflects the degree of seminiferous tubular damage [37, 60, 71]. Furthermore, inhibin B exerts negative feedback regulation on the pituitary production and release of FSH [22]. In a study examining the gonadal status of childhood brain tumor survivors, researchers found a significant inverse correlation between basal FSH and inhibin B, as well as a significant correlation between inhibin B and total testicular volume [71].

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 fertilization and, hence, 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, as such evaluation is indicated.

14.6 Management of Established Problems

14.6.1 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 it should be offered to all newly diagnosed, postpubertal males at risk for potential infertility. Many improvements have been made in the techniques used to store sperm. There have also been advancements in assisted reproductive technology using intracytoplasmic sperm injection (ICSI). As a result, there is an increased chance of successful pregnancy using banked sperm [53, 58, 62].

Ejaculatory azoospermia is not the same as testicular azoospermia [14]. Hence, studies on the gonadotoxicity of chemotherapy have to be interpreted in light of the fact that assisted reproductive technology makes it possible to use testis sperm to conceive. The level of sperm necessary for sperm to exist in the testis is far less than the level required for sperm in the ejaculate [14]. As a result, testis sperm extraction (TESE), followed by ICSI, now makes it possible for patients who have azoospermia on semen analysis, and did not sperm bank, to father children. A retrospective study by Damani et al. evaluated 23 men with ejaculatory azoospermia and a history of chemotherapy. All men underwent TESE in search of usable sperm. Spermatozoa were found in 15 (65%). The subsequent fertility rate was 65% and pregnancy occurred in 31% of cycles [21]. This illustrates the importance of performing a full evaluation on men with post-chemotherapy azoospermia before diagnosing them as sterile.

Unfortunately, at this time there are no feasible options for prepubertal male patients. There has been no demonstrated protective effect of using GnRH analogues with or without testosterone to suppress testicular function during chemotherapy [38, 57, 89]. As pediatric oncologists, we must continue to attempt to reduce the gonadotoxicity of our treatment regimens while maintaining superior cure rates.

14.6.2 Method to Minimize Testicular Radiation Dose

As discussed above, in most cases, the testicular dose from a radiation treatment is due to internal scatter, not direct irradiation. Internal scatter is difficult to prevent, but methods have been developed to decrease the dose. Frass et al. reported on a gonadal shield that formed a cup around the testes to reduce the testicular dose [23, 74]. They found that this led to a 3–10-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. Therefore, for a patient receiving 5000 cGy to a pelvic field, the dose to the testes would be less than 50 cGy. This most likely would prevent permanent azoospermia, and it almost certainly would prevent a decline in testosterone levels.

References

1. Ahmed SR, Shalet SM, Campbell RH, Deakin DP (1983) Primary gonadal damage following treatment of brain tumors in childhood. J Pediatr 103:562–565
2. Albers-Schonberg HE (1903) Über eine bisher unbekannte Wirkung der Roengenstrahlen auf den Organismus der Tiere. Munch Med Wochenschr 50:1859–1860
3. Andersson AM, Muller J, Skakkeaek NE (1998) Different roles of prepubertal and postpubertal germ cells and Sertoli cells in the regulation of serum inhibin B levels. J Clin Endocrinol Metab 83:4451–4458
4. Ash P (1980) The influence of radiation on fertility in man. Br J Radiol 53:271–278
5. Aubier F, Flamamant F, Brauner R, Caillaud JM, Chaussain JM, Lemerle J (1989) Male gonadal function after chemotherapy for solid tumors in childhood. J Clin Oncol 7:304–309
6. Bakker B, Massa GG, Oostdijk W, van Weel-Sipman MH, Vossen JM, Wit JM (2000) Pubertal development and growth after total-body irradiation and bone marrow transplantation for haematological malignancies. Eur J Pediatr 159:31–37
7. Ben Arush MW, Solt I, Lightman A, Linn S, Kuten A (2000) Male gonadal function in survivors of childhood Hodgkin and non-Hodgkin lymphoma, Pediatr Hematol Oncol 17: 239–245
8. Blatt J, Sherins RJ, Niebrugge D, Bleyer WA, Poplack DG (1985) Leydig cell function in boys following treatment for testicular relapse of acute lymphoblastic leukemia. J Clin Oncol 3:1227–1231
9. Brauner R, Czernichow P, Cramer P, Schaison G, Rappaport R (1983) Leydig-cell function in children after direct testicular irradiation for acute lymphoblastic leukemia. N Engl J Med 309:25–28
10. Buchanan JD, Fairley KF, Barrier JU (1975) Return of spermatogenesis after stopping cyclophosphamide therapy. Lancet 2:156–157
11. Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K (1987) Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 19:1315–1321
12. Castillo LA, Craft AW, Kernahan J, Evans RG, Aynsley-Green A (1990) Gonadal function after 12-Gy testicular irradiation in childhood acute lymphoblastic leukaemia. Med Pediatr Oncol 18:185–189
13. Centola GM, Keller JW, Henzler M, Rubin P (1994) Effect of low-dose testicular irradiation on sperm count and fertility in patients with testicular seminoma. J Androl 15:608–613
14. Chan PT.K, Palermo GD, Veeck LL, Rosenwaks Z, Schlegel PN (2001) Testicular sperm extraction combined with intracytoplasmic sperm injection in the treatment of men with persistent azoospermia post-chemotherapy. Cancer 92:1632–1637
15. Charak BS, Gupta R, Mandrekar P, Sheth NA, Banavali SD, Saikia TK, Gopal R, Dinshaw KA, Advani SH (1990) Testicular dysfunction after cyclophosphamide-vincristine-procarbazine-prednisolone chemotherapy for advanced Hodgkin's disease. A long-term follow-up study. Cancer 65:1903–1906
16. Colvin M (1982) The comparative pharmacology of cyclophosphamide and ifosfamide. Semin Oncol 9:2–7
17. Conte FA, Grumbach MM (1990) Pathogenesis, classification, diagnosis and treatment of anomalies of sex. In: Degroot LJ (ed) Endocrinology. Saunders, Philadelphia
18. Couto-Silva AC, Trivin C, Thibaud E, Esperou H, Michon J, Brauner R (2001) Factors affecting gonadal function after bone marrow transplantation during childhood. Bone Marrow Transplant 28:67–75
19. Czeizel A, Erodi E, Toth J (1981) Genetics of undescended testes. J Urol 126:528
20. Da Cunha MF, Meistrich ML, Fuller LM (1984) Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. J Clin Oncol 2:571–577
21. Damani MN, Masters V, Meng MV, Burgess C, Turek P, Oates RD (2002) Post-chemotherapy ejaculatory azoospermia: fatherhood with sperm from testis tissue with intracytoplasmic sperm injection. J Clin Oncol 20:930–936
22. de Kretser DM, McFarlane JR (1996) Inhibin in the male. J Androl 17:179–182
23. Fraass BA, Kinsella TJ, Harrington FS, Glatstein E (1985) Peripheral dose to the testes: the design and clinical use of a practical and effective gonadal shield. Int J Radiat Oncol Biol Phys 11:609–615
24. Giwercman A, von der Maase H, Berthelsen JG, Rorth M, Bertelsen A, Skakkebaek NE (1991) Localized irradiation of testes with carcinoma in situ: effects on Leydig cell function and eradication of malignant germ cells in 20 patients. J Clin Endocrinol Metab 73:596–603
25. Hahn EW, Feingold SM, Nisce L (1976) Aspermia and recovery of spermatogenesis in cancer patients following incidental gonadal irradiation during treatment: a progress report. Radiology 119:223–225
26. Hahn EW, Feingold SM, Simpson L, Batata M (1982) Recovery from aspermia induced by low-dose radiation in seminoma patients. Cancer 50:337–340
27. Hansen PV, Hansen SW (1993) Gonadal function in men with testicular germ cell cancer: the influence of cisplatin-based chemotherapy. Eur Urol 23:153–156

28. Hansen PV, Trykker H, Helkjoer PE, Andersen J (1989) Testicular function in patients with testicular cancer treated with orchiectomy alone or orchiectomy plus cisplatin-based chemotherapy. J Natl Cancer Inst 81:1246–1250
29. Hassel JU, Bramswig JH, Schlegel W, Schellong G (1991) Testicular function after OPA/COMP chemotherapy without procarbazine in boys with Hodgkin's disease. Results in 25 patients of the DAL-HD-85 study. Klin Padiatr 203:268–272
30. Hayes FJ, Hall JE, Boepple PA, Crowley WF (1998) Differential control of gonadotropin secretion in the human: endocrine role of inhibin. J Clin Endocrinol Metab 83:1835–1841
31. Heikens J, Behrendt H, Adriaanse R, Berghout A (1996) Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. Cancer 78:2020–2024
32. Heyn R, Raney RB, Jr, Hays DM, Tefft M, Gehan E, Webber B, Maurer HM (1992) Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. J Clin Oncol 10:614–623
33. Howell S, Shalet S (1998) Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Am 27:927–943
34. Howell SJ, Shalet SM (2001) Testicular function following chemotherapy. Hum Reprod Update 7:363–369
35. Howell SJ, Shalet SM (2002) Effect of cancer therapy on pituitary-testicular axis. Int J Androl 25:269–276
36. Izard MA (1995) Leydig cell function and radiation: a review of the literature. Radiother Oncol 34:1–8
37. Jensen TK, Andersson AM, Hjollund NH (1997) Inhibin B as a serum marker of spermatogenesis: correlation to differences in sperm concentration and follicle-stimulating hormone levels. A study of 349 Danish men. J Clin Endocrinol Metab 82:4059–4063
38. Johnson DH, Linde R, Hainsworth JD, Vale W, Rivier J, Stein R, Flexner J, van Welch R, Greco FA (1985) Effect of luteinizing hormone releasing hormone agonist given during combination chemotherapy on post-therapy fertility in male patients with lymphoma: preliminary observations. Blood 65:832–836
39. Kenney LB, Laufer MR, Grant FD, Grier H, Diller L (2001) High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 91:613–621
40. Khan F (2003) The physics of radiation therapy, 3rd edn. Lippincott, Willimas and Wilkins, Philadelphia
41. Kinsella TJ, Trivette G, Rowland J, Sorace R, Miller R, Fraass B, Steinberg SM, Glatstein E, Sherins RJ (1989) Long-term follow-up of testicular function following radiation therapy for early-stage Hodgkin's disease. J Clin Oncol 7:718–724
42. Kreuser ED, Hetzel WD, Heit W, Hoelzer D, Kurrle E, Xiros N, Heimpel H (1988) Reproductive and endocrine gonadal functions in adults following multidrug chemotherapy for acute lymphoblastic or undifferentiated leukemia. J Clin Oncol 6:588–595
43. Kulkarni SS, Sastry PS, Saikia TK, Parikh PM, Gopal R, Advani SH (1997) Gonadal function following ABVD therapy for Hodgkin's disease. Am J Clin Oncol 20:354–357
44. Lampe H, Horwich A, Norman A, Nicholls J, Dearnaley DP (1997) Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 15:239–245
45. Leiper AD, Grant DB, Chessells JM (1986) Gonadal function after testicular radiation for acute lymphoblastic leukaemia. Arch Dis Child 61:53–56
46. Leiper AD, Stanhope R, Lau T, Grant DB, Blacklock H, Chessells JM, Plowman PN (1987) The effect of total body irradiation and bone marrow transplantation during childhood and adolescence on growth and endocrine function. Br J Haematol 67:419–426
47. Livesey EA, Brook CG (1988) Gonadal dysfunction after treatment of intracranial tumours. Arch Dis Child 63:495–500
48. Longhi A, Macchiagodena M, Vitali G, Bacci G (2003) Fertility in male patients treated with neoadjuvant chemotherapy for osteosarcoma. J Pediatr Hematol Oncol 25:292–296
49. Mackie EJ, Radford M, Shalet SM (1996) Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol 27:74–78
50. Marshall WA, Tanner JM (1970) Variation in pattern of pubertal changes in boys. Arch Dis Child:45:13–23
51. Moore KL (1988) The urogenital system. The developing human. Saunders, Toronto
52. Morris ID (1996) The testis: endocrine function. In: Hiller SG, Kitchener HC, Neilson JP (eds) Scientific essentials of reproductive medicine. Saunders, London, pp 160–171
53. Muller J, Sonksen J, Sommer P, Schmiegelow M, Petersen PM, Heilman C, Schmiegelow K (2000) Cryopreservation of semen from pubertal boys with cancer. Med Ped Oncol 34:191–194
54. Muller U, Stahel RA (1993) Gonadal function after MACOP-B or VACOP-B with or without dose intensification and ABMT in young patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 4:399–402
55. O'Dell WD (1989) Puberty. In: DeGroot LJ (ed) Endocrinology, 2nd edn. Saunders, Philadelphia
56. Ogilvy-Stuart AL, Clark DJ, Wallace WH, Gibson BE, Stevens RF, Shalet SM, Donaldson MD (1992) Endocrine deficit after fractionated total body irradiation, Arch Dis Child, 67:1107–10
57. Ortin TT, Shostak CA, Donaldson SS (1990) Gonadal status and reproductive function following treatment for Hodgkin's disease in childhood: the Stanford experience. Int J Radiat Oncol Biol Phys 19:873–880
58. Palermo GD, Cohen J, Alikani M, Adler A, Rosenwaks Z (1995) Intracytoplasmic sperm injection: a novel treatment for all forms of male factor infertility. Fertil Steril 63: 1231–1240

59. Papadakis V, Vlachopapadopoulou E, van Syckle K, Ganshaw L, Kalmanti M, Tan C, Sklar C (1999) Gonadal function in young patients successfully treated for Hodgkin disease. Med Pediatr Oncol 32:366–372
60. Petersen PM, Andersson AM, Rorth M, Daugaard G, Skakkeaek NE (1999) Undetectable inhibin B serum levels in men after testicular irradiation. J Clin Endocrinol Metab 84:213–215
61. Petersen PM, Giwercman A, Daugaard G, Rorth M, Petersen JH, Skakkeaek NE, Hansen SW, von der Maase H (2002) Effect of graded testicular doses of radiotherapy in patients treated for carcinoma-in-situ in the testis. J Clin Oncol 20:1537–1543
62. Pfeifer SM, Coutifaris C (1999) Reproductive technologies 1998: options available for the cancer patient. Med Ped Oncol 33:34–40
63. Pryzant RM, Meistrich ML, Wilson G (1993) Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphomas. J Clin Oncol 11:239–247
64. Radford JA, Clark S, Crowther D, Shalet SM (1994) Male fertility after VAPEC-B chemotherapy for Hodgkin's disease and non-Hodgkin's lymphoma. Br J Cancer 69:379–381
65. Regaud C, Blanc J (1906) Extreme sensibilite des spermatogonies a ces rayons. CR Soc Biol Paris 61:163–165
66. Rivkees SA, Crawford JD (1988) The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 259:2123–2125
67. Sandeman TF (1966) The effects of x irradiation on male human fertility. Br J Radiol 39:901–907
68. Sanders JE, Pritchard S, Mahoney P, Amos D, Buckner CD, Witherspoon RP, Deeg HJ, Doney KC, Sullivan KM, Appelbaum FR et al. (1986) Growth and development following marrow transplantation for leukemia. Blood 68:1129–1135
69. Sarafoglou K, Boulad F, Gillio A, Sklar C (1997) Gonadal function after bone marrow transplantation for acute leukemia during childhood. J Pediatr 130:210–216
70. Schilsky RL (1989) Infertility in patients with testicular cancer: testis, tumor, or treatment? J Natl Cancer Inst 81:1204–1205
71. Schmiegelow M, Lassen S, Poulsen HS, Schmiegelow K, Hertz H, Andersson AM, Skakkebaek NE, Muller J (2001) Gonadal status in male survivors following childhood brain tumors. J Clin Endocrinol Metab 86:2446–2452
72. Shalet SM, Horner A, Ahmed SR, Morris-Jones PH (1985) Leydig cell damage after testicular irradiation for lymphoblastic leukaemia. Med Pediatr Oncol 13:65–68
73. Shalet SM, Tsatsoulis A, Whitehead E, Read G (1989) Vulnerability of the human Leydig cell to radiation damage is dependent upon age. J Endocrinol 120:161–165
74. Shapiro E, Kinsella TJ, Makuch RW, Fraass BA, Glatstein E, Rosenberg SA, Sherins RJ (1985) Effects of fractionated irradiation of endocrine aspects of testicular function. J Clin Oncol 3:1232–1239
75. Sherins RJ, Olweny CL, Ziegler JL (1978) Gynaecomastia and gonadal dysfunction in adolescent boys treated with combination chemotherapy for Hodgkins disease. N Engl J Med 299:12–16
76. Sklar C (1999) Reproductive physiology and treatment-related loss of sex hormone production. Med Pediatr Oncol 33:2–8
77. Sklar CA, Robison LL, Nesbit ME, Sather HN, Meadows AT, Ortega JA, Kim TH, Hammond GD (1990) Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. J Clin Oncol 8:1981–1987
78. Smith EP, Boyd J, Frank GR (1994) Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 331:1056–1061
79. Smith KD, Rodgriguez-Rigau LJ (1989) Laboratory evaluation of testicular function. In: Degroot LJ (ed) Endocrinology. Saunders, Philadelphia
80. Speiser B, Rubin P, Casarett G (1973) Aspermia following lower truncal irradiation in Hodgkin's disease. Cancer 32:692–698
81. Spitz S (1948) The histological effects of nitrogen mustards on human tumors and tissues. Cancer 1:383–398
82. Steinberger E (1989) Structural consideration of the male reproductive system. In: DeGroot LJ (ed) Endocrinology. Saunders, Philadelphia
83. Styne DM (1982) The testes: disorders of sexual differentiation and puberty. In: Kaplan SA (ed) Clinical pediatric endocrinology. Saunders, Philadelphia
84. Thomson AB, Campbell AJ, Irvine DC, Anderson RA, Kelnar CJ, Wallace WH (2002) Semen quality and spermatozoal DNA integrity in survivors of childhood cancer: a case-control study. Lancet 360:361–367
85. Tsatsoulis A, Shalet SM, Morris ID, de Kretser DM (1990) Immunoactive inhibin as a marker of Sertoli cell function following cytotoxic damage to the human testis. Horm Res 34:254–259
86. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G (1985) Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol 21:601–605
87. Wallace WH, Shalet SM, Lendon M, Morris-Jones PH (1991) Male fertility in long-term survivors of childhood acute lymphoblastic leukaemia, Int J Androl 14:312–319
88. Watson AR, Rance CP, Bain J (1985) Long-term effects of cyclophosphamide on testicular function. Br Med J 291:1457–1460
89. Waxman JH, Ahmed R, Smith D, Wrigley PF, Gregory W, Shalet S, Crowther D, Rees LH, Besser GM, Malpas JS (1987) Failure to preserve fertility in patients with Hodgkin's disease. Cancer Chemother Pharmacol 19:159–162
90. Willemse PH, Sleijfer DT, Sluiter WJ, Schraffordt Koops H, Doorenbos H (1983) Altered Leydig cell function in patients with testicular cancer: evidence for bilateral testicular defect. Acta Endocrinol (Copenh) 102:616–624

Genitourinary

Lawrence Marks · Nicole Larrier

Contents

15.1 Introduction

This chapter addresses the long-term effects of the treatment of childhood cancer on the genitourinary (GU) tract, primarily focusing on the kidneys, ureters, bladder, urethra, prostate, vagina and uterus. The effects on ovaries and testes are reviewed in Chapters 13 and 14. The most common pediatric cancers that occur in the GU tract include Wilms' tumor, neuroblastoma and rhabdomyosarcoma. The median age of children affected with these tumors ranges from 3 years (Wilms' tumor, neuroblastoma) to 6 years (rhabdomyosarcoma). Growth and development of the GU tract in the following years may be compromised by the cancer treatment, including surgery, radiation therapy (RT) or chemotherapy; see Table 15.1. Recent changes in cancer therapy, including bone marrow transplantation, intraoperative radiation therapy and high-dose rate brachytherapy, pose new risks that have not been clearly defined. Furthermore, GU organs may be incidentally damaged by therapies used to treat tumors in non-GU organs. For example, many of the chemotherapeutic agents used to treat both GU and non-GU tumors are potentially toxic to the kidney and/or bladder. In addition, radiation fields designed to treat the liver or pelvic bones usually include portions of the kidney or bladder.

Table 15.1. Summary of late organ damage

Organ	Surgery	Radiation Therapy	Chemotherapy
Kidney	Unilateral loss of renal function due to surgery or RT is generally not a problem if the remaining kidney is normal. Bilateral injury can lead to renal failure		Glomerular and tubular injury can lead to variable degrees of renal dysfunction (cisplatin)
Ureter	Urinary diversion may be necessary after resection or injury	Fibrosis is unusual and occurs only after high doses or after intraoperative irradiation	
Bladder	Dysfunction due to partial or total organ loss may occur	Fibrosis and loss of capacity after irradiation of a large fraction of the organ. Focal ulcerations are possible	Hemorrhagic cystitis, contracture, and functional loss can occur. Cancer induction is possible (cyclophosphamide, ifosfamide)
Urethra	Stricture requiring dilation following surgery or RT		
Vagina	Dysfunction due to partial or total organ loss may occur	Fibrosis, ulceration, fistula and maldevelopment are possible	
Uterus	Dysfunction due to partial or total organ loss may occur	Maldevelopment and fibrosis is possible	
Prostate	Dysfunction due to partial or total organ loss may occur	Loss of glandular function is possible	

15.2 Pathophysiology

15.2.1 Normal Organ Development

Normal fetal development of the GU structures begins with successive development of pronephric, mesonephric and metanephric tubules around the third, sixth, and twelfth weeks of gestation in the embryo, respectively. After 12 weeks, the urinary bladder has developed and separated from the rectum. The prostate and testes in boys, and the ovaries and uterus in girls, are also formed at approximately 12 weeks gestation. The vagina develops somewhat later. After birth, prostatic and vaginal-uterine growth proceeds very slowly until adolescence, when the organs enlarge during pubertal growth.

15.2.2 Organ Damage and Developmental Problems

The multimodal treatment of cancers with surgery, RT and chemotherapy may cause structural or functional impairment of the GU organs and tissues. Table 15.1 summarizes late organ damage to the GU system.

15.2.3 Surgery

Removal of a paired structure, such as a kidney, is not usually associated with subsequent functional impairment, unless the remaining organ has been damaged from either therapy or the tumor. (In fact, the remaining kidney may undergo compensatory hypertrophy [1]). Conversely, the removal of a non-paired structure such as the bladder, prostate or uterus can produce severe and life-long impairment, such as urinary incontinence or infertility. Urinary diversion after total cystectomy for bladder sarcoma in childhood can be associated with infection and eventual renal impairment from pyelonephritis, ureteral or stomal obstruction or both [2, 3]. In addition, ureterocolic diversion and bladder augmentation have occasionally been associated with early development of colon cancer [4] (This is reported in the urology literature. It is also seen with reconstruction of the neurogenic bladder. The hypothesis is that the

irritation of urine on bowel mucosa can be carcinogenic. An interesting canine study showed hyperplasia at the anastomoses [5]. Continent diversion techniques, using repeated catheterization of an indwelling ileal or colonic bladder, may provide better results [6]. Continent diversion is accomplished by creating a reservoir – usually of bowel – that the patient empties periodically via catheterization throughout the day.

15.2.4 Radiation Therapy

Organ injury following RT is generally classified as acute (occurring during or soon after therapy) and late (occurring months to years following therapy). Whereas the acute effects are usually transient, late effects are usually progressive. Acutely, RT frequently causes irritation of the mucosa of the bladder and urethra (causing cystitis and urethritis) or of the vagina and vulva (causing pruritus and discomfort). These symptoms usually occur after approximately 20 Gy of radiation. Because almost all children receiving GU tract irradiation are also receiving chemotherapy, normal acute tissue toxicities are seen earlier than they would be seen without concurrent chemotherapy. Typically, cystitis occurs after three to four weeks of radiation, but it can occur after two weeks with concurrent therapy. Occasionally, some morbidity is seen after doses as low as 8–10 Gy. Acute injury of the kidney, prostate and uterus is generally not clinically apparent. The later effects of RT are dose-dependent and due to progressive vascular and parenchymal cell damage, generally leading to scarring, fibrosis and sometimes necrosis. Malignant tumors can be seen following irradiation, generally occurring a minimum of 4–5 years following completion of radiation [7]. A discussion of the late effects for each organ follows.

15.2.4.1 Kidney

Irradiation appears to cause renal dysfunction secondary to tubular damage. Nephropathy generally occurs when doses in excess of 20–25 Gy are delivered to both kidneys [8]. When chemotherapeutic agents are used as well, lower doses (10–15 Gy) can cause significant injury. In general, if only a portion (less than one half to one third) of the kidney is irradiated, then higher doses may be tolerated without demonstrable functional deficits. The sequelae may be more prominent and occur at lower doses in infants. Hyper-renin hypertension can also occur secondary to radiation-induced renal artery narrowing. This phenomenon has been noted most often in children (especially infants) and should be distinguished from other types of renal radiation-induced hypertension. Irradiation to the remaining kidney following nephrectomy may hinder the normal hypertrophic response.

15.2.4.2 Bladder, Ureter and Urethra

Radiation can induce inflammation and fibrosis and cause dysfunction due to a reduction in bladder capacity and contractility. Although it is not certain, the underlying etiology seems to be radiation-induced vascular ischemia of the muscular wall [9–11]. The risk of developing bladder dysfunction is related to both the radiation dose and the percentage of the bladder wall irradiated [9, 12]. In data compiled in adults, it is clear that a small volume of the bladder can tolerate fairly high does of radiation [9, 12]. (Radiation for prostate or bladder cancer in adults routinely results in irradiation of portions of the bladder with 60–70 Gy.) However, high doses may cause focal injury to part of the bladder wall, resulting in bleeding and stone formation [13–17]. It is believed that stone formation is associated with bacteruria, which can occur after damage to the bladder. When the entire bladder is irradiated, doses of >50 Gy may result in severe contraction and secondary whole organ dysfunction. Consequently, both the radiation dose and volume of organ irradiated must be considered when assessing the risk of injury. Similarly, scarring and fibrosis can occur in the urethra and ureter, causing dysfunction of these structures [7, 18, 19]. Doses less than 50 Gy may slow or hamper the full development of the bladder, due to lesser degrees of fibrosis.

15.2.4.3 Prostate, Uterus and Vagina

The exact pathophysiology of radiation-induced late effects is less well defined than for the kidneys and bladder. When irradiated to high doses in an adult, the vagina undergoes loss of the epithelium and slow re-epithelization over a 2-year period [20]. It is likely that the prominent late effects in the uterus and vagina are related to progressive fibrosis, leading to loss of function. The prostate may lose its secretory capacity, resulting in ejaculatory dysfunction.

15.2.5 Chemotherapy

The major chemotherapeutic agents that cause damage to the GU tract are the platinum compounds (Cisplatin and Carboplatin) and alkylating agents (cyclophosphamide and ifosfamide). The toxicity of the antimetabolite, methotrexate, is largely preventable and reversible.

15.2.5.1 Kidney

Cisplatin causes both glomerular and renal tubular damage, with wasting of divalent and monovalent cations (magnesium, calcium and potassium). Cumulative doses as low as 450 mg/m2 are associated with some renal toxicity. Proximal tubular damage predominates, especially in a low chloride environment [21]. Elevated serum concentration of creatinine and decreased glomerular filtration rate (GFR) with azotemia also occur and are dose and age- related. These effects vary both in severity and chronicity [22, 23]. Prior cisplatin administration may delay the renal clearance of methotrexate [24]. Carboplatin has a better renal toxicity profile than cisplatin. The replacement of cisplatin with carboplatin in standard regimens is being tested in large studies. At present, the routine use of Amifostine to protect renal integrity and function is not indicated [25, 26]; however, its routine use as a renal-protector is being investigated in clinical trials.

The acute effects of ifosfamide, seen most commonly in young (<3 year old) children with prior renal dysfunction or nephrectomy, include renal tubular damage with hyperphosphaturia, glycosuria and aminoaciduria, followed by the inability to acidify the urine – the so-called Fanconi syndrome [27, 28]. Hypophosphatemia and acidosis can lead to inhibition of statural growth, as well as to bone deformity (renal rickets) in prepubertal and pubertal children. Glomerular damage may accompany the tubular damage, leading to diminished GFR, with increased serum creatinine and azotemia. Median doses of 54 g/m^2 have been reported to cause progressive glomerular toxicity [29], and chronic glomerular and tubular toxicity has been reported [29, 30]. Risk factors include total ifosfamide dose [30], prior cisplatin administration [27, 28] and age. Recovery of renal function is possible over time [31].

Methotrexate toxicity is usually acute and reversible. The drug and its metabolites precipitate in the renal tubules. Adequate hydration and leucovorin administration will prevent most renal damage. (Doses of 1-12g/m2 can be given safely if the appropriate precautions are taken [32].)

15.2.5.2 Bladder

Bladder damage, including hemorrhagic cystitis, fibrosis and occasional bladder shrinkage, can occur following chronic administration of alkylating agents such as cyclophosphamide [33] and ifosfamide [34]. The metabolic byproducts of these drugs include acrolein (of the same chemical class as the aniline dyes), which is excreted in the urine and irritates the bladder mucosa. This leads to exposure of submucosal blood vessels and subsequent bleeding [35]. Fortunately, drug-induced hemorrhagic cystitis and related fibrosis can nearly always be prevented by increased hydration during drug administration and the concomitant administration of intravenous or oral mercaptoethane sulfonate (MESNA). MESNA serves as a chemical sponge that binds the metabolites, thereby inactivating them and preventing their toxic action on the urothelium. Cyclophosphamide has also been associated with the induction of bladder tumors [36]. The interaction between RT and chemotherapy and their effects on hemorrhagic cystitis are discussed in section 15.3.

Radiation may interact with a number of chemotherapeutic agents in an additive or synergistic fash-

ion. The most notable example for the organs of the GU tract, particularly the kidneys, is the interaction between radiation and the antibiotics, actinomycin-D and doxorubicin [37]. There is a significant enhancement of the radiation effects when the agents are given concurrently, but this may also occur when the modalities are used sequentially. Radiation may also interact with cyclophosphamide, increasing the severity and chronicity of hemorrhagic cystitis. Therefore, great care is necessary when evaluating patients who have received or will receive RT to fields that include the kidney or bladder, if those patients also have received or will receive chemotherapy. This is of particular importance in patients who have nephrectomy or a fused or ectopic kidney, where the functional renal tissue may have been purposefully or inadvertently irradiated. It is critical in these cases to have precise information on the definition of the radiation portals.

Conditioning regimens for bone marrow transplantation often include chemotherapy and total body irradiation. Data is emerging on late renal toxicity, such as hematuria and renal insufficiency [38]. Renal biopsy reveals both parenchymal and vascular glomerular changes [39]. This data is from two published sources of the effects on ALL (n=44) and neuroblastoma (n=15) patients. Most patients received twice daily radiation (interfraction time of 4–6 h) to total doses equaling 12–14 Gy. Hemorrhagic cystitis after bone marrow transplantation may also be associated with BK polyomavirus [40].

15.3 Clinical Manifestations

Table 15.2 summarizes the available data for the late genitourinary effects in childhood survivors of cancer. Each organ system is discussed below.

15.3.1 Kidney

15.3.1.1 Surgery

Unilateral nephrectomy in childhood results in contralateral hyperplasia [41–43]. Normal kidney function is usually seen following resection of one of the two kidneys [42, 44]. Normal function can continue with as little as one-third of one kidney remaining. Radiation in moderate doses (14–15 Gy) to the remaining kidney may decrease the amount of hyperplasia that otherwise would have taken place [45, 46].

15.3.1.2 Radiation

Acute radiation nephropathy is an extremely uncommon occurrence, requiring greater than 30–40 Gy to the kidney. Subacute radiation nephropathy, characterized by hypertension and a decreased GFR, may occur 6–8 weeks to several months after doses equal to or greater than 15 Gy of radiation to both kidneys.

Significant late renal dysfunction occurs following radiation doses >20 Gy [45]. In children, even lower doses (5–20 Gy) can cause renal dysfunction. If a significant volume of the renal tissue is left unirradiated, the damage may not be clinically significant, although regional dysfunction within the irradiated portions of the kidney can be demonstrated. However, if all or the majority of the patient's renal tissue is irradiated, clinical renal dysfunction will result.

15.3.1.3 Chemotherapy

A variety of metabolic effects of chemotherapy on renal function have been noted. Long-term glomerular injury secondary to cisplatin may improve slowly over time [23]. However, tubular injury manifested by hypomagnesemia appears to persist. Chronic glomerular and tubular toxicity from ifosfamide has been observed [27].

Table 15.2. Incidence of Late Genitourinary effects following treatment for childhood cancer

Author	Tumor	Therapy	N	Follow up (yrs)	End point studied	Result
Barrera	Wilms'	Nephrectomy	16	>13	Mild proteinuria Tubular function DBP > 90	12% Normal 25%
Ritchey	Wilms': unilateral	Nephrectomy	5368	>10	Renal failure	0.28%
Makipernaa	Wilms'	Nephrecotomy + ipsilateral RT (20–40Gy)	30	19	HTN BUN/Creatinine	17% Normal
Paulino	Wilms'	Nephrectomy + RT (12–40 Gy) + CT	42	15	Serum BUN and Creatinine HTN	Elevated in 1 patient 7%
Thomas	Wilms'	Nephrectomy + RT (15–44 Gy)	24	13	Low grade renal failure and UTIs	4%
Wikstad	Wilms'	Nephrectomy + ipsilateral RT+ contralateral kidney RT (5–15 Gy)	22	13	GFR BP	82% compared to normal controls; stable over time Normal
Raney	Bladder or prostate sarcoma	Surgery +CT+/– RT(25–55 Gy)	109	8	Bladder dysfunction Urinary diversion HTN Elevated BUN/Cr Hematuria (intact bladder vs. diversion) Bacteriuria (intact bladder vs. diversion) Abnormal renal imaging (intact bladder vs. diversion)	25% 50% 1% 6% 20% vs. 39% 8% vs. 35% 20% vs. 37%
Heyn	Paratesticular rhabdomyo-sarcoma	Surgery + RT (16–58 Gy) + CT	86	>4	Ejaculatory dysfunction Normal blood pressure Normal BUN and creatinine Ureteral obstruction Hemorrhagic cystitis Normal bladder function	7% 96% 100% 3% 34% 100%
Hale	Germ cell tumors	Surgery +/– RT (20–40 Gy) +/– CT	73	11	Neurogenic bladder Hemorrhagic cystitis Recurrent UTI Ureteral/urethral stenosis Bladder atrophy Hydronephrosis	15% 13% 9% 3% 75% 100%
Ritchey	Retroperi-toneal tumors	Surgery +EBRT (18–50 Gy) + IORT (10–25 Gy)	4	2	Bilateral hydronephrosis Renal artery stenosis Renal atrophy	50% 4% 25%
Stea	Pelvic sarcomas	CT + RT (55–60 Gy) +/– IORT +/– BMT (with TBI)	23	2	Vaginal stenosis Cystitis Fistulas (IORT)	4% 4% 100%
Tarbell; Guinan	ALL neuroblastoma	BMT (with TBI)	28 11	2	Renal dysfunction	32% 64%

15.3.1.4 Aging Effects

The influence of aging on the expression of damage is primarily related to growth of the patient. Renal functional impairment may not become prominent until the growing child reaches a size that exceeds the ability of the remaining renal tissue to accommodate the need for metabolic adjustments and excretion. The child may therefore outgrow the kidney and require management of renal failure.

15.3.2 Bladder

15.3.2.1 Surgery

Bacteruria is more prevalent in patients with urinary diversion than those with an intact bladder [2]. However, the clinical significance of this is unclear. Neurogenic bladder has been reported in 14% of patients undergoing surgery and RT for pelvic germ cell tumors [47].

15.3.2.2 Radiation

Bladder dysfunction after irradiation for bladder and prostate sarcomas (median dose of 40 Gy) is reported to be 27% [2]. This includes incontinence, urinary frequency and nocturia. It should be noted that most of these patients also received cyclophosphamide.

15.3.2.3 Chemotherapy

The onset and timing of hemorrhagic cystitis secondary to the administration of chemotherapeutic agents varies, with some patients experiencing this complication during therapy, and others developing it several months following cessation of therapy [2]. The hematuria may be microscopic or macroscopic, including clot passage, and can even result in significant anemia. Urgency, increased frequency of urination and difficulty voiding can also occur. Cyclophosphamide appears to be associated with the development of transitional cell carcinoma of the bladder [36].

The impact of aging on the bladder is similar to the effects of aging on the kidney.

15.3.3 Prostate

The effects of surgical and radiation injury are not seen until puberty, because the gland is nonfunctional during the prepubescent years. Atrophy of the normal glandular tissue in the prostate can be seen following moderate or high doses of radiation [48]. Impaired growth of the seminal vesicles, with consequent decreased production of and storage capacity for seminal fluid, may result in a diminished ejaculum volume. Since the normal ejaculate is a combination of fluids derived from the gonads, seminal vesicles and prostate, dysfunction of any of these structures theoretically can lead to abnormalities in ejaculation or the ejaculate volume.

15.3.4 Vagina

Fibrosis and diminished growth secondary to surgical procedures or RT have been described [49–51]. Vaginal mucositis can occur acutely during RT or following chemotherapy, notably with methotrexate, actinomycin-D and doxorubicin. In patients who have received prior RT, the administration of actinomycin-D or doxorubicin can result in a "radiation recall" reaction with vaginal mucositis. Significant fibrosis of the vagina can occur after high-dose RT, or after more modest doses of radiation, when combined with chemotherapy. These therapies interfere with normal development of the vagina and therefore have a negative impact on sexual function. Both the size and flexibility of the vagina may be adversely affected. At extremely high doses of RT, soft tissue necrosis of the vaginal wall can occur. In adults, this appears to be more common in the posterior and inferior portions of the vagina [52]. Fistula formation (rectovaginal, vesicovaginal and urethrovaginal) is the end stage of this event [53].

15.3.5 Uterus

Decreased uterine growth can be seen following exposure to 20 Gy of radiation [51, 54, 55]. Scarring may be produced at higher doses. The resultant decreased uterine size may prevent the successful completion of pregnancy or result in low-birth

weight babies [54]. Decreased uterine blood flow has been seen in women who received pelvic irradiation as children. This may be related to smooth muscle proliferation surrounding small and medium sized arterioles [53].

15.3.6 Ureter

Limited data exist for ureteral damage in children [47, 56]. The data in adults suggest that the ureter is fairly resistant to irradiation [9, 18]. Injury appears to be related to the dose and length of the ureter in the radiation field. A higher incidence of ureteral injury is seen when the ureter is included in the field during intraoperative RT [56].

15.3.7 Urethra

There is no good data related to urethral injury and long-term sequelae of cancer therapy in children. The limited information in adults suggests that ureteral stricture occurs very infrequently (0–4%) following RT alone. However, stricture is more commonly seen (5–16%) in patients who undergo surgical manipulation of the urethra in addition to RT [9].

15.4 Detection and Screening

15.4.1 Evaluation of Overt Sequelae

The structure and function of the GU tract can be assessed by a variety of techniques. Simple screening methodologies include the history, with particular attention to urinary incontinence, urine volumes and urine character (bloody or foamy), as well as, the urinalysis. Creatinine clearance is a simple, cost-effective screen of kidney function. Structural abnormalities can be investigated by several tests, including ultrasound, IVP, CT scan and MRI. Retrograde studies may be useful for structural and functional evaluation of the bladder and ureters. Cystoscopy may be necessary to evaluate hematuria in the long-term survivor. In patients with late-onset hemorrhagic cystitis, cystoscopy may be useful to assess the degree of mucosal damage and to evaluate the etiology of the hematuria. Patients with late-onset hemorrhagic cystitis are at risk for transitional cell carcinomas of the bladder that may be accompanied by hematuria. An IVP or retrograde study of the upper tracts may be necessary to identify other abnormalities that can cause bleeding.

For young girls who have had pelvic tumors, gynecologic examinations may be necessary at a young age. The vagina, cervix and uterus are best examined under direct visualization using a speculum. General anesthesia may be required to produce adequate relaxation and to decrease motion. The uterus may be examined by ultrasound, CT and MRI; injection of contrast-enhancing dye is not generally necessary. Young women who have difficulty becoming pregnant need to be evaluated for hormonal dysregulation versus late structural (uterine) injury.

Young boys with pelvic tumors may also need imaging studies to evaluate the growth of their pelvic organs. The bladder and prostate are readily visualized with ultrasound.

Consultation with an experienced radiologist, nephrologist, urologist and gynecologist may assist in planning individualized investigations.

15.4.2 Screening for Preclinical Injury

Because the kidneys have a large functional reserve, clinical renal function usually remains normal until there is serious derangement of glomerular or tubular function. Urinalysis is not very quantitative, but it is the cheapest, simplest and most useful test – along with the assessment of blood pressure – for periodically re-evaluating patients for the development of nephropathy. Elevated serum concentrations of blood urea nitrogen (BUN) and creatinine suggest a need for a more accurate assessment of glomerular function. Creatinine clearance and radionuclide scanning both provide quantitative measures of glomerular function. Tubular dysfunction may be identified by quantitative tests of phosphate, bicarbonate, magnesium, potassium, glucose, amino acids and beta-2 microglobulin. Injury to the bladder wall may be screened by urinalysis, looking for microscopic hematuria.

Table 15.3. Methods of evaluating organ function

Organ	History	Physical	Laboratory	Radiologic	Surgical
Kidney	Hematuria Fatigue	Blood pressure Growth parameters	BUN, creatinine, Creatinine clearance, urinalysis, serum and urine electrolytes, beta-2 miroglobin, Hemaglobin/hematocrit	Ultrasound, intravenous pyelogram, CT, MRI, nuclear medicine scans	
Ureter				IVP, retrograde ureterograms	
Bladder	Urinary frequency Hematuria		Urinalysis	IVP, retrograde studies, ultrasound	Cystoscopy volumetrics
Urethra	Urinary stream Urinary frequency Hematuria			Voiding cystogram	
Prostate	Ejaculatory function			Ultrasound	
Vagina	Painful intercourse Dryness	Pelvic examination			
Uterus	Abnormal menses Difficult pregnancies	Pelvic examination			

15.4.3 Guidelines for Follow-up of Asymptomatic Patients

A detailed annual history and physical examination are recommended (Table 15.3) for all patients. Patients who have received therapies with known renal toxicities may benefit from simple screening tests (including hemoglobin or hematocrit, urinalysis, BUN and creatinine), as well as from blood pressure-monitoring [57–59]. A determination of the serum electrolyte concentrations and more definitive tests, such as creatinine clearance, may be indicated in selected cases.

After nephrectomy, preservation of the residual kidney function is essential. Participation in contact sports, especially football, is not advised. Kidney guards are often recommended, although there is no data regarding their efficacy in injury prevention. More likely, the appliance serves to remind the individual of vulnerability. Although urinary tract infection should be treated aggressively in all patients, this is especially important in those with a single kidney or with renal dysfunction. To rule out obstruction, patients with anatomic alteration of the GU tract may need periodic imaging studies; they may also need periodic urine cultures to assess urine sterility. The role of chronic antimicrobial prophylaxis in patients with urinary diversion is controversial [60, 61]. Urinalysis is a good screening tool following therapy for assessing possible damage to the bladder wall.

15.4.4 Management of Established Problems

15.4.4.1 Therapy

Kidney

If preclinical abnormalities are found, serial follow-ups at 3–6 month intervals are recommended. A pediatric nephrologist may need to follow such patients. Although little evidence is available that improvement in renal plasma flow or GFR occur with time, tubular function does appear to undergo some recovery; therefore, efforts to support and treat the patient until such recovery occurs is appropriate. In the event of severe renal failure, the choice between dialysis and renal transplantation should rest with

the patient, the family, the oncologist and the nephrologist. Due to improved renal graft survival, using organs from living donors should be considered in the decision-making process. For children who have undergone irradiation to one kidney and who develop renal-vascular hypertension, unilateral nephrectomy is potentially curative if no contralateral renal changes have occurred. The medications for controlling hypertension and electrolyte imbalances should also be prescribed.

Bladder

Hemorrhagic cystitis may require cystoscopy and cauterization of bleeding sites. Persistent or refractory late-onset hemorrhagic cystitis may be treated with formalin instillation into the bladder. However, this procedure is not without risk. A complication rate as high as 14% has been reported using higher concentrations of formalin [62]. Hyperbaric oxygen has become widely used in the adult population and may be considered [63]. Severe bleeding may necessitate partial or total cystectomy, with reconstruction.

Ureter and Urethra

Stricture of the urethra is usually relieved by dilatation. Obstruction of the ureter can usually be treated with a stent. Urinary diversion is, at times, necessary [3].

Prostate, Vagina and Uterus

Late structural defects may be treated using reconstruction with plastic srugery. Topical estrogen and vaginal dilators are described in the adult population, but their role has not been established in the pediatric group.

Rehabilitation

As the patient matures, rehabilitation efforts may well be needed both for physical and psychological problems. For example, children undergoing urinary diversion will need education and psychosocial support in dealing with their stoma and its proper hygiene. As the child grows older and learns that he or she is physically different from other children, careful discussion of this problem with the pediatric oncologist, the surgeon and a psychologist is of paramount importance in defining the rehabilitative treatments and allaying the patient's anxiety about the future. Adult cancer survivors report significant sexual dysfunction and decreased sexual activity [53]. Adult survivors of childhood cancer will likely experience similar problems. This information may not be volunteered, and careful questioning at follow-up is needed to ensure appropriate referral for psychological counseling. In addition, some survivors are not knowledgeable about the treatment that they received as a child [64]. Therefore, they may not recognize certain symptoms as a late effects of cancer therapy.

15.5 Conclusion

This chapter described the risk, evaluation and treatment of the late genitourinary effects of cancer therapy in children. Unfortunately, some studies do not provide systematic reporting of such effects. Effects on the kidney and bladder have been described the most. The effects on the ureters, urethra, prostate, vagina and uterus are less well documented. Additionally, the data on psychological effects, especially related to sexual matters, in the pediatric population are difficult to find. Newer reporting systems will hopefully provide a clearer sense of the problem.

We have learned through following childhood cancer survivors over several decades that there is no substitute for a caring, knowledgeable primary physician as captain of the team. Internists should also be involved in the care of patients who reach adulthood. Ideally, these physicians should be knowledgeable about pediatric cancer patients; however, if this is not the case, the pediatric oncologist will need to provide information about the late effects of treatment to the patient's other physicians. Good communication between the initial treatment team and follow-up clinic and consultants should lead to optimum care of the long-term survivor of childhood cancer.

Acknowledgements. The authors wish to acknowledge B. Raney, R. Heyn and R. Cassaday.

References

1. Schmidt A (1992) Long term results after partial and unilateral nephrectomy in childhood. Eur J Pediatr Surg 2:269–273
2. Raney B et al. (1993) Sequelae of treatment of 109 patients followed for five to fifteen years after diagnosis of sarcoma of the bladder and prostate: a report from the Intergroup Rhabdomyosarcoma Study (IRS Committee). Cancer 71: 2387–2394
3. Wespes E, Stone AF, King LR (1986) Ileocaecocystoplasty in urinary tract reconstruction in children. Br J Urol 58: 266–272
4. Filmer RB, Spencer JR (1990) Malignancies in bladder augmentations and intestinal conduits. J Urol 122:163–164
5. Gitlin J et al. (1999) New concepts of histological changes in experimental augmentation cystoplasty. Urol 162:1096–1100
6. Golomb J, Klutke CG, Raz S (1989) Complications of bladder substitution and continent urinary diversion. Urology 34:329–338
7. Meadows AT et al. (1985) Second malignant neoplasms in children: an update from the late effects study group. J Clin Oncol 3:532–538
8. Cassady JR (1995) Clinical radiation nephropathy. Int J Radiat Oncol Biol Phys 31:1249–1256
9. Marks LB et al. (1995) The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 31:1257–1280
10. Stewart FA (1986) Mechanism of bladder damage and repair after treatment with radiation and cytostatic drugs. Br J Cancer 53:280–291
11. Suresh UR et al. (1993) Radiation disease of the urinary tract: histological features of 18 cases. J Clin Pathol 46: 228–231
12. Dewit L, Ang KK, Vanderschueren E (1983) Acute side effects and late complications after radiotherapy of localized carcinoma of the prostate. Cancer Treat Rep 10:79–89
13. Montana GS, Fowler WC (1989) Carcinoma of the cervix: analysis of bladder and rectal radiation dose and complications. Int J Radiat Oncol Biol Phys 16:95–100
14. Perez CA et al. (1984) Radiation therapy alone in the treatment in the treatment of carcinoma of the uterine cervix II. Analysis of complications. Cancer 54:235–246
15. Perez CA et al. (1986) Radiation therapy alone in the treatment of carcinoma of the uterine cervix: a 20-year experience. Gynecol Onocol 23:127–140
16. Pourquier H et al. (1987) A quantified approach to the analysis and prevention of urinary complications in radiotherapeutic treatment of cancer of the cervix. Int J Radiat Oncol Biol Phys 12:1025–1033
17. Ryu JK et al. (2002) Interim report of toxicity from 3D conformal radiation therapy (3D-CRT) for prostate cancer 3dOG/RTOG 9406, level III (79.2 Gy). Int J Radiat Oncol Biol Phys 54:1036–1046
18. Buglione M et al. (2002) Post-radiation pelvic disease and ureteral stenosis : pathophysiology and evolution in the patient treated for cervical carcinoma. Review of the literature and experience of the Radium Institute. Arch Ital Urol Androl 71:6–11
19. Kontturi M, Kauppila A (1982) Ureteric complications following treatment of gynaecological cancer. Ann Chir Gynaecol 71:232–238
20. Abitol MM, Davenport JH (1974) The irradiated vagina. Obstetr Gynecol 44:249–256
21. Kapoor M, Chan G (2001) Malignancy and renal disease. Crit Care Chirurgy 17(3):571–598
22. Stewart DJ et al. (1985) Renal and hepatic concentrations of platinum: relationship to cisplatin time, dose and nephrotoxicity. J Clin Oncol 3:1251–1256
23. Brock PR et al. (1991) Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr 118:531
24. Crom WR et al. (1984) The effect of prior cisplatin therapy on the pharmacokinetics of high-dose methotrexate. J Clin Oncol 2:655–661
25. Petrilli AS et al. (2002) Use of amifostine in the therapy of osteosarcoma in children and adolescents. J Pediatr Hematol Oncol 24:188–191
26. Renner S et al. (2000) Effect of amifostine on neuroblastoma during high dose chemotherapy: in vivo and in vitro investigations. Anticancer Res 20:4531–4538
27. Skinner R et al. (1990) Nephrotoxicity after ifosfamide. Arch Dis Child 65:732–738
28. Vogelzang NJ (1991) Nephrotoxicity from chemotherapy: prevention and management. Oncology 5:97–112
29. Prasad et al. (1996) Progressive glomerular toxicity of ifosfamide in children. Med Pediatr Oncol 27:149
30. Skinner R, Cotterill SK, Stevens MC (2000) Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG late effects group study. Br J Cancer 82:1636–1645
31. Raney B et al. (1992) Renal toxicity in patients treated with ifosfamide in Intergroup rhabdomyosarcoma study (IRS)-IV pilot regimens. Med Pediatr Oncol 20:429
32. Hempel L (2003) Influence of high-dose methotrexate therapy (HD-MTX) on glomerular and tubular kidney function. Med Peditatr Oncol 40:348–354
33. Levine LA, Richie JP (1989) Urological complications of cyclophosphamide. J Urol 141:1063–1069
34. Sarosy G (1989) Ifosfamide – pharmacologic overview. Semin Onocl 16:2–8
35. Sklar CA, LaQuaglia MP (2000) The long term complications of chemotherapy in childhood genitourinary tumors. Urol Clin North Am 27:563–568
36. Samra Y, Hertz M, Lindner A (1985) Urinary bladder tumors following cyclophosphamide therapy: a report of two cases with a review of the literature. Med Pediatr Onocl 12:86–91
37. Tefft M et al. (1976) Acute and later effects on normal tissues following combined chemo-and radiotherapy for childhood rhabdomyosarcoma and Ewing's sarcoma. Cancer 37:1201–1213

38. Tarbell NJ et al. (1990) Renal insufficiency after total body irradiation for pediatric bone marrow transplantation. Radiother Oncol 18 [Supp 1]:139–142
39. Guinan EC et al. (1988) Intravascular hemolysis and renal insufficiency after bone marrow transplantation. J Clin Oncol 72:451–455
40. Vogeli TA (1999) Urological treatment and clinical course of BK polyomavirus-associated hemorrhagic cystitis in children after bone marrow transplantation. Eur Urol 36:252–257
41. Walker RD et al. (1982) Compensatory renal growth and function in post-nephrectomized patients with Wilms' tumor. Urology 19:127
42. Wikstad I et al. (1986) A comparative study of size and function of the remnant kidney in patients nephrectomized in childhood for Wilms' tumor and hydronephrosis. Acta Paediatr Scand 5:408
43. Luttenegger TJ et al. (1975) Compensatory renal hypertrophy after treatment for Wilms' tumor. Am J Roentgenol 125:348
44. Cassidy MJD, Beck RM (1988) Renal functional reserve in live related kidney donors. Am J Kidney Dis 11:468–472
45. Cassidy JR et al. (1981) Effect of low dose irradiation on renal enlargement in children following nephrectomy for Wilms' tumor. Acta Radiol Oncol 20:5–8
46. Vaeth JM (1964) The remaining kidney in irradiated survivors of Wilms' tumor. Am J Roentgenol 92:148
47. Hale GA et al. (1999) Late effects of treatment for germ cell tumors during childhood and adolescence. J Ped Hem Onc 21:115–122
48. Gill WB et al. (1980) Sandwich radiotherapy (3000 and 4500 rads) around radical retropubic prostatectomy for stage C prostatic carcinoma. Urology 16:470–475
49. El-Mahdi AM et al. (1974) Sequelae of pelvic irradiation in infancy. Radiology 110:665–666
50. Flamant F et al. (1979) Embryonal rhabdomyosarcoma of the vagina in children. Conservative treatment with curietherapy and chemotherapy. Eur J Cancer 15:527–532
51. Flamant F et al. (1990) Long-term sequelae of conservative treatment for vulvar and vaginal rhabdomyosarcoma in children. J Clin 8:1847–1853
52. Rotman M, Aziz H, Choi KN (1989) Radiation damage of normal tissues in the treatment of gynecologic cancers. In: Vaeth JM, Meyer JL (eds) Frontiers of radiation therapy and oncology. Basel, Karger (Radiation tolerance of normal tissues, vol 23)
53. Grigsby PW et al. (1995) Late injury of cancer therapy on the female reproductive tract. Int J Radiat Oncol Biol Phys 31:1281–1299
54. Li FP et al. (1987) Outcome of pregnancies in survivors of Wilms' tumor. JAMA 257:216–219
55. Piver MS, Rose PG (1988) Long-term follow-up and complications of infants with vulvovaginal embryonal rhabdomyosarcoma treated with surgery, radiation therapy and chemotherapy. Obstet Gynecol 71:435–437
56. Ritchey ML et al. (1996) Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. Med Ped Oncol 26:75–80
57. Langer T et al. (2000) Basic method and the developing structure of a late effects surveillance system (LESS) in the long-term follow up of pediatric cancer patients in Germany. Med Pediatr Oncol 34:348–351
58. Oeffinger KC et al. (2000) Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. Cancer 88:1687–1695
59. Schwartz CL (1999) Long-term survivors of childhood cancer: the late effects of therapy. Oncologist 4:45–54
60. Cronan JJ et al. (1989) Antibiotics and nephrostomy tube care: preliminary observations, part II. Bacteremia. Radiology 172:1043–1045
61. Wood DP et al. (2003) Incidence and significance of positive urine culture in patients with an orthotopic neobladder. J Urol 169:2196–2199
62. Dewan AK, Mohan GM, Ravi R (1996) Intravesical formalin for hemorrhagic cystitis following irradiation of cancer of the cervix. Int J Gynaecol Obstet 42:131
63. Corman JM et al. (2003) Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. J Urol 169: 2200–2202
64. Kadan-Lottick NS et al. (2002) Childhood survivors' knowledge about their past diagnosis and treatment: childhood cancer survivor study. JAMA 287:1832–1839
65. Barrera, Roy LP, Stevens M (1989) Long-term follow-up after unilateral nephrectomy and radiotherapy for Wilms' tumor. Pediatr Nephrol 3:430–432
66. Heyn R et al. (1992) Late effects of therapy in patients with paratesticular rhabdomyosarcoma. J Clin Oncol 10:614–623
67. Jaffe N (1987) Renal toxicity with cumulative doses of cis-diamminedichloroplatinum-II in pediatric patients with osteosarcoma. Effect on creatinine clearance and methotrexate excretion. Cancer 59:1577–1581
68. Makipernaa A et al. (1991) Renal growth and function 11–28 years after treatment for Wilms' tumors. Eur J Pediatr 150: 444–447
69. Michalski JM et al. (2003) Preliminary evaluation of low-grade toxicity with conformal radiation therapy for prostate cancer on RTOG 9406 dose levels I and II. Int J Radiat Oncol Biol Phys 56:192–198
70. Paulino AC et al. (2000) Late effects in children treated with radiation therapy for Wilms' tumor. Int J Radiat Oncol Biol Phys 46:1239–1246
71. Stea B et al. (1987) Treatment of pelvic sarcomas in adolescents and young adults with intensive combined modality therapy. Int J Radiat Oncol Biol Phys 13:1797–1805
72. Thomas PRM et al. (1983) Late effects of treatment for Wilms' tumor. Int J Radiat Oncol Biol Phys 9: 651–657

Musculoskeletal, Integument, Breast

Robert B. Marcus, Jr. · Matthew R. DiCaprio · Dieter M. Lindskog · Brian E. McGrath · Kathy Gamble · Mark Scarborough

Contents

16.1 Introduction

Some of the most common late effects of therapy involve the musculoskeletal skeletal system. While the growth deficits of radiation are well known, it is important to realize that surgery and sometimes chemotherapy affect the developing musculoskeletal system as well. In general, the treatment of sarcomas leads to the most severe late effects with all therapies because the underlying malignancy originates in a muscle or bone, and often an extremity. In spite of the advances in modern surgery, the removal of a muscle or bone has permanent consequences, that completely change a child's life. Likewise, irradiation of developing bone and muscle yields permanent effects. Usually, the younger the child, the more severe the late effects of therapy. It is important to understand the causes and the rehabilitation of limb length discrepancies, amputation, scoliosis, and other complications of therapy. Therapy is often more successful if the consequences are correctly anticipated and prevented, rather than waiting for deficits to develop.

Therapy can cause permanent deficits in the developing breast and skin. These may not appear at first to be as devastating as musculoskeletal late effects, but they may be much more severe than appreciated by the treating physicians and other members of the team.

In addition to the physical consequences, it is necessary to anticipate the psychological and social consequences, so that the child can understand the changes in his or her life. Treating the child and curing the cancer is not enough; understanding and dealing with the long-term consequences of treatment is critical as well.

16.2 Musculoskeletal

16.2.1 Pathophysiology

16.2.1.1 Normal Organ Development

The musculoskeletal system develops from the mesoderm and the neural crest. The mesoderm forms a series of tissue blocks on each side of the neural tube, which differentiate into the sclerotome (ventromedially) and the dermomyotome (dorsolateral). By the end of the fourth week of gestation, the sclerotome cells form a loose tissue called the mesenchyme, which then migrates and differentiates into fibroblasts, chondroblasts, and osteoblasts [63]. Cells from the myotome region of the dermomyotomes become elongated, spindle-shaped cells called myoblasts. These embryonic muscle cells fuse to form multinucleated muscle cells called muscle fibers. The dermatome regions of the dermomyotomes give rise to the dermis of the skin [38].

In the flat bones of the skull and face the mesenchyme develops directly into bone (membranous ossification); however, most of the remainder of the skeleton first forms hyaline cartilage, which in turn ossifies (endochondral ossification). Most of the ossification in the long bones occurs during fetal life.

The axial skeleton consists of the skull, the vertebrae, the sternum, and the ribs. The bones of the limbs make up the appendicular skeleton. The bones of the axial skeleton are flat or irregularly shaped. Most of the bones of the appendicular skeleton are long bones (see Fig. 16.1) [64] and have a shaft (diaphysis), a medullary cavity and two enlarged ends (epiphyses). The epiphysis at each end extends from articular cartilage to the epiphyseal growth plate. The metaphysis is the region between the epiphyseal plate and the diaphysis. After initial ossification in utero, longitudinal growth of the bone occurs only at the epiphyseal plate (physis). The mechanism of growth at the physis is the proliferation of a layer of chondroblasts, which in turn form a layer of cartilage (Fig. 16.2). Small blood vessels invade the cartilage, increasing oxygen tension and stimulating the formation of osteoblasts. The osteoblasts create osteoid that calcifies into bone [60, 61].

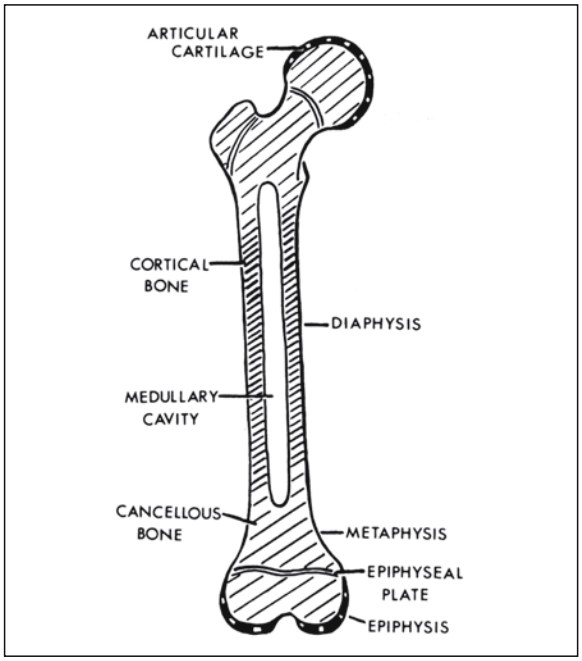


Figure 16.1

Schematic of a growing long bone. The shaft of the bone is called the diaphysis and contains the medullary cavity, which is 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. (From [64], Fig. 2.3, p. 8.)

Most skeletal muscle also develops before birth, although some muscle formation continues until the end of the first year of life. No new muscle cells are created after that time; muscle tissue enlarges due to increases in the number of myofilaments within each fiber, which result in an increase in the diameter of the individual muscle cells.

16.2.1.2 Organ Damage Induced by Cytotoxic Therapy

Direct damage to the developing musculoskeletal system from cytotoxic therapy is most often caused by irradiation. The cells most sensitive to irradiation

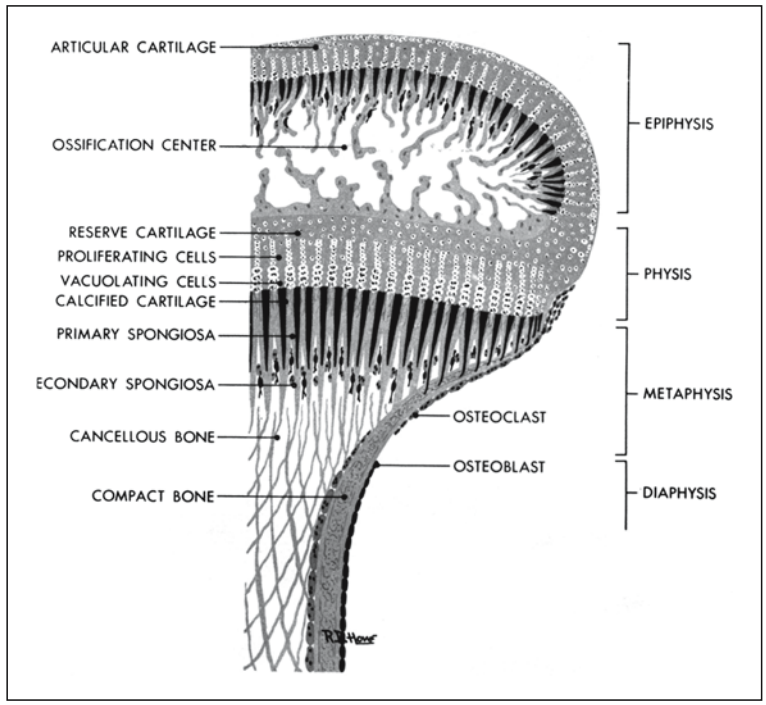


Figure 16.2

A close-up of the region of the metaphysis and epiphysis. The proliferating cells (chondroblasts) are shown in the region of the physis. (From [61].)

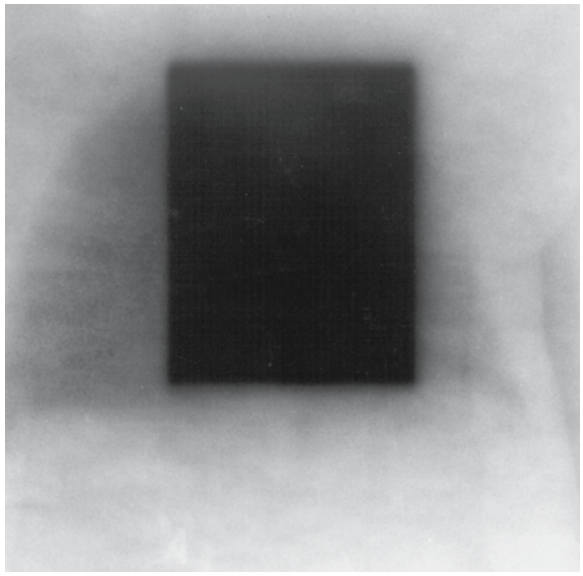
appear to be the growth plate chondrocytes [18, 60, 83]. Low total doses reduce cell mitosis, promote premature terminal differentiation and apoptosis, and completely disrupt cytoarchitecture. Surviving chondroblast clones repopulate the physis (although not always completely) if the total dose is below 20 Gy. Above this level, little repopulation occurs.

Recent evidence shows that the effect of radiation is very specific and leads to a decrease in the mRNA expression of PTHrP, which is an important stimulus for mitosis of chondrocytes [50]. The mechanism that triggers the decrease appears to be an increase in cytosolic calcium. The introduction of EGTA, a calcium chelator, inhibits the rise of cytosolic calcium and prevents most of the radiation damage [45]. In animal experiments, pentoxifylline can also decrease the effect of radiation on growth plate chondrocytes by mediating a decrease in cytosolic calcium [46].

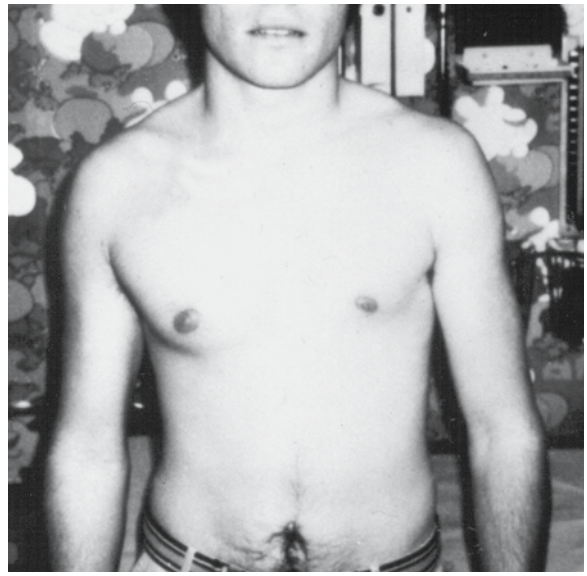
Although osteoblasts are damaged only by high doses of RT, radiation quickly increases vascularity of the bone, particularly in the metaphysis. This increases the resorption of bone, thereby increasing its porosity and the demineralization of the immature metaphysis [42].

The major risk factors for producing musculoskeletal late effects secondary to irradiation are: 1) age at the time of treatment; 2) quality of radiation (dose per fraction and total dose); 3) volume irradiated; 4) growth potential of the treated site; 5) individual genetic and familiar factors; and 6) coexisting therapy – surgery or chemotherapy [14].

There are too many variables to determine the effect of each individually. In general, though, if the radiation dose is fractionated normally (1–2 Gy per day), the total dose is one of the most important factors. The epiphyseal plate is the most sensitive structure, although for total doses of less than 10 Gy, there are few detectable long-term changes. Doses of 10–20 Gy will produce partial growth arrest of the epiphysis. Doses of greater than 20 Gy will usually result in complete arrest. However, the response to radiation is not an all-or-nothing phenomena; the higher the total dose and the younger the age at treatment, the greater the ultimate deficit [65]. This is



a



b

c

Figure 16.3 a–c

A 3-month-old boy who was treated in 1962 for a thoracic neuroblastoma using approximately 20 Gy in 10 fractions to the mediastinum and much of the left chest. **a** An AP-PA technique with 2mev photons was used. **b, c** The patient 20 years later. Mild hypoplasia of the left chest is present.

probably because the epiphyseal plate appears to close more quickly with increasing levels of dose (Fig. 16.3 a–c).

One of the goals of hyperfractionated irradiation (the use of small doses two or more times a day) is to decrease the extent of late effects. Studies are only now beginning to accumulate data, but data from Marcus and associates in the treatment of Ewing's sarcoma indicate that fractions of 1.2 Gy B.I.D. to 50.4–63.2 Gy produce fewer musculoskeletal late effects than would be expected from similar doses using fractions of 1.8–2.0 Gy once a day (Fig. 16.4) [7, 35].

Other factors influence late sequelae. Orthovoltage irradiation, dose-for-dose, causes more growth deficits in the bone than megavoltage irradiation because of the increased bone absorption. Field size is important: the larger the field of irradiation, the more significant the late effects [8].

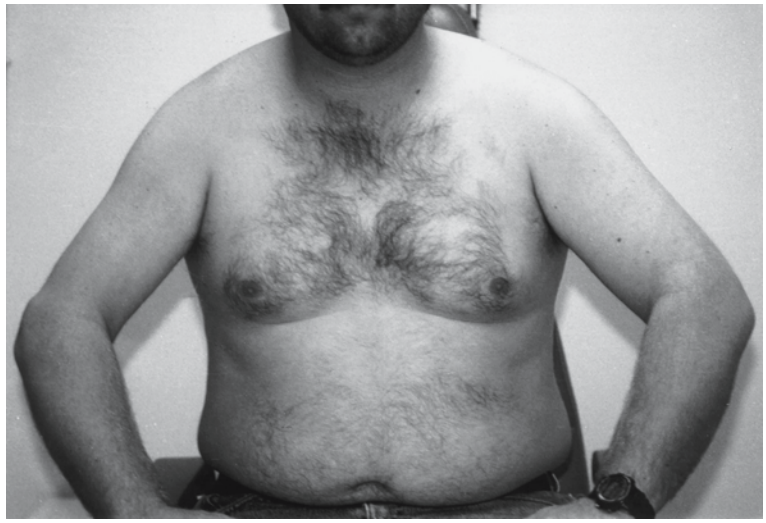


Figure 16.4

A 14-year-old boy, treated for an Ewing's sarcoma of the right humerus using 50.4 Gy in a fractionation scheme of 1.2 Gy B.I.D. There was little noticeable difference between the muscle development in his upper arms until he started weight-lifting. The left (untreated) arm responded, but the muscles in the radiation field did not increase as much in size or strength. In a picture taken 11 years after treatment, the area of hypoplasia from the field of irradiation can be clearly seen.

Similar dose levels apply to muscle development as well. Doses of <10 Gy cause virtually no detectable defect, and doses of 10–20 Gy produce some hypoplasia. Higher doses produce more significant problems.

Although high single-doses of radiation can cause necrosis of muscle cells, in clinical practice such an event is extremely rare [83]. More commonly, even with fractionated treatment, radiation damages the small vessels in muscles, preventing the full development of the muscle due to relative ischemia. Higher doses can give rise to atypical fibroblasts, which lay down excessive fibrin in the tissues, causing fibrosis [83].

There is sparse data on the pathophysiology of damage to growing muscle and bone by cytotoxic drugs. However, high or prolonged courses of steroids can cause the development of avascular necrosis of the femoral head. The exact mechanism is poorly understood, but there is evidence in animals to support a temporary decrease in blood flow through bones during treatment with steroids. Because the vasculature of the femoral and humeral heads is fragile, these structures are the most easily damaged by the decrease in blood flow, resulting in necrosis [15].

Chemotherapeutics have been shown to retard the proliferation of growth plate chondrocytes in both in-vitro and in-vivo experiments [55]. Chemotherapy retards growth during the course of treatment, but after the end of active therapy, most reports indicate that patients return to their normal growth rate or even exhibit catch-up growth [49]. Histologic examination of human growth plates after neoadjuvant chemotherapy and surgical excision has shown maintenance of the overall epiphyseal architecture, with growth arrest and then resumption of growth [6]. Most evidence would indicate that the deficit is temporary or primarily caused by endocrine dysfunction [4, 9].

A more serious complication is rhabdomyolysis, a rare complication of cytarabine and other drugs, including cyclophosphamide, 5-azacytidine, interferon-A, and interleukin-2 [73]. It is thought that the ability of cytarabine to trigger the release of cytochrome-c from the mitochondria could lead to uncoupling of the oxidative phosphorylation with subsequent depletion of ATP reserves at the skeletal muscle, resulting in rhabdomyolysis. Whatever the cause, the syndrome is complicated by acute renal failure often requiring hemodialysis [73].

16.2.2 Clinical Manifestations

Surgery, radiation therapy, and chemotherapy can all produce long-term sequelae in the developing musculoskeletal system; the effects of surgery and radia-

tion have been more thoroughly studied than those of chemotherapy.

Most of the following text will focus on the late effects of irradiation; however, it is important to remember that the surgical removal of a portion of the musculoskeletal system can result in the same physical and psychological late effects as damage to the same portion from radiation therapy or chemotherapy. The loss of a muscle group in the proximal lower extremity will cause weakness and gait disturbances; the amputation of an entire extremity will require the abrupt need for extensive rehabilitation. Limb-length discrepancies often result from the unilateral surgical removal of one or more growth plates. The fact that the deficit is planned does not imply that the late effects should be discounted.

16.2.2.1 Bone

The adverse effects of irradiation on growing bone are: 1) bone density changes; 2) physical injuries; 3) pathologic fractures; and 4) osteonecrosis, most commonly of the femoral head.

Bone Density Changes

Radiation therapy can produce osteopenia in children. More information is needed to elucidate all the parameters involved, but the risk is probably 8%–23% at doses above 20 Gy. Chemotherapy may influence this risk. It may not be detectable until after 30 weeks following treatment. The relationship between osteopenia and pathologic fracture remains unclear [25].

Physeal Injury

The physical effects are secondary to damage to the chondroblasts. This results in a slowing of, or arrested, physical growth, producing abnormal development of the involved bone. This can give rise to: 1) spinal abnormalities; 2) leg or arm-length discrepancies; 3) angular deformities at joints; 4) slipped capitofemoral epiphyses; and 5) osteocartilaginous exostoses.

Spinal Abnormalities. Spinal abnormalities most commonly consist of decreased stature or scoliosis, although lordosis or kyphosis can also occur [8, 42, 65]. Except for decreased growth, severe spinal complications are less common after megavoltage RT, compared with the orthovoltage era, if the entire vertebral body is within the treatment field [53]. Although curvature can occur, it is usually due to the tethering that occurs due to decreased muscle development as a result of irradiating just one side of the abdomen as is often done in Wilms' tumor.

On standard radiographs, vertebral bodies show subcortical lucent zones within 9–12 months after the end of RT. The subcortical lucent zones progress over the next 1–2 years to form growth arrest lines, which parallel the epiphysis of the vertebral body [62]. Following the development of these arrest lines, little or no further growth occurs. The higher the dose, the quicker growth arrest occurs. Other changes may also be seen on x-rays. During the first few months after irradiation, vertebral bodies may have a more bulbous contour [28]. Scalloping of the physical cartilage plates may also be observed, and not infrequently the final appearance is that of rounded vertebral bodies with central beaking [62].

Clinically, the deleterious effect of radiation on growing bone has been known for a long time. Neuhauser and associates [42] reported on 24 children who received orthovoltage irradiation to the spine during their treatment for Wilms' tumor or neuroblastoma. Doses below 10 Gy (using orthovoltage irradiation) caused no detectable vertebral abnormality regardless of the age at treatment. Higher doses caused severe late effects in the spine. Mayfield and coworkers [36] reported on 28 children with neuroblastoma who received irradiation to their spine. Scoliosis was the most common sequelae and occurred most severely at doses above 30 Gy with orthovoltage irradiation. Megavoltage irradiation appears to cause fewer severe orthopedic complications. Rate et al. reported on a series of 31 Wilms' tumor patients irradiated between 1970 and 1984. Three out of ten patients treated with orthovoltage irradiation developed late orthopedic abnormalities requiring intervention. None of the 21 patients receiving megavoltage treatment developed such com-

plications, even at doses of 4,000 cGy. Scoliosis was related to a higher median dose (2,890 cGy) and a larger field size (150cm^2); this sequela did not result for patients receiving smaller doses to a smaller field size (2,580 cGy to 120 cm^2) [52]. Paulino et al. report a lower incidence of scoliosis with a dose of <2,400 cGy than with higher doses [47]. Both orthovoltage and megavoltage irradiation was used. Probert and Parker were the first investigators to attempt to evaluate bone growth alterations secondary to megavoltage irradiation. They noted a deficit in sitting height for patients who received radiation to the spine for medulloblastoma, leukemia and Hodgkin's disease [50, 51]. Doses of greater than 35 Gy were found to produce a significantly greater deficit in sitting height, compared with doses of less than 25 Gy.

Silber and coworkers, using data from 36 children whose spine or pelvis was irradiated, have developed a mathematical model for predicting stature loss [69]. The model is based on the radiation dose in Gray, the location of the therapy (including whether or not the capitofemoral epiphysis was treated), gender, and the ideal adult height. Figure 16.5 shows an example of the model, based on four different irradiation doses. The model agrees closely with a report by Hogeboom et al., who calculated the height deficit after flank RT for Wilms' tumor patients at different ages and doses of radiation therapy [24]. In both reports, even a dose of 10 Gy at age 2 produced a height deficit of 2.3–2.4 cm by age 18 [24, 68]. For infants less than 12 months of age receiving 10 Gy or more, the height deficit was 7.0 cm more than their unirradiated counterparts [24]. Although chemotherapy did not appear to increase the effect of radiation therapy in Hogeboom's study, there was a deficit associated with doxorubicin that – although it could be explained, at least partially, by other factors – does not completely rule out a permanent doxorubicin effect on bone growth.

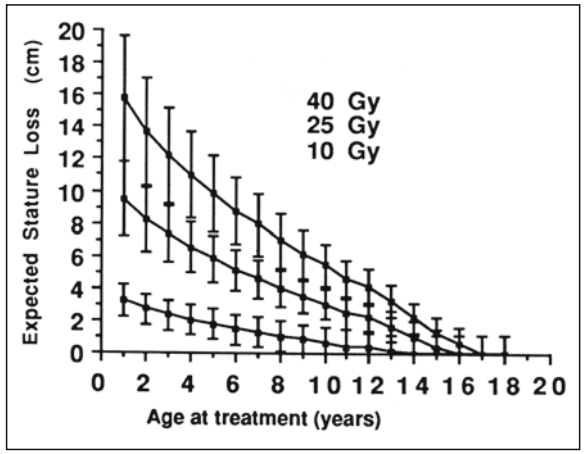


Figure 16.5

An example of the model for expected stature loss after radiation therapy to the spine during childhood, as proposed by Silber and coworkers. The hypothetical male patient was treated from T10–11 to L4–5 and his Ideal Adult Stature was 176.8 cm. Each point corresponds to the age when irradiated, the dose in Gray and stature loss, plus or minus one standard deviation. (From [69], p. 309.)

Limb Length Discrepancy/Angular Deformity. Irradiation of the extremities or hip usually produces more long-term symptomatic sequelae than irradiation of the spine, particularly when an epiphysis is treated. Radiographic changes first reveal metaphyseal irregularities and epiphyseal widening. Later changes include sclerosis around the physis and eventually sclerosis and closure of the epiphyseal plate. Such premature closure can cause a discrepancy in ultimate length between the irradiated and unirradiated extremity. In addition, if the entire physis is not included in the radiation port, then juxta-articular angular deformities can result [54].

Slipped Capitofemoral Epiphysis. Patients with slipped capitofemoral epiphyses present with pain in the hip or knee (referred from the hip). The pain can be either of acute onset or chronic in nature, since slippage of the capitofemoral epiphysis often proceeds slowly. There are a number of causes for this condition. Wolf and associates [81] first reported cases of slipped capitofemoral epiphysis as a result of childhood irradiation. These occurred 1–6 years post-therapy with doses of 28.5–54 Gy, usually after the onset of puberty, when there is a change in the angle of the femoral shaft in relation to the femoral neck

and head. This change increases the susceptibility to stress from excess weight and other factors. Children developing a slipped epiphysis after irradiation were generally 2–3 years younger than the average patient with idiopathic-slipped capitofemoral epiphysis, had two times the risk of bilateral involvement (20%–50%) if both proximal femurs were exposed to radiation and, furthermore, did not usually fit the generally obese body habitus of the average patient presenting with the idiopathic variety [5, 78, 82]. Paulino et al. reported on 4 infants (<6 months) irradiated to the hip to doses of 20 Gy or higher for neuroblastoma. Two developed slipped capitofemoral epiphysis, at 25.5 Gy and 36 Gy. The other two patients received doses of 20 Gy and did not develop the problem [48]. Slippage of the physis is thought to occur as a result of excess stress, either from obesity or from a weakening of the bone and physis secondary to radiation therapy. The threshold dose is thought to be about 25 Gy.

The use of chemotherapy has caused a reduction in the shear strength of the physis in an animal model [73]. Theoretically, chemotherapy would also appear to predispose patients to developing SCFE, but this has not been studied in humans.

Exostosis. Osteocartilaginous exostoses are benign outgrowths of the physis. They have been reported to occur in up to 18% of children treated with radiation therapy [1], although the incidence in the megavoltage era is much less. The etiology is unknown, but thought to be due to an injury to the periphery of the growth plate. The lesion is a combination of a radiolucent cartilaginous cap with areas of ossification and calcification. It has a typical cauliflower appearance and the base may be narrow or broad. On physical examination, a hard mass is palpable adjacent to a joint [65]. Lesions may continue to grow slowly throughout childhood, although by the third decade growth should cease.

There is a small incidence of malignant degeneration that presents with pain and occurs after skeletal maturation.

Pathologic Fractures

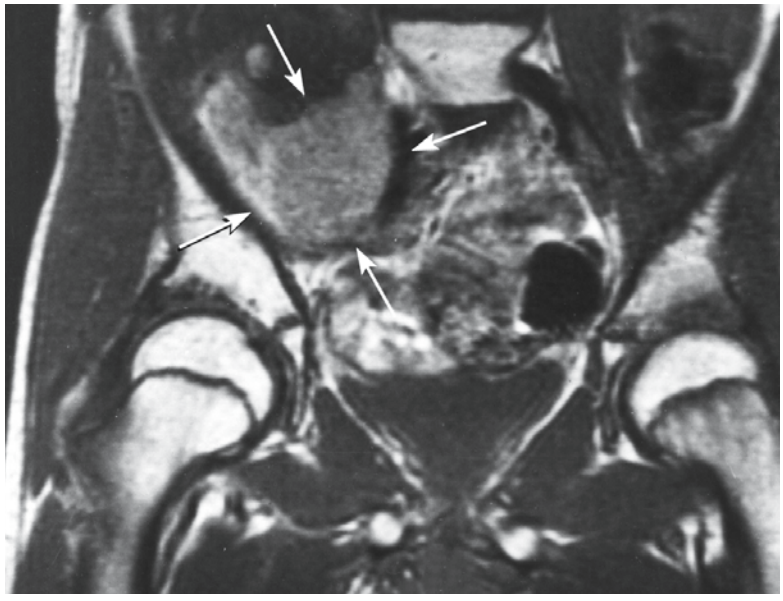
Irradiation of the metaphyseal portion of the bone may temporarily cause increased porosity and demineralization; x-rays will show cortical thinning and irregularities during this time. The irradiated segment of bone therefore acts as a stress concentrator and predisposes the bone to fracture [23]. This is particularly true in patients in whom the irradiated bone has been weakened by tumor involvement, such as in Ewing's sarcoma of the humerus and femur. It is also true if the cortex of the bone has been biopsied, particularly in the area of the femoral neck [77]. Pathologic fractures usually occur within three years after treatment [23]. The most common site is the upper third of the femur, and, since fractures can be caused by tumor recurrence, a full reevaluation of the patient should be performed to ensure that it is not related to relapse [77].

Osteonecrosis

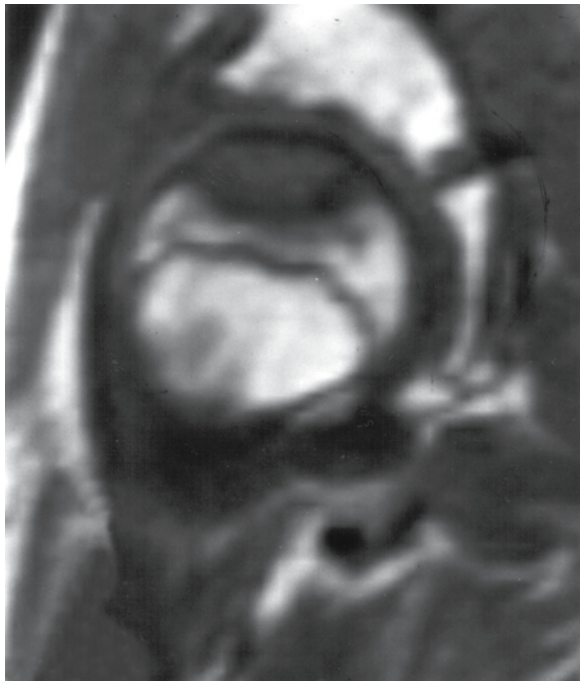
Osteonecrosis of the femoral head is an unusual late effect seen primarily in adults, but occasionally it also occurs in children. It seen primarily at doses above 60 Gy and is caused by radiation damage to the tenuous blood supply to the femoral head. It presents with pain, either acute in onset or more chronic. The typical radiographic picture is shown in Fig. 16.6 a–d.

16.2.2.2 Muscle

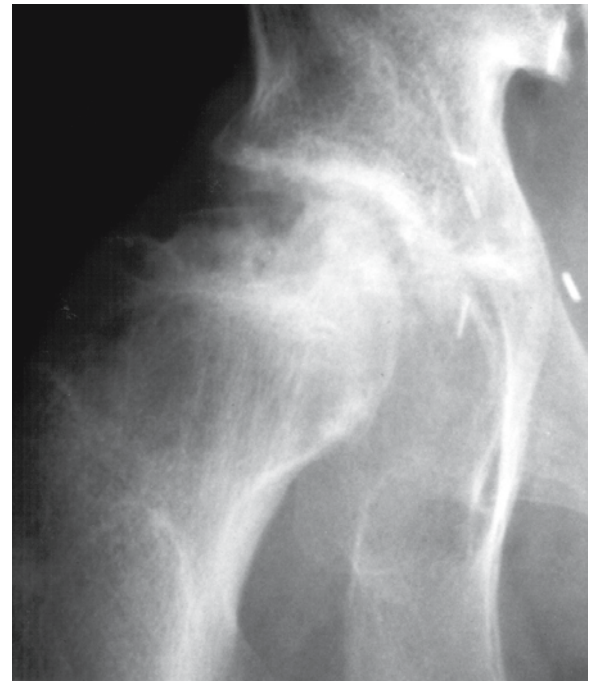
The most common late effect secondary to irradiation of developing muscle tissues is diminished development (hypoplasia). The muscles treated are smaller and functionally not as strong as the patient's unirradiated muscle tissues. Still, the differences in strength are not pronounced, and for the majority of patients, it is more of a cosmetic problem than a functional one. However, it is common; Macklis et al. reported that 13/14 long-term survivors of Wilms' tumor treated with low-dose pulmonary irradiation had musculoskeletal hypoplasia [32]. With higher doses, these tissues can develop marked fibrosis, which can produce stiffness, a decrease in range of motion of a joint and even pain. In mild cases, the stiffness or pain occurs primarily in the early morn-



a



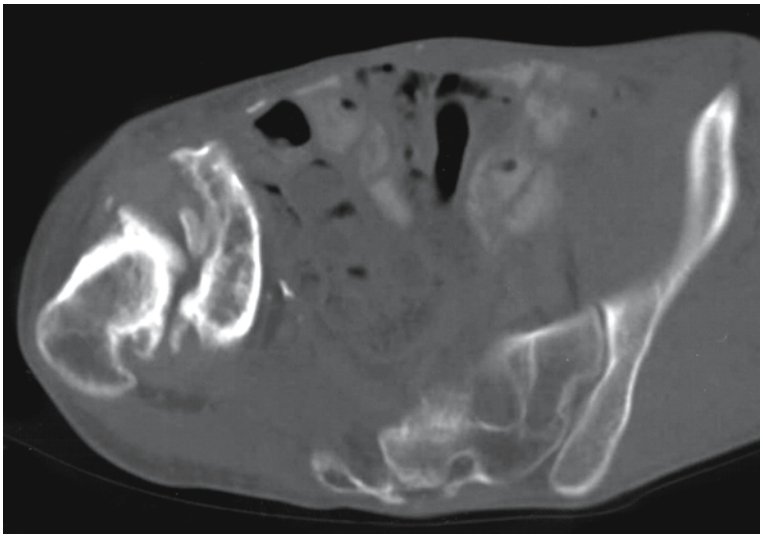
b



c

Figure 16.6 a–d

A 14 year-old boy treated with preoperative irradiation (61 Gy) and chemotherapy for a synovial cell sarcoma of the right iliopsoas muscle. **a** Tumor (arrows) and normal femoral heads. **b** An MR scan six months later showing a close-up of the right femoral head. The scalloped, non-enhancing lesion in the femoral head is typical for an osteonecrosis. **c** A plain radiograph one year later, showing healing of the femoral head.
(Fig. 16.6 d see next page)



d

Figure 16.6 d

d The early healing was not permanent, however, and CT 13 years after treatment demonstrates collapse of the femoral head, chronic dislocation of the femoral head and extensive degenerative changes. Severe scoliosis resulted as well.

ing and is improved by use of the involved muscles. Occasionally, the patient may have pain that is more persistent, lasts all day and, even with use, does not improve.

16.2.3 Impact of Aging

In general, growth deficits of the musculoskeletal system from irradiation are amplified with increasing years after treatment. Obviously, when all epiphyses are closed, further bone growth deficits do not occur. However, other late effects of bone will continue to occur, and muscular hypoplasia (and fibrosis) may become more significant.

16.2.4 Detection/Screening

A thorough history and physical is critical in the evaluation of musculoskeletal treatment sequelae. It is necessary to know exactly when a deformity became symptomatic, the symptom complex and the details of the previous cytotoxic treatment related to the deformity. Attention should be given to the types of surgical procedures, the location of radiation fields and doses used and the details (including doses) of the chemotherapy regimen.

The physical examiner should look for skin changes from the cytotoxic treatment, as well as any obvious deformity. The musculoskeletal assessment should include serial measures of weight, height, and sitting height (crown to rump). These measurements should be plotted on growth velocity charts to assess whether growth rate is within normal limits. Most normal children will grow a minimum of 5 cm/year between age 3 and puberty. A patient in that age group who grows less than 5 cm per year, or whose serial heights on growth charts begin to fall into lower percentiles, may be experiencing growth failure [40].

Any joints involved in the radiation fields, or affected by surgery, should be put through passive and active ranges of motion, and comparisons should be made with the contralateral side. Joint measurements should be taken if indicated by abnormalities in "performance" range of motion – for example, if the active motion of a particular joint is less than the passive range of motion. In the event that there are performance range-of-motion abnormalities, further assessments are indicated. Other joint problems that can occur include pain, crepitation, swelling, loss of mobility, and weakness [34].

Observation of gait and posture must be included in the musculoskeletal assessment. As indicated by treatment received, the muscles to be examined can be assessed by functional groups, and comparisons can be made bilaterally for symmetry, tone, size and strength. Any areas of deformity, swelling, atrophy, or weakness should be noted [34].

The patient should be assessed for level of functioning and participation in normal daily activities, such as school and after school activities. Normal growth and development parameters should be incorporated into this assessment, as developmental stages may influence the patient's participation in some activities. Another influence on level of functioning or decreased participation in activities could be the lack of adjustment to body image changes.

There is no current method of completely preventing the development of late musculoskeletal effects from surgery or radiotherapy. The patient who has experienced an amputation or a significant growth deficit due to radiotherapy may or may not have incorporated this long-term effect into a new, positive body image. Many other factors contribute to general growth and development, such as nutritional deficits, other tissue damage and hormonal influences. The examiner should not rush to attribute the entire problem to the cytotoxic treatment [40]. If the right assessment is made, intervention can sometimes prevent an asymptomatic or mildly symptomatic problem from becoming more clinically significant. At the very least, the appropriate intervention may be able to assist the patient in adapting to body image changes.

16.2.4.1 Spinal Sequelae

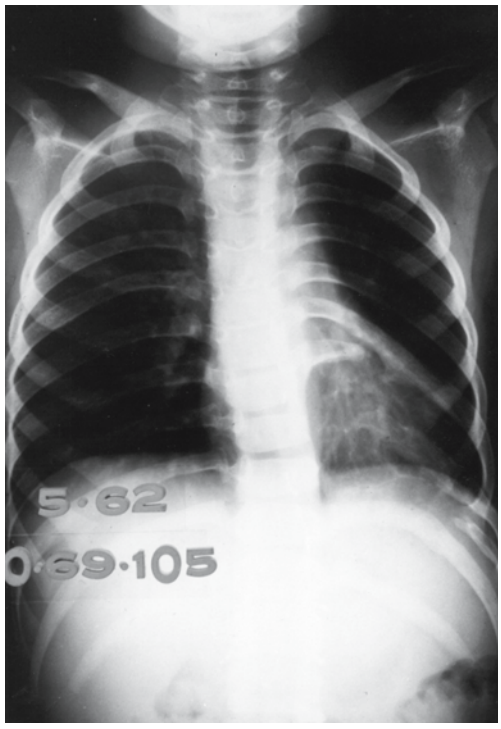
The evaluation of spinal sequelae should include the region of curvature, the magnitude of the curve, the deviation from vertical, the degree of shoulder asymmetry, the position of any rib humps or rib flare, and the type and degree of any gait abnormality. Usually the best way to examine the back is with the patient bending over with the arms touching the toes and the knees straight. At each visit, measurements should be taken of the standing and sitting heights. The spinal shortening that occurs as a direct effect of irradiation is not correctable, but, 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 used to screen for this. It is also important to be able to inform the patients of the height deficit to be expected. Figure 16.5 shows a model of expected stature loss by age at treatment for three dose levels for a hypothetical male patient receiving radiation from T10-T11 to L4-5 [69].

If the spine has been irradiated, standard scoliosis x-rays should be taken every 1–2 years until skeletal maturity to detect early scoliosis or kyphoscoliosis (Fig. 16.7). After that, films should still be taken every 1–2 years if some curvature is already present. It is rare to develop curvature after skeletal maturity if none was present before.

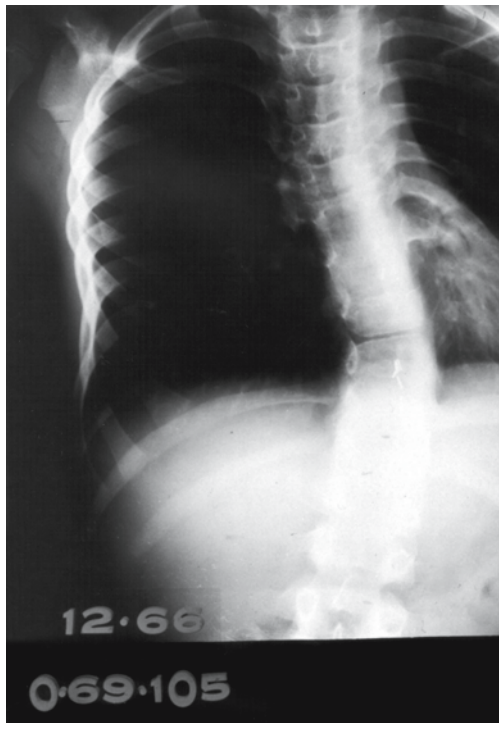
The most common method for measuring spinal curvature is the Cobb technique. The two end vertebrae of the curvature, the ones most tilted from the horizontal on the upright film, are selected. A line is drawn along the upper end plate of the upper end vertebra and along the lower end plate of the lower end vertebra. The angle of intersection of the perpendiculars from these lines is the angle of the curvature (see Fig. 16.8). It is extremely important to perform these measurements carefully and accurately. In the event of a double curvature, both sites 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 [81, 83].

16.2.4.2 Limb Length Discrepancy

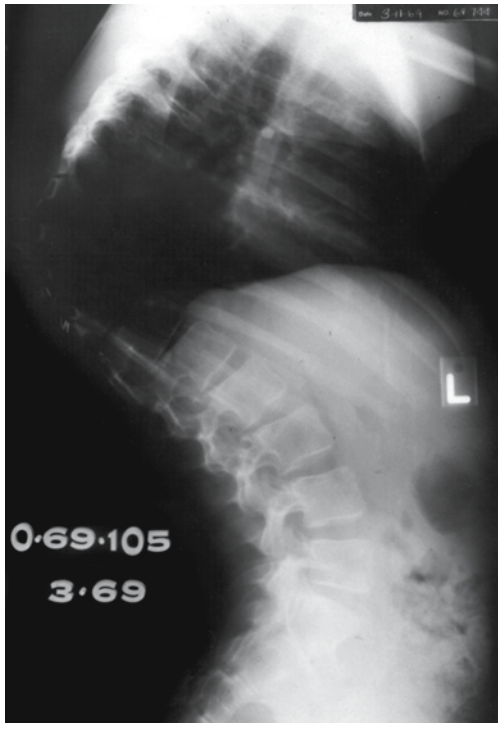
Limb length discrepancies are usually more significant. Differences in length between upper extremities are not often a problem, but leg length discrepancies can cause significant functional deficits. It is therefore important to be able to predict the ultimate outcome when radiotherapy is chosen. To do so, knowledge of the future growth of all epiphyses is necessary. In the lower extremity, 65% of future growth comes from the knee, 37% from the distal femoral physis, and 28% from the proximal tibial physis. Only



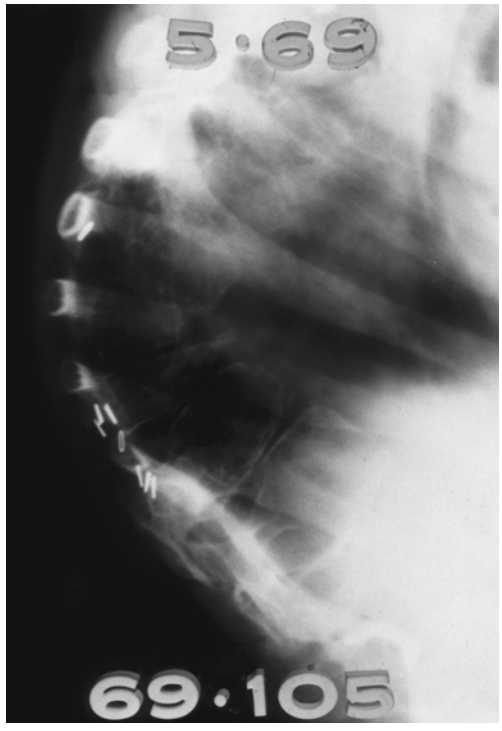
a



b



c



d

Table 16.1. Average growth (in cm) remaining for each lower extremity epiphysis by age and sex (adapted from [2] Table V, p. 11]).

Epiphysis	Boys (age in years)					Girls (age in years)				
	8	10	12	14	16	8	10	12	14	16
Proximal femur	3.5	3.0	2.0	0.8	<0.5	2.8	1.9	0.8	<0.5	0
Distal femur	8.5	7.5	5.0	2.0	0.5	7.0	4.7	2.0	0.8	0
Proximal tibia	6.0	5.0	3.5	1.0	<0.5	4.5	3.0	1.0	<0.5	0
Distal tibia	4.2	3.7	2.5	1.0	<0.5	3.4	2.3	1.0	<0.5	0

◀ **Figure 16.7 a–d**

A 2-year-old girl treated with orthovoltage irradiation to the abdomen and spine (dose unknown) for a neuroblastoma in 1960. **a** Two years after treatment, mild scoliosis developed. **b–c** Progression of kyphoscoliosis occurred over the next seven years. **d** A close-up of the spine nine years post-therapy shows osteoporosis of vertebral bodies and wedge-shaped compression fractures.

15% occurs at the proximal femoral plate and 20% from the distal tibial plate [39, 83]. Table 16.1 provides rough estimates, by age of the patient, of the growth remaining for the four major lower extremity epiphyses. Information such as this can be used to calculate the probable discrepancy that may develop, assuming that there is no growth of the irradiated physis after treatment. This is not completely accurate, since some growth may occur for a short time, and other untreated growth plates in the same extremity may partially compensate for the closed physis.

The evaluation of a limb length discrepancy on physical examination is also primarily based on accurate measurements. The patient should be undressed completely for the measurements to avoid tenting of the tape around folds in the patient's clothes. The real length of each leg is measured from the anterior superior iliac spine to the tip of the medial malleolus (Fig. 16.9a). The apparent length is measured from the umbilicus to the tip of the medial malleolus. The real length is the more important measurement because pelvic obliquity does not

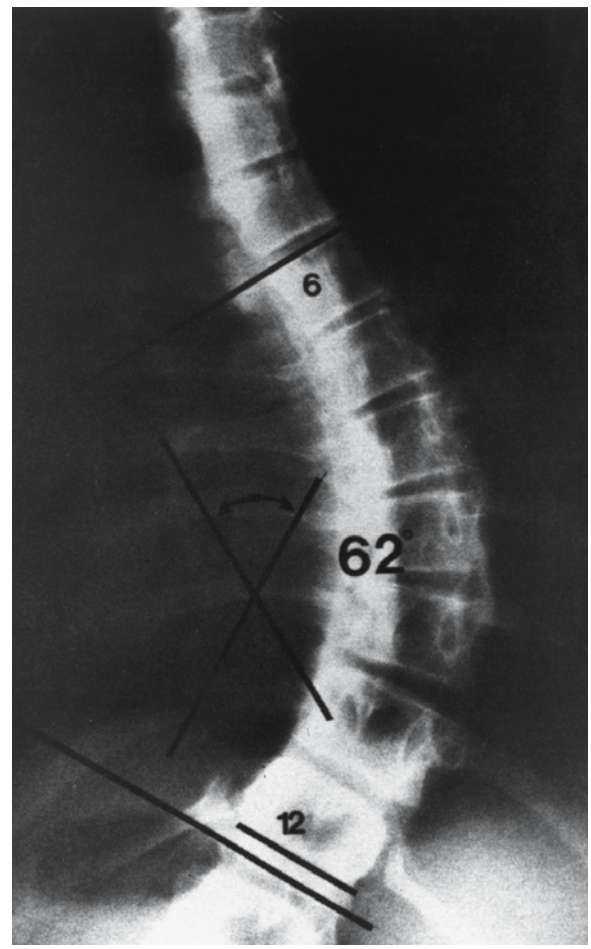
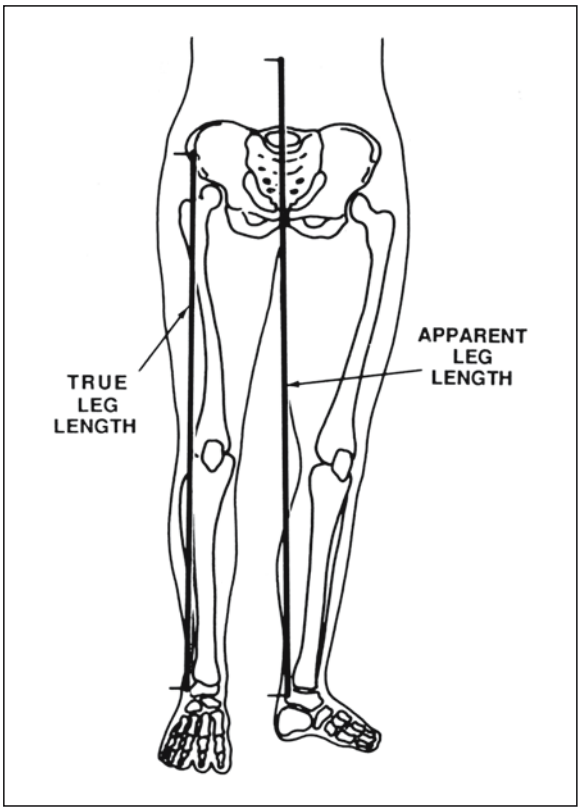
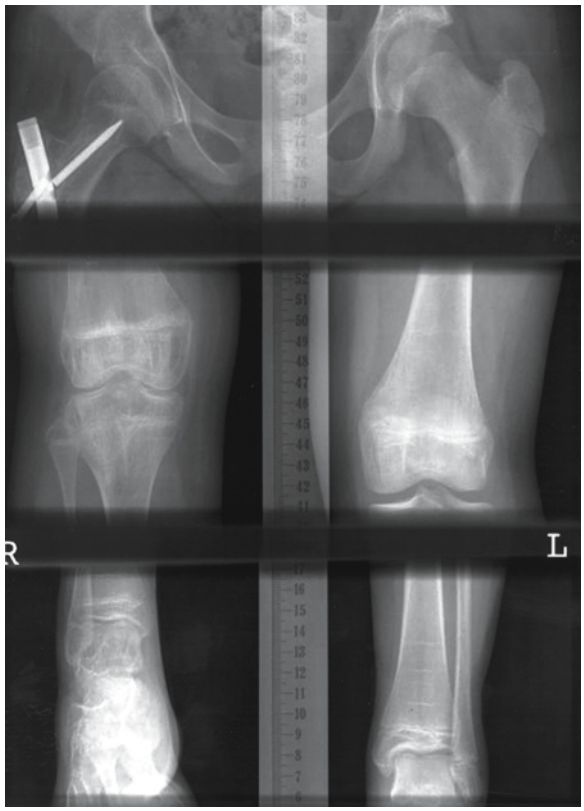


Figure 16.8

The Cobb technique for measuring the angle of spinal curvature. See text for a description. (From [81].)



a



b

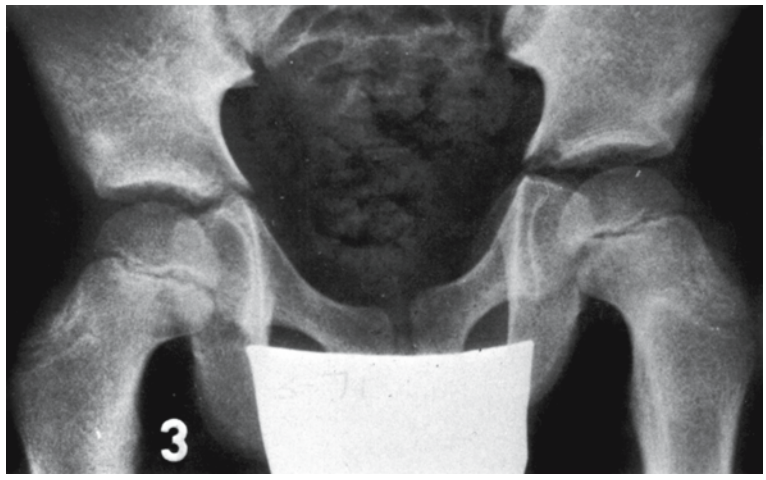
Figure 16.9 a, b

Measurement of leg-length discrepancy. See text for details. **a** Clinical measurement. (From [39]) **b** Leg-length scanogram of a 12-year old girl initially treated at age six for Ewing's sarcoma of her right femur. The scanogram is more accurate than a clinical measurement.

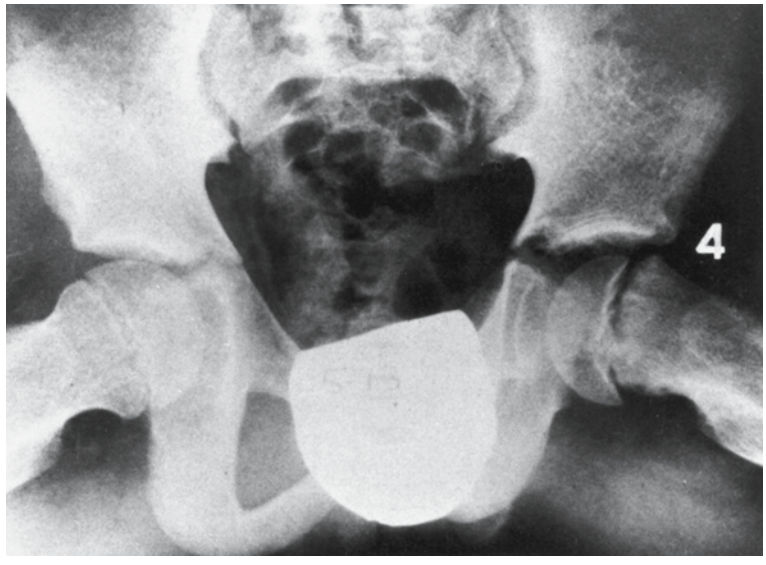
influence this measurement. The apparent length informs the evaluating physician of the compensation by the patient for the limb length discrepancy. To detect developing leg length discrepancies, measurements should also be taken at least once a year to follow the extent of the evolving discrepancy. If there is a high chance of a significant discrepancy developing, then film measurements should be taken as well. There are several accepted radiographic methods for evaluating limb length differences, and mistakes are easy to make in such measurements. Because of this, it is ideal if the same physician is able to evaluate the patient repetitively, but, as this is not always possible, it is important for any evaluating physician to carefully review the previous films (not just the reports) before using surgery to correct the defect. To evaluate the radiographic difference, a single exposure is taken of both legs on a long film, usually with the patient standing, and a radiographic ruler is placed on the cassette. The real length can then be measured from the anterior iliac spine to the medial malleolus [39, 83] (Fig. 16.9b).

Figure 16.10 a, b

A 4-year-old boy treated for a lymphoma of the testicle. **a** At age nine, a routine follow-up radiograph shows hypoplasia of the left ischium and pubis, with a normal left femoral head and neck. **b** Two years later, at age 11, slippage of the left femoral capital epiphysis developed. (From [82], p. 783.)



a



b

16.2.4.3 Other Bony Sequelae

Other bony sequelae are usually acutely symptomatic. A slipped capitofemoral epiphysis causes pain, and can be diagnosed using a radiograph of the involved hip (Fig. 16.10 a, b). A pathologic fracture also will be symptomatic and readily apparent on x-ray.

16.2.4.4 Muscle

To evaluate a deficit in muscle development, measurements of the circumferences of the involved extremity should be performed, and a determination of the range of motion of all joints in the involved limb should be made. Measurements of the opposite normal extremity should be taken as well for comparison.

16.2.5 Management of Established Problems

16.2.5.1 Management

It is not possible to prevent many of the late effects of irradiation. Of the common deficits that develop, scoliosis and leg length discrepancies need intervention most often.

Scoliotic curve progression beyond 30 degrees (or curves over 20 degrees with rapid progression) generally require bracing. Curves greater than 40 degrees, particularly in skeletally immature patients, should be instrumented and fused.

Table 16.2 shows the recommended treatment for categories of leg-length discrepancies [39, 83]. 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. This prevents 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 long bones. These uncommon growth aberrations are difficult to treat and often require complete physical arrest and osteotomies for correction. Their infrequent occurrence now is 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. Correcting the problem requires an *in situ* pin fixation to prevent a slipped capitofemoral epiphysis in the other leg if it also has been irradiated. Prophylactic pinning of capitofemoral epiphysis in the other leg should be considered as well. Severe slips (greater than 60 degrees) may require a proximal femoral osteotomy and osteoplasty [5]. Total hip replacement may be needed at times, although every attempts should be made to manage the condition more conservatively in children.

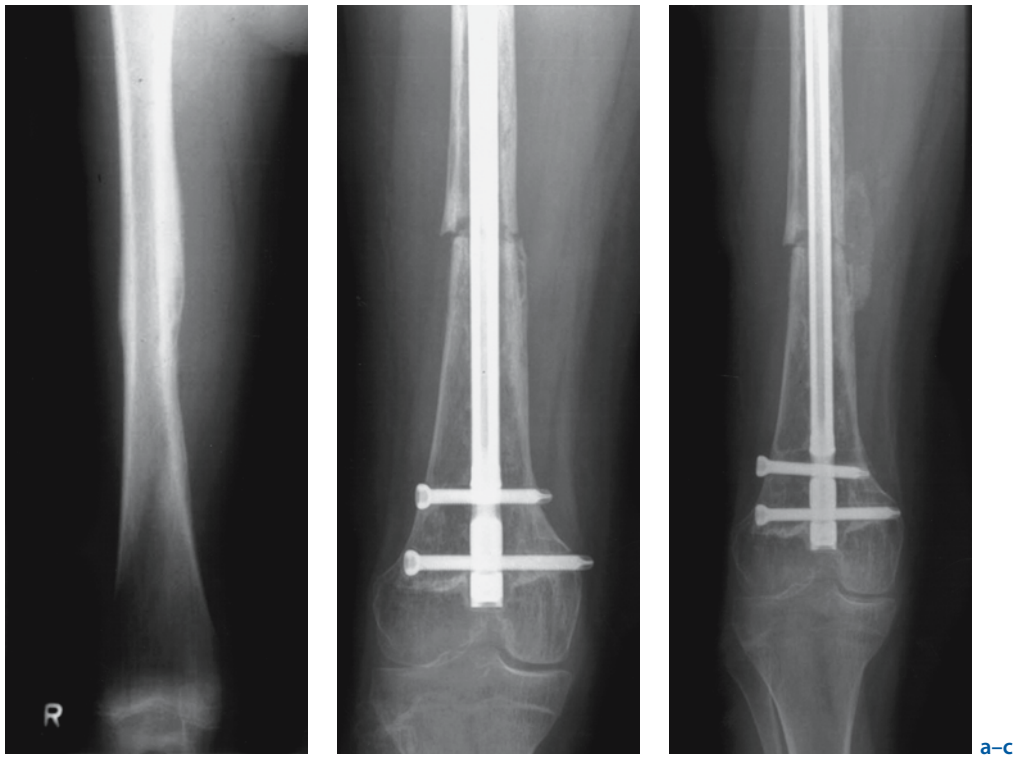
Table 16.2. Recommended treatment for categories of leg-length discrepancies (from [39], p. 784, list on p 795).

Leg-length discrepancy	Treatment
0–2 cm	None required
2–6 cm	Shoe lift, epiphysiodesis
6–15 cm	Leg lengthening
>15 cm	Prosthetic fitting

A few exostoses may require excision because of symptoms or malignant degeneration.

Pathologic fractures in the irradiated field, more common if the irradiated bone was biopsied or involved with tumor, rarely heal without internal fixation [23, 31]. Fractures through radiated bone are a challenging problem and often require long periods of treatment and multiple procedures to obtain union. 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 post-operative infection. Rigid internal fixation is mandatory, and bone grafts should be utilized liberally (Fig. 16.11 a–c). Vascularized bone grafts are the gold standard for obtaining union in patients whose fractures have failed to unite after other procedures [69] (Fig. 16.12 a, b). In the event of severe wound complication and non-union, an amputation should be considered.

Muscular atrophy is usually a cosmetic problem for which there is no treatment. Even patients who strenuously pursue weight-lifting or similar activities to build muscle strength find that the irradiated area rarely responds. However, appropriate exercise will prevent contractures and further decreases in muscle strength, as well as the loss of the range of motion of joints.

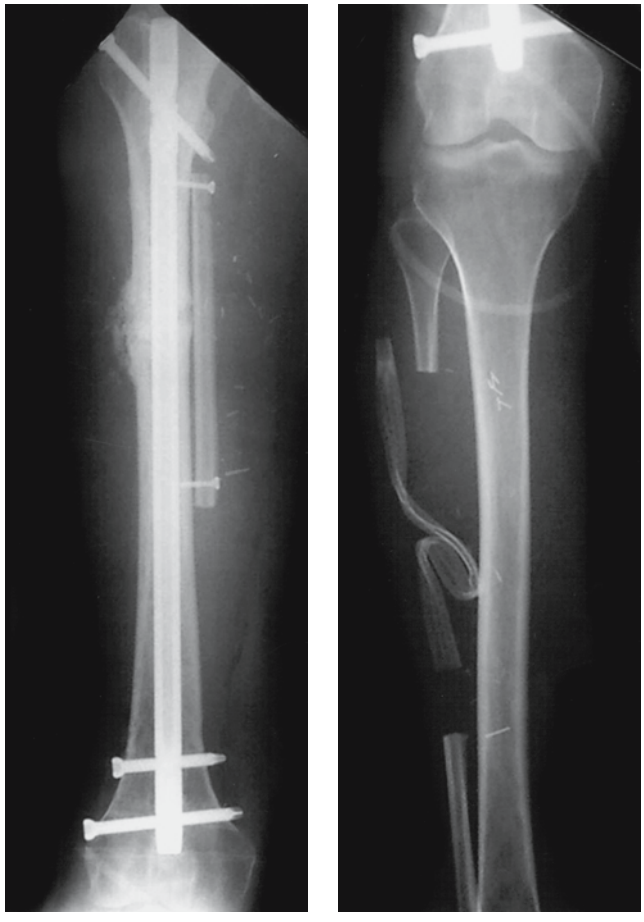


a–c

Figure 16.11 a–c

a AP radiograph of a 15-year-old girl treated with radiation therapy to her right femur at age 12. Shortly after this film was taken, she developed a fatigue fracture of the femur. **b** Internal fixation is required for pathologic fractures after radiation therapy, and she underwent intramedullary rodding of the fracture. In spite of the rodding, a non-union occurred, as shown in this radiograph two years after the fracture. **c** The internal fixation was revised with the application of an autograph from her iliac crest to the nonunion site. As shown on this radiograph, there is consolidation of the graph and bridging union across the old fracture site. She is currently pain-free. It is often necessary to bring unirradiated bone into the fracture zone to produce healing.

Radiation-induced 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 of 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 [12].



a b

Figure 16.12 a, b

Another method of repairing a pathologic fracture from radiation therapy is the application of a vascularized fibula graft. **a** AP of the femur shows an intramedullary rod stabilizing the fracture and the fibula graft; the rod has been placed medially along the femur and held is in place with two screws. The graft is typically placed medially to allow close proximity to the femoral vessels for facilitating vessel anastomosis to the fibular vessels. **b** Radiograph of the donor site from the ipsilateral leg.

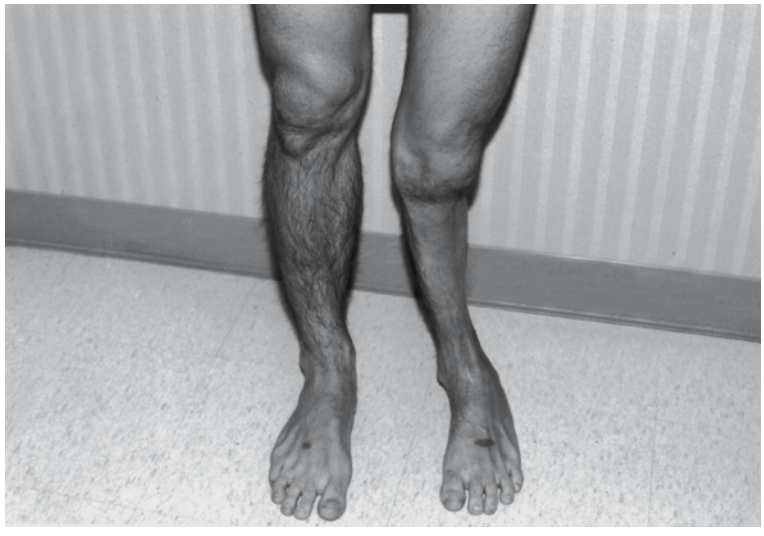


Figure 16.13

An 18-month-old boy was treated post-operatively 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, and 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.

16.2.5.2 Rehabilitation

In most cases, late effects from cytotoxic therapy 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 do develop (Fig. 16.13). Whether or not surgery is required, one necessary portion of the management is a good exercise program. Range-of-motion exercises should progress slowly to weight-bearing, then muscle-strengthening exercises. The battle with sequelae may be life long, and a proper exercise program will combat the progression of damage, and it may even help retrieve functionality previously lost. However, caution should be used in recommending vigorous exercise regimens for patients who have received high doses of doxorubicin, since cardiac decompensation may result.

The psychological adaptations to the long-term sequelae of treatment also need attention. Novotny [44] observed that one's body image is composed of fluctuating physical, psychological, and social aspects. A positive adjustment to changes in body image requires discarding the previously-held perception of one's body and incorporating the changes into a new perception. If the previous body image cannot be put aside so that the changes can be integrated and accepted, a negative body image may result.

Medical personnel can assist patients and their families in making a positive adaptation to changes in body image. Strategies for promoting acceptance of treatment-related body image changes must be individualized to each situation [44]. The initial approach should begin with facilitating open, honest communication within the family about their previous experiences, current and anticipated concerns and their educational needs. This information can then serve as the foundation on which to develop a plan of care.

Novotny provided general guidelines for building an individualized plan to assist the patient and family in positive coping with body image changes [44]. The guidelines include are as follows.

1. Assessing the level of knowledge and adaptation:
   a. encouraging patient and family verbalization of fears, concerns, and questions;
   b. providing anticipatory guidance for the expected physical changes.
2. Promoting family unity and coping skills:
   a. assisting parents, siblings, significant friends, and school personnel in creating a supportive environment;
   b. providing education and emotional support to the significant others in the patient's life.
3. Reaffirming adaptive behaviors:
   a. promoting participation in the "normal" activities of the peer group to meet developmental and psychosocial needs;
   b. advocating school attendance and participation.
4. Changing maladaptive behaviors:
   a. supporting the initiative and independence of the patient;
   b. encouraging the maintenance of usual family roles and discipline;
   c. emphasizing abilities instead of disabilities.

These strategies can be implemented on an ongoing basis. As the patient grows older, adjustments will need to be made continuously. Alteration in body image is a fluid process, and assisting the patient with coping during the various stages of life may be necessary.

Another ongoing process is meeting the educational needs of the patient and family. Patients who were diagnosed at a young age should be educated and re-educated at age-appropriate levels about their diseases, treatments, and actual, as well as potential, late effects [11]. The musculoskeletal physical examination is a good opportunity to explain what the examiner is looking for, and why. Patients who have not evidenced musculoskeletal late effects within a short time after treatment may still be at risk for the remainder of their lives. Awareness of potential problem areas may assist in future detection of late effects.

In general, patient and family education about musculoskeletal late effects should include the following information and recommendations [37]:

1. nutritional influences on musculoskeletal growth, and nutritional counseling;
2. the importance of avoiding excessive weight gain;
3. participation in non-contact sports/refraining from contact sports;
4. realistic expectations about functional abilities and growth patterns;
5. general health education, especially cancer prevention;
6. the importance of life-long surveillance care by knowledgeable health care professionals.

The patient who is biologically cured of cancer must still live with the after-effects of the disease and its treatment. A thorough assessment of the many factors affecting each patient's growth and development, promoting positive coping with changes, and providing ongoing education can result in an overall improved quality of life for the patient and family.

16.3 Integument and Breast

16.3.1 Pathophysiology

16.3.1.1 Brief Overview of Normal Organ Development

Skin

The skin develops from two sources: the superficial layer (epidermis) from the surface ectoderm and the deep layer (dermis) from mesoderm. Early in development, the fetus is covered with a single layer of ectodermal cells. In the beginning of the second month through the fourth month, the four layers of the epidermis form: a) the basal layer, which is responsible for the production of new cells and is known as the germinative layer; b) a thick, spinous layer, consisting of large polyhedral cells; (c) the granular layer, the cells of which contain small keratohyalin granules; and (d) the horny layer, forming the tough, scale-like surface of the epidermis, and made up of closely packed, dead cells, loaded with keratin. Also during the first three months, cells of neural crest origin invade the epidermis. These cells (melanocytes) synthesize melanin pigment, which can be transferred to other cells of the epidermis through the dendritic processes.

The dermis develops during the third and fourth months. The dermis consists of a layer of connective tissue and fatty tissue and contains a number of structures, including hair. Hair starts as solid epidermal proliferations penetrating the underlying dermis. Nerve endings and blood vessels develop with the hair papillae, and cells from outbuddings of the follicle walls form the *sebaceous glands,* which degenerate, thereby forming a fat-like substance that is secreted into the hair follicle and then to the skin.

Breast

The mammary glands are a specialized skin structure. The first indication is found in the form of a band-like thickening of epidermis, the mammary line or ridge. This extends on each side of the body from the base of the forelimb to the region of the hindlimb by the seventh week of gestation. Most of the mammary line disappears quickly, but a small portion in the thoracic region persists and penetrates the underlying mesenchyme, forming the breast bud. The bud sprouts 16–24 cords, which ultimately form the lactiferous ducts surrounded by the alveoli of the gland. The ducts at first open into a small epithelial pit in the bud, but shortly after birth, this pit matures into the nipple by proliferation of the underlying mesenchyme [63]. At birth, the breast of both the male and female is identical. At puberty the female breast bud enlarges first, then the mammary glands enlarge, and an extensive deposition of fat occurs. The nipple and areola enlarge as well [38].

16.3.2.2 Organ Damage Induced by Cytotoxic Therapy

Skin

Both radiation therapy and chemotherapy can cause acute and late effects on the skin and subcutaneous tissues. Radiation damage to the skin is primarily owing to effects on the germinative layer of the epidermis. Even low doses quickly diminish mitotic activity, so that cell replacement is nearly zero. The cells of the basal layer become swollen and vacuolated, with nuclear pleomorphism and binucleation. The epider-

mis becomes thin, with flattening of the papillae. Epidermal cell maturation no longer occurs, causing incomplete keratinization of the superficial cells and, thus, producing desquamation. This is caused by intracellular edema with enhancement of the intercellular bridges. With high enough doses, the epidermis may slough, exposing the dermal surface, which becomes coated with a layer of fibrin. After treatment, reepithelialization occurs, although the effectiveness of this process will depend upon the extent of the damage. If all the basal cells are not killed, there is a radiation-induced increase in enzyme activity in the melanocytes, which is transmitted to the newly formed squamous cells, causing them to become very dark as they shed.

In the dermis, radiation first causes signs of acute inflammation: edema and a lymphocytic infiltrate. High doses produce nuclear swelling and unequal nuclear divisions of the fibroblasts. Because the papilla of the hair follicle is easily damaged, radiation quickly stops mitotic activity and the hair root eventually separates from the papilla and is shed. Sweat glands are about 2–3 mm below the surface of the skin, have long lives, and only occasionally undergo mitosis. However, the cells that compose sweat glands can be destroyed by high doses of irradiation. Sebaceous glands are more easily destroyed, partially because the normal life cycle includes cell death to produce sebum and, thus, there is a need for continual replacement through cellular proliferation.

Late dermal reactions are caused by the development of subendothelial fibrous hyperplasia in the blood vessels. This causes telangiectasia and a decreased blood supply to the dermis, which results in increased fibroblastic activity. The skin then takes on a woody texture called fibrosis [41].

The skin changes resulting from radiation therapy are related to the total dose and fractionation of the radiation employed. There are differences between acute and late effects, however. Acute effects are dependent primarily upon the total dose and the overall time in which the radiation is delivered from the beginning to the end of the course of treatment. The higher the total dose and the shorter the overall time, the more significant are the acute effects. Late effects are heavily dependent on the dose per fraction, as well as the total dose. Doses greater than 2 Gy per fraction cause an increase in late effects to the skin and subcutaneous tissues. Most "curative" fractionation schemes include doses per fraction of less than 2 Gy. This is particularly true in treating children, in whom late effects are of even more concern.

Modern megavoltage irradiation is "skin-sparing," which means that the full buildup of irradiation does not occur at the surface of the skin, but rather at some depth below. The higher the energy of the beam used, the deeper the maximum dose to the tissue. Thus, the severe skin changes seen in orthovoltage irradiation used before 1960–1970 (depending upon the institution), in which the maximum dose was at the surface of the skin, do not occur as often now, unless for some clinical reason it is necessary to produce a high dose at the surface of the skin. With the skin-sparing capabilities of high-energy beams and the use of multiple fields to converge on the tumor, thus further limiting the dose to the skin in each treatment field, the true skin dose usually is not enough to cause severe skin injury. At times, during the treatment of skin lesions – or in the event of unusual situations – the skin receives a dose high enough to cause desquamation. Technical factors in the delivery of the radiation can also cause a higher dose to the skin: these include a tangential arrangement of the radiation beams employed, the use of bolus (tissue-equivalent material) on the skin, or when the lead blocks and blocking tray used to shape the radiation fields are too close to the patient.

A number of chemotherapy-induced skin changes occur, since anti-neoplastic drugs interfere with nucleic acid formation, ribosomal function and other components of protein synthesis. Rapidly dividing tissues are the most sensitive; the skin damage is, therefore, primarily to the germinative layer, the hair follicles and the melanocytes. Certain drugs, bleomycin, in particular, occasionally cause increased melanogenesis. Biopsies of the epidermis after bleomycin have shown larger melanocytes, with larger and more complex dendritic processes [10].

16.3.3 Clinical Manifestations

Damage to skin can be divided into acute effects and late effects. During a course of high-dose irradiation to the skin, the first sign of a skin reaction is faint erythema around the hair follicles. If the radiation is fractionated conventionally (less than 2 Gy per fraction), a dose of 20 Gy will usually produce erythema. Higher doses cause a progression to a generalized erythema, epilation and a decrease in sweating, as well as diminished sebaceous gland secretion. The skin next becomes brightly erythematous, warm and edematous, as well as painful to touch, all of which are sharply limited to the irradiation field. Dry desquamation (occurring at 30 Gy), then moist desquamation follows (occurring at about 40 Gy), leaving the dermis bare with a layer of fibrin covering it. After treatment, these effects heal, usually within 1–2 weeks [80]. Most children never develop such a severe reaction, since usually the dose to any region of skin is considerably less than the dose to the tumor and a total dose of 40 Gy to the skin is rarely reached. However, any cream or other foreign substance present on the skin during treatment will enhance the skin reaction to radiation.

Doses of even a few Gray will cause temporary alopecia. Recovery takes 8–12 weeks after the end of treatment; the hair starts re-growing at that point and usually grows at a normal rate thereafter. The hair can return a different texture or color; the same phenomenon occurs after chemotherapy. Doses of 40 Gy and above to the hair follicles will cause permanent alopecia.

High doses of radiation may cause a skin necrosis destruction of tissue in the area treated. This is extremely rare now with megavoltage therapy.

The first noticeable late effect consists of very slowly progressing atrophy, starting in the first few months after radiotherapy. The skin also loses its elasticity. If the injury is severe, telangiectasia (a spidery pattern of small blood vessels easily visible beneath the surface) will occur. In the dermis, fibrosis develops, with contraction and scarring in the field treated. Epilation can persist and nails will become brittle. Glands will no longer function normally; the involved skin will not sweat, nor produce sebaceous secretions. The formation of comedones has been reported, though this is rare [79]. Related skin structures, such as the breast bud, will not develop normally, nor secrete normally. This means that breast development may be hypoplastic or not occur at all.

Radiation effectively accelerates skin aging. Therefore, as the irradiated person grows older, the skin prematurely develops changes consistent with aging. It becomes drier, less flexible and it may develop "aging" spots or other discolorations. The extent of all these changes is dose-related. Doses below 10 Gy (to the skin) rarely cause noticeable problems, while the risk of such late effects increases above 30 Gy [19].

Another potential late sequelae of treatment is the risk of the development of a secondary skin cancer, usually a basal cell carcinoma [19, 56, 68]. Basal cell carcinomas are observed in patients with no evidence of chronic skin changes secondary to radiotherapy [19]. The exact risk of a secondary basal cell carcinoma is small; in one series the calculated excess risk was $0.31/10^4$ patient-years per Gray [56]. The latency period is usually at least 20 years. There may be no excess risk for a skin surface dose of less than 10 Gy for patients receiving standard fractionations, but this conclusion is controversial.

Radiation therapy in childhood has also been implicated in the development of malignant melanoma later in life. In a study utilizing data from five Nordic National Cancer Registries, as well as eight centers in France and Great Britain, between 1960 and 1987, it was found that children receiving greater than 15 Gy had a risk of developing melanoma 13 times as great, compared with non-irradiated children. The risk was in the radiation therapy field [22].

There are at least three skin reactions to chemotherapy: 1) changes related to cytotoxicity; 2) pigment alterations and 3) rashes and eruptions. Cytotoxic changes related to nucleic acid synthesis, ribosomal function, etc., rarely appear after chemotherapy alone. However, "radiation recall" may be owing to cytotoxic changes in the skin. This phenomenon consists of erythema, blistering, and, sometimes, moist desquamation, in an area previously irradiated. It usually occurs a few weeks to a few months after radiotherapy subsequent to a course of chemotherapy containing doxorubicin HCl or dactinomycin (or,

Table 16.3. Pigment changes from chemotherapy (from [43]).

Abnormality	Associated drugs
Generalized hyperpigmentation	5-Fluorouracil, busulfan
Localized hyperpigmentation	Adriamycin, cyclophosphamide, and other alkylating agents, bleomycin, mithramycin, dactinomycin, various hormones
Hyperpigmentation of nails	Adriamycin, cyclophosphamide, nitrogen mustard, 5-fluorouracil, methotrexate, nitrosoureas, DTIC, others
Linear hyperpigmentation	Most cytotoxics (along veins); bleomycin (on trunk and extremities separate from venous channels)

occasionally, a number of other drugs, particularly if given in high doses). The same drugs cause increased radiation reactions if given concomitantly with radiation therapy. The etiology is probably renewed damage by chemotherapy to stem cells, which have residual injury from irradiation.

Alopecia occurs through damage to the hair follicles. It is the most predictable skin reaction to chemotherapy. Drugs that cause alopecia include cyclophosphamide, doxorubicin, dactinomycin and others – the list of agents is very long. Alopecia of the scalp does not appear to require a large threshold dose and occurs after each cycle of the drug; however, it is almost always reversible. Alopecia involving the eyelids and eyelashes is less predictable. Usually it requires higher and more prolonged courses of chemotherapy, but when it happens, it may sometimes be permanent [66]. In addition, permanent alopecia of the scalp and other hair-bearing regions has been noted after a busulfan/cyclophosphamide conditioning regimen for bone marrow transplantation. Over 30% of patients receiving busulfan as part of a chemotherapy-alone conditioning regimen experience some degree of permanent alopecia [3, 76]. The presence of chronic graft versus host disease increases the risk [76].

Drugs reported to cause pigment changes are shown in Table 16.3. While some, including doxorubicin, have been postulated to have a direct effect on melanocytes [13], the mechanism essentially remains undefined. Generalized hyperpigmentation from bleomycin therapy is probably the most common of these abnormalities, but other drugs such as busulfan, cyclophosphamide, dactinomycin, 5-Fluorouracil, hydroxyurea, and methotrexate can also do this on occasion [13]. This generalized hyperpigmentation usually resolves slowly with time, but it can be permanent.

Antimitotic agents can also cause banding of the nails, either vertical or horizontal, as well as black pigmentation. The latter occurs first at the base of the nails, and then moves distally [43, 67]. Although usually these changes reverse when the drug is withdrawn, nail hyperpigmentation can be permanent [67].

The drug, 5-Fluorouracil, as well as high doses of methotrexate, dactinomycin, and doxorubicin, can cause skin eruptions, including urticaria – a generalized erythematous rash. They can also cause hyperpigmented, brawny, indurated plaques, particularly of the hands and feet, as well as nodularity of the hands and feet [10, 17]. These effects are temporary.

Children receiving chemotherapy have been reported to develop increased numbers of benign melanocytic nevi after treatment [26].

In the growing breast, the most sensitive structure is the breast bud. Doses of as little as 10 Gy to the breast bud will cause the breast to be underdeveloped (hypoplastic); doses above 20 Gy may ablate development altogether [20, 27]. In patients treated with pulmonary irradiation for Wilms' tumor, four out of ten females had hypoplastic breast development, including two who received less than 20 Gy [32]. Doses of 20 Gy or more to regions of the anterior chest other than the breast bud may prevent breast development in that area. Low doses of radiation may result in a failure to lactate [59].

16.3.4 Detection/Screening

It is usually not difficult to predict the extent of the acute changes during treatment based on the dose and fractionation schedule of the course of radiotherapy, and on the chemotherapy regimen used. The patient (and parents) can therefore anticipate the severity of the reaction. This will usually diminish some of the anxiety that inevitably accompanies the reaction.

Late effects progress with time, and may be subtle at first. Careful physical exams are necessary in order to detect any cutaneous late effects. These exams should be performed by a physician who is knowledgeable of the treatment received. Areas of pigmentation changes, dryness, atrophy, telangiectasia, contraction, and scarring should be noted and carefully recorded. If chemotherapy has been given, then skin coloration should be checked as well, along with the status of the nail beds.

After the completion of treatment, physical examinations should be performed 2–3 times a year for at least two years, then at least one a year. If the radiation field included the breast, then careful monitoring of this area should occur as well, particularly as puberty approaches. Tanner staging should be done with each follow-up examination to document the expected physical maturation.

While a reversal of skin changes secondary to irradiation and chemotherapy is not possible (although subcutaneous tissues will occasionally soften with time), education of the patient and family can be effective in decreasing the long-term effects. Since radiation damage and sun damage to the skin are similar, it is important for the patient to avoid severe sun exposure after treatment. Sun exposure will increase the aging process started by irradiation. If heavy sun exposure is anticipated, a strong sunscreen (SPF 15 or above) must be used on the treated region.

Most chemotherapy-related skin changes require no specific care, but it is important to carefully check the status of all benign nevi after treatment with chemotherapy. Increased numbers of benign melanocytic nevi appears to be one of the strongest risk factors in the development of malignant melanoma. Since it has been reported that children treated with chemotherapy have more nevi than normal, careful assessments are required [26, 72].

16.3.5 Management of Established Problems

16.3.5.1 Management and Rehabilitation

Although the acute effects of irradiation are less common now, they can be alarming when they occur. It is important to remember that healing will generally occur spontaneously within 2– 4 weeks.

There is no clinically accepted way to reverse late radiation skin changes, though celecoxib has been reported to decrease skin damage after radiation in mice [30]. Because of the lack of sebaceous secretions after treatment, it may be helpful to use Vaseline or a moisturizing cream for patient comfort.

Temporary alopecia from radiotherapy or chemotherapy needs no particular treatment and will resolve in time. Permanent alopecia from radiation therapy cannot be reversed, but hair transplants have been reported to be effective. This can only be done if there remains a large portion of unaffected scalp from which to harvest plugs of normal hair, and if the area of alopecia involves well-healed scalp [27]. Hair transplantation has also been reported to be effective following permanent busulfan alopecia, used during bone marrow transplantation. Although allotransplantation is usually unsatisfactory, it will work if the hair grafts are harvested from the same patient that provided the donor marrow [57].

Breast hypoplasia can be corrected by breast augmentation. This procedure should be performed by someone who is familiar with the treatment the patient received, as healing may be retarded or difficult in regions previously irradiated. A downside of the procedure is that breast augmentation may make follow-up of the region more difficult.

Guidance needs to be provided for the female who can expect, or has developed, breast hypoplasia from irradiation. Development of a positive body image is an especially difficult task for adolescent females who expect normal development. A female teenager who has the potential for unequal breast development is particularly at risk for developing a negative body image, with accompanying lowered self-esteem. The

impact on present and future sexuality cannot be overlooked. Likewise, adolescent males who develop unilateral gynecomastia may become quite concerned and self-conscious. Family and peer support and understanding can be critical for these patients. Anticipatory guidance and suggestions for coping with these late effects may assist the adolescent in positive adaptation. The strategies suggested by Novotny [44] and discussed earlier in this chapter will be helpful here as well.

The female patient who had already experienced breast development when radiation treatment was given may be at risk for decreased skin elasticity and fibrosis. All patients who received breast irradiation should be counseled on performing monthly breast self-examinations, as there may be an increased risk of breast cancer if the breast was irradiated. A more complete discussion of possible complications, as well as recommendations for follow-up, is provided in the chapter on secondary malignancies.

If fertility is intact (depending on the sites of previous cancer and the treatments used), the female patient should be informed that the affected breast may not lactate after childbearing. If the other breast was not within the radiation field, the patient can expect to breastfeed normally from the untreated side.

References

1. Ackman JD, Rouse L, Johnston CE II (1988) Radiation induced physeal injury. Orthopaedics 11:343–349
2. Anderson M, Green WT, Messner MB (1963) Growth and predictions of growth in the lower extremities. J Bone Joint Surg [Am] 45:1–14
3. Baker BW, Wilson CL, Davis AL et al. (1991) Busulphan/cyclophosphamide conditioning for bone marrow transplant may lead to failure of hair regrowth. Bone Marrow Transplant 7:43–47
4. Bajorunas DR et al. (1980) Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. J Clin Endocrinol Metab 50:329–335
5. Barrett IR (1985) Slipped capitol femoral epiphysis following radiotherapy. J Pediatr Orthop 5:268–273
6. Bar-On E et al. (1993) Effects of chemotherapy on human growth plate. J Pediatr Orthop 13:220–224
7. Bolek TW et al. (1996) Local control and functional results after twice-daily radiotherapy for Ewing's sarcoma of the extremities. Int J Radiat Oncol Biol Phys 35:687–692
8. Butler MS, et al. (1990.Skeletal sequelae of radiation therapy for malignant childhood tumors. Clin Orthop 251:235–240
9. Clayton PE et al. (1988) Growth in children treated for acute lymphoblastic leukaemia. Lancet 1:460–462
10. Cohen IS et al. (1973) Cutaneous toxicity of bleomycin therapy. Arch Dermatol 107:553–555
11. D'Angio G (1988) Cure is not enough: late consequences associated with radiation treatment. J Assoc Pediatr Oncol Nurses 5:20–23
12. Delanian S, Balla-Medias S, Lefaix JL (1999) Striking regression of chronic radiotherapy damage in a clinical trial of pentoxifylline and tocopherol. J Clin Oncol 17:3283–3290
13. DeSpain JD (1992) Dermatologic toxicity of chemotherapy. Semin Oncol 19:501–507
14. Donaldson SS (1992) Effects of irradiation on skeletal growth and development. In: Green DM, D'Angio GJ (eds) Late effects of treatment for childhood cancer. Wiley-Liss, New York
15. Drescher W, Schneider T, Becker C, Hobolth J (2001) Selective reduction of bone blood flow by short-term treatment with high-dose methylprednisolone. An experimental study in pigs. J Bone Joint Surg Br 83:274–277
16. Eifel PJ, Donaldson SS, Thomas PR (1995) Int J Radiat Oncol Biol Phys 31:1301–1307
17. Etcubanas E, Wilbur J (1974) Uncommon side effects of adriamycin (letter). Cancer Chemother Rep 58:757–758
18. Fajardo LF (1982) Pathology of radiation injury. Masson, New York
19. Fragu P et al. (1991) Long-term effects in skin and thyroid after radiotherapy for skin angiomas: a French Retrospective Cohort study. Eur J Cancer 27:1215–1222
20. Furst CJ, Lundell M, Ahlback SO, Holm LE (1989) Breast hypoplasia following irradiation of the female breast in infancy and early childhood. Acta Oncol 28:519–523
21. Glasser DB, Duanne K, Lane JM, Healey JH, Caparros-Sison B (1991) The effect of chemotherapy on growth in the skeletally immature individual. Clin Orthop 262:93–100
22. Guerin S et al. (2003) Radiation dose as a risk factor for malignant melanoma following childhood cancer. Eur J Cancer 39:2379–2386
23. Helmstedter CS et al. (2001) Pathologic fractures after surgery and radiation for soft tissue tumors. Clin Orthop 389:165–172
24. Hogeboom CJ et al. (2001) Stature loss following treatment for Wilms' tumor. Med Pediatr Oncol 36:295–304
25. Hopewell JW (2003) Radiation therapy effects on bone density. Med Pediat Oncol 41:208–211
26. Hughes BR, Cunliffe WJ, Bailey CC (1989) Excess benign melanocytic naevi after chemotherapy for malignancy in childhood. Br Med J 299:88–91
27. Jacobs JB, Monell C (1979) Treatment of radiation-induced alopecia. Head Neck Surg 2:154–159

28. Katzman H, Waugh T, Berdon W (1969) Skeletal changes following irradiation of childhood tumors. J Bone Joint Surg [Am] 51-A:825–842
29. Kew MC et al. (1977) Melanocyte stimulating hormone levels in doxorubicin induced hyperpigmentation. Lancet I:811
30. Liang L, Dongping H, Weimin L (2003) Celecoxib reduces skin damage after radiation: selective reduction of chemokine and receptor mRNA expression in irradiated skin but not in irradiated mammary tumor. Am J Clin Oncol 26:S114–S121
31. Lin PP, Boland PJ, Healey JH (1998) Treatment of femoral fractures after irradiation. Clin Orthop 352:168–178
32. Macklis RM, Oltikar A, Sallan SE (1991) Wilms' tumor patients with pulmonary metastases. Int J Radiation Oncol Biol Phys 21:1187–1193
33. Maeda M et al. (1988) Effects of irradiation on cortical bone and their time-related changes: a biomechanical and histomorphological study. J Bone Joint Surg [Am] 70:392–399
34. Malasonos L et al. (1981) Musculoskeletal assessment. In: Health assessment, 2nd edn. Mosby, St Louis
35. Marcus RB Jr et al. (1991) Local control and function after twice-a-day radiotherapy for Ewing's sarcoma of bone. Int J Radiat Oncol Biol Phys 21:1509–1515
36. Mayfield JK et al. (1981) Spinal deformity in children treated for neuroblastoma: the effect of radiation and other forms of treatment. J Bone Joint Surg [Am] 63A:183–193
37. Meadows AT (1988) The concept of care for life. J Assoc Pediatr Oncol Nurses 5:7–9
38. Moore KL (1988) Essentials of human embryology. Decker, Toronto
39. Mosely CF (1990) Leg-length discrepancy. In: Lovell WW, Winter RB (eds) Pediatric orthopedics, 3rd edn. Lippincott, Philadelphia
40. Moshang T Jr, Lee MM (1988) Late effects: disorders of growth and sexual maturation associated with the treatment of childhood cancer. J Assoc Pediatr Oncol Nurses 5:14–19
41. Moss WT, Brand W (1969) The bone. In: Therapeutic radiology: rationale, technique, results, 3rd edn. Mosby, St Louis
42. Neuhauser EBD et al. (1952) Irradiation effects of roentgen therapy on the growing spine, Radiology 59:637–650
43. Nixon DW et al. (1981) Dermatologic changes after systemic cancer therapy. Cutis 27:181–194
44. Novotny MP (1986) Body image changes in amputee children: How nursing theory can make the difference. J Assoc Pediatr Oncol Nurses 3:8–13
45. Pateder DB et al. (2001) The role of autocrine growth factors in radiation damage to the epiphyseal growth plate. Radiat Res 155:847–857
46. Pateder DB et al. (2002) Role of pentoxifylline in preventing radiation damage to epiphyseal growth plate chondrocytes. Radiat Res 157:62–68
47. Paulino AC et al. (2002) Late effects in children treated with radiation therapy for Wilms' tumor. Int J Rad Oncol Biol Phys 46:1239–1246
48. Paulino AC et al. (2002) Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. Int J Rad Oncol Phys Biol 52:1025–1031
49. Pinkel D (1971) Five-year follow-up of "total therapy" of childhood lymphocytic leukemia. JAMA 216:648–652
50. Probert JC, Parker BR (1975) The effects of radiation therapy on bone growth. Radiology 114:155–162
51. Probert JC, Parker BR, Kaplan HS (1973) Growth retardation in children after megavoltage irradiation of the spine. Cancer 32:634–639
52. Rate WR et al. (1991) Late orthopedic effects in children with Wilms' tumor treated with abdominal irradiation. Med Pediatri Oncol 19:265–268
53. Riseborough E et al. (1976) Skeletal alterations following irradiation for Wilms' tumor. J Bone Joint Surg [Am] 58A: 526–536
54. Robertson WW et al. (1991) Leg length discrepancy following irradiation of childhood tumors. J Pediatr Orthop 11:284–287
55. Robson H, Anderson E, Eden OB, Isaksson O, Shalet, S (1998) Chemotherapeutic agents used in the treatment of childhood malignancies have direct effects on growth plate chondrocyte proliferation. J Endocrinol 157:225–235
56. Ron E et al. (1991) Radiation-induced skin carcinomas of the head and neck. Radiat Res 125:318–325
57. Rosati P, Bergarno A (1999) Allogenic hair transplant in a bone marrow transplant recipient. Dermato Surg 25:664
58. Rosenfield NS, Hler JO, Berdon WE (1989) Failure of development of the growing breast after radiation therapy. Pediatr Radiol 19:124–127
59. Rostom AY, O'Cathail S (1986) Failure of lactation following radiotherapy for breast cancer (letter). Lancet 1:163–164
60. Rubin P (1964) Dynamic classification of bone dysplasia. Year Book Medical Publishers, Chicago
61. Rubin P et al. (1959) Radiation induced dysplasias of bone. Am J Roentgenol 82:206–216
62. Rutherford H, Dodd GD (1974) Complications of radiation therapy: growing bone. Semin Roentgenol 9:15–27
63. Sadler TW (1990) Langman's medical embryology, 6th edn. Williams and Wilkins, Baltimore
64. Salter RB (1983) Textbook of disorders and injuries of the musculoskeletal system, 2nd edn. Williams and Wilkins, Baltimore
65. Schriock EA et al. (1991) Abnormal growth patterns and adult short stature in 115 long-term survivors of childhood leukemia. J Clin Oncol 9:400–405
66. Seipp CA (2001) Adverse effects of treatment: hair loss. In: DeVita VT, Hellman S, Rosenberg SA (eds) Cancer, principles and practice of oncology, 6th edn. Philadelphia, Lippincott Williams and Wilkins, p 2922

67. Shah PC, Rao KRP, Patel AR (1978) Cyclophosphamide induced nail pigmentation. Br J Dermatol 98:675–680
68. Shore RE et al. (1984) Skin cancer incidence among children irradiated for ringworm of the scalp. Radiat Res 100:192–204
69. Silber JH, Littman PS, Meadows AT (1990) Stature loss following skeletal irradiation for childhood cancer. J Clin Oncol 8:304–312
70. Springfield DS, Pagliarulo PAC (1985) Fractures of long bones previously treated for Ewing's sarcoma. J Bone Joint Surg [Am] 67A:477–481
71. Springfield DS (1990) Bone and soft tissue tumors. In: Lovell WW, Winter RB (eds) Pediatric orthopedics. Lippincott, Philadelphia
72. Swerdlow AJ et al. (1986) Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J 292:1555–1559
73. Truica CI, Frankel SR (2002) Acute rhabdomyolysis as a complication of cytarabine chemotherapy for acute myeloid leukemia: a case report and review of the literature. Am J Hematol 70:320–323
74. Van Leeuwen BL et al. (2003) Chemotherapy decreases epiphyseal strength and increases bone fracture risk. Clin Orthop 413:243–254
75. Van Leeuwen BL et al. (2000) Effect of single chemotherapeutic agents on the growing skeleton of the rat. Ann Oncol 11:1121–1126
76. Vowels M et al. (1993) Factors affecting hair regrowth after bone marrow transplantation. Bone Marrow Transplant 23:347–350
77. Wagner LM et al. (2001) Fractures in pediatric Ewing's sarcoma. J Pediat Hematol Oncol 23:568–571
78. Walker SJ et al. (1981) Slipped capital femoral epiphysis following radiation and chemotherapy. Clin Orthop Relat Res 159:186–193
79. Walter JF (1980) Cobalt radiation-induced comedones. Arch Dermatol 116:1073–1074
80. White DC (1924) An atlas of radiation histopathology. Oak Ridge, Tennessee, USERDA Technical Information Center
81. Winter RB (1990) Spinal problems in pediatric orthopaedics. In: Lovell WW, Winter RB (eds) Pediatric orthopedics, 3rd edn. Lippincott, Philadelphia
82. Wolf EL et al. (1977) Slipped femoral capital epiphysis as a sequela to childhood irradiation for malignant tumors. Radiology 125:781–784
83. Zeman W, Solomon M (1971) Effects of radiation on striated muscle. In: Berdjis CC (ed) Pathology of irradiation. Williams and Wilkins, Baltimore

Hematopoietic Stem Cell Transplantation

Nancy Bunin · Constance DiDomenico · Virginia Guzikowski

Contents

Hematopoietic stem cell transplant (HSCT) is increasingly used for the treatment of both leukemias and solid tumors. This has been made possible by several factors, including expansion of the unrelated donor pool and advances in mobilization and collection of autologous cells. Although transplant-related mortality and relapse remain obstacles, an increasing number of children are surviving following HSCT. Both the HSCT antecedent therapy and the post-transplant complications have multi-system effects, and understanding and anticipating these are important in caring for the children affected. This chapter will provide a brief overview, as many of these complications are discussed in more depth in other chapters of this book.

17.1 Conditioning

All children undergoing HSCT for malignancies receive conditioning (high dose chemotherapy, with or without total body irradiation) prior to the infusion of the hematopoietic stem cells. The agents used are determined by the underlying disease, patient condition and the type of graft. HSCT for hematologic malignancy are usually performed using allogeneic grafts that may be from a related or an unrelated donor, or cord blood. To achieve sustained engraftment with an allogeneic donor, the conditioning regimens must be extremely immunosuppressive, and they generally include an alkylating agent, usually cyclophosphamide, and total body irradiation or busulfan. Other drugs, such as etoposide, cytosine arabinoside, melphalan or thiotepa, are sometimes added. Total body irradiation is now generally delivered over several days in fractions of 150–200 cGy,

with total doses range from 1000–1450 cGy. Fractionation allows for partial recovery of normal tissues between fractions. This may reduce the risk of long-term complications (e.g. cataracts and pulmonary restrictive disease) that are commonly noted with single-fraction total body irradiation (TBI). Complications such as graft versus host disease (GVHD) after allogeneic HSCT may play a significant role in the development of sequelae.

More recently, non-myeloablative conditioning regimens have been developed for patients undergoing allogeneic HSCT. These regimens also are extremely immunosuppressive, as is necessary to permit engraftment, but may be less toxic in the immediate post-transplant period and in the long-term. GVHD remains a significant potential complication with these regimens.

HSCT for solid tumors usually uses autologous hematopoietic cells that have been collected and cryopreserved prior to conditioning. Chemotherapy agents selected for solid tumor conditioning regimens are those that can be safely dose- escalated and have differing methods of action and non-overlapping extramedullary toxicities. In some situations, TBI may be used as part of the conditioning. Local irradiation may also be used for tumor control, either before or after the HSCT. To improve survival, tandem transplants over a period of several months are used for some diseases, such as neuroblastoma and brain tumors.

17.2 Endocrine System

The endocrine system is affected in almost all patients who receive a HSCT. The extent of damage is dependent upon prior cytotoxic therapy and the particular agents selected for the conditioning regimen. Growth, reproduction, thyroid and glucose metabolism may be affected.

17.2.1 Growth

The grow of those who have undergone an HSCT is affected by many factors, including genetic, nutritional, hormonal and therapeutic factors. Effects are most commonly attributed to radiation of the hypothalamic pituitary axis, which can result in either growth hormone deficiency or abnormal secretion of growth hormone. Direct impairment of bone growth may also occur. The risk of growth failure is enhanced by TBI and by cranial irradiation as a component of prior therapy. Higher risk is also associated with young age at the time of HSCT and male gender [8, 13, 19, 52]. Children with neuroblastoma are at particular risk, due to their young age at the time of transplant [18, 29]. The greatest effect on growth occurs in those who received cranial irradiation prior to TBI [19].

Impaired growth manifests as a decrease in growth velocity or in height standard deviation score (SDS). In general, growth hormone deficiency increases with time from TBI [13]. Growth of peri-pubertal patients at HSCT may be further impacted by impairment of normal mechanisms leading to the pubertal growth spurt [25]. Since current treatment protocols use only low-dose cranial radiation, and since they are limited to patients with overt CNS disease or with a very high-risk profile, the number of patients at risk for severe growth impairment may be decreasing.

The incidence of growth hormone deficiency varies widely in different studies, ranging from 20–70% [13, 18, 19]. Some studies fail to show a correlation between growth rate and growth hormone secretion with stimulation testing [6, 8], and many children will achieve final heights within the normal range [8]. IGF-1 and IGFBP-3 studies are not useful predictors of GH deficiency, although lower IGF-1 and IGFBP-3 values are noted in those who receive TBI, compared with those not given TBI [6]. In one study with repeated evaluation of GH status, improvement was noted over time [17], although further confirmation of these results is needed.

The role of growth hormone replacement is controversial. Growth hormone replacement has been found to ameliorate poor growth rate as a result of radiation [6, 13, 19], but, because most studies are short term, there is little data beyond three years. In a study by Brauner et al., no catch-up growth was observed. Patients who received fractionated TBI were less affected at two years post HSCT than those

Table 17.1. Endocrine: summary and suggested follow-up

Evaluation		
Growth	Height, bone age, Somatomedin C, IGFBP-3	TBI and/or cranial irradiation: refer to endocrinologist for GH provocative testing; growth hormone may be indicated
Thyroid	Physical assessment, Free T_4, T_3, TSH	Elevated TSH: may repeat in 3–6 months if mild elevation; thyroxine replacement
Reproductive	Tanner assessment	Post-pubertal females: estrogen replacement; pre-pubertal children: refer to endocrinologist if delayed puberty or low testosterone/estradiol
	Males: FSH, LH, testosterone (>13 years) Females: FSH, LH, estradiol (>12 years)	
Glucose metabolism	Height, weight Fasting cholesterol, triglycerides	

who received single fraction TBI, but at 5 years, both groups had similar height decrements [6]. Resistance of the bone to IGF-1 induced by radiation has been proposed as the explanation for the lack of catch-up growth observed [6]. Skeletal abnormalities have been more commonly noted in children younger than eight years who were given TBI [10].

There have been some reports following chemotherapy-only conditioning of growth disturbances [1,3]. However, most children who receive chemotherapy-only conditioning regimens have relatively normal growth, although both the long-term use of steroids for chronic GVHD and prior cranial irradiation are known to affect growth [13, 25, 51, 52].

17.2.2 Thyroid

Thyroid dysfunction is a well-described complication after HSCT. Although it occurs most commonly after TBI, there are reports of thyroid dysfunction in patients who received chemotherapy-alone. The incidence varies widely in studies, depending upon the technique of TBI. Up to 70% of patients receiving single-dose TBI develop hypothyroidism, compared with 15–20% of those who receive fractionated TBI [5, 21, 47]. Compensated hypothyroidism has a median time of onset of 12 months post HSCT, and may be transient [21]. Replacement therapy is indicated for persistent elevation of TSH. Since radiation may increase the risk of thyroid neoplasms, patients who received TBI should have annual physical assessments of the thyroid gland.

Compensated primary hypothyroidism has been noted in 10–15% of patients who received chemotherapy without radiation therapy [2, 49]. The etiology of hypothyroidism in this group is unclear; but it is believed that the high doses of drugs associated with chemotherapy may be involved. Chemotherapy-only regimens have been associated with euthyroid sick syndrome, in which the T3 and T4 are low, and the TSH is either normal or low. This syndrome has been reported in 29% of patients at 14 months post therapy [49]. The clinical significance of this is not clear.

17.2.3 Diabetes and Metabolic Syndrome

Survivors of HSCT may be at risk for insulin resistance, impaired glucose tolerance and type II diabetes [45]. Risk factors relevant to the development of these problems include obesity, family history of diabetes, inactivity, diet, use of growth hormone and race. In one study of 748 patients evaluated for type II diabetes, 34 had developed this condition at a median follow-up of 11 years. The prevalence of type II diabetes was 9% among the survivors of leukemia, with CML patients at highest risk [15]. The prevalence was age-related, with 12% occurring among leukemia

Table 17.2. Organ systems: suggested follow-up

Organ	Suggested evaluation
Heart	ECG, echocardiogram, exercise stress test: yearly to every 3–5 years
Pulmonary	PFTs: yearly to every 3–5 years
Renal	Blood pressure, urinalysis, BUN, creatinine, erythropoietin level if evidence of thrombotic microangiopathy
Dental	Semi-annual dental evaluation
Hearing	Audiogram for patients at risk (prior cisplatin, carboplatin, cranial irradiation)
Eyes	Annual ophthalmologic evaluation, artificial tears if sicca syndrome
Bone	Physical assessment, bone density evaluation (DXA, pQCT)
Brain	Neuropsychologic assessment 1–3 years post BMT in patients at risk (<6 years with TBI, hearing loss)

survivors 20–39 years old and 43 % occurring among survivors 40–49 years [15]. The prevalence of diabetes type I, although less common, was three times higher than in the general population. Most patients evaluated were not obese and experienced a relatively early onset of type II diabetes. Racial minorities were more likely to develop diabetes; TBI was not a risk factor in this analysis.

Hyperinsulinemia and hypertriglyceridemia [45] have been described post HSCT. Therefore, post-HSCT patients, particularly those who were treated for leukemia, merit close observation for the development of diabetes, as well as lipid abnormalities.

17.2.4 Reproductive

Gonadal dysfunction is common following HSCT, a finding attributable to the use of alkylating agents, such as cyclophosphamide, and radiation therapy. Busulfan, as a radiation "substitute," also causes a high incidence of gonadal failure [2, 46]. Gonadal dysfunction results in infertility in most affected patients, with some patients also having difficulties with pubertal development.

In males, the Sertoli and germ cells are more vulnerable to radiation and chemotherapy than the Leydig cells. FSH levels are usually elevated, with normal LH levels. Testosterone levels may be normal with reduced or absent spermatogenesis. Most boys will undergo pubertal development without the addition of testosterone. Testicular irradiation (usually for leukemia) is associated with low testosterone levels. Boys who have undergone testicular irradiation should be followed closely as they enter puberty.

Estrogen is necessary for breast development and for the growth spurt that occurs at puberty. In prepubertal females who undergo HSCT, the recovery of ovarian function may be more likely than in post-pubertal patients, [36], but approximately 70 % will have hypogonadotropic hypogonadism and require estrogen replacement therapy [34]. Failure of progression through puberty is often an indication for the need for estrogen replacement. Patients without breast development who have increased FSH and LH levels should be given supplemental estrogen/progestin. The dose of hormonal replacement will require adjustment with age in order to ensure progression through puberty and cyclic menstruation. Estrogen replacement for post-pubertal females should be initiated three to six months after HSCT. It has been suggested that replacement be stopped for two months at around one year post HSCT to evaluate for ovarian recovery [46].

The incidence of pregnancy is less than 3 % for females who received TBI or busulfan, although there are scattered reports of successful pregnancies following TBI [35, 36]. Most males will also be sterile after TBI. Options for preservation of fertility should be discussed prior to HSCT. For pubertal males, sperm banking should be encouraged. Prior therapy may limit this option for some males. For post-pubertal females, cryopreservation of ovarian tissue or oocytes is currently being done on a research- basis. Gamete preservation is not yet available on a non-research basis. There have been reports of pregnancy from embryos with donated oocytes, with hormonal support [33]. Pregnancies that do occur following TBI are more likely to result in miscarriage, pre-term labor and low birthweight infants [36].

With non-myeloablative conditioning regimens, the endocrine effects, particularly gonadal function, are unknown. Effects may be dependent upon the dose and timing of the agents used.

17.3 Pulmonary

The assessment of the effects of HSCT conditioning on pulmonary function is usually limited by the age of the patient, as very young children cannot perform pulmonary function tests. The spectrum of long-term pulmonary complications differs among patients who received allogeneic vs autologous HSCT. This is due to the effects of chronic GVHD, which may result in changes called bronchiolitis obliterans. Other factors that may impact pulmonary function post HSCT include prior chemotherapies such as bleomycin, TBI during conditioning and thoracic irradiation.

There are three categories of PFT abnormalities: obstructive, restrictive and those that result from a decrease in diffusion capacity. Obstructive abnormalities result in decreased FEV1 and in a decreased FEV1/FVC ratio. These occur as a result of small airway closure or obstruction of expiration. Bronchiolitis obliterans is the most common cause of obstructive abnormalities post HSCT. Radiation, pulmonary infection and pneumonitis may all result in restrictive lung disease, with decreased total lung capacity (TLC) and preserved FEV1/FVC ratio. Decreased DLCO, or diffusion capacity for carbon monoxide, may be a result of an abnormal alveolar–capillary interface. Anemia will result in a low DLCO as well.

Up to 85% of patients will have abnormal PFTs 3–6 months post HSCT, with a restrictive pattern being the most common abnormality [7]. Late abnormalities are often associated with chronic GVHD, although prior aggressive therapy for advanced-stage disease may also have a negative impact on pulmonary function [7]. The most common late abnormality is a decrease in DLCO, followed by restrictive defects [23]. GVHD is associated with the risk of chronic aspiration pneumonia, particularly in patients with esophageal involvement. GVHD is also associated with the risk of bronchiolitis obliterans (BO) in up to 37% [38] of post- HSCT patients, and with the risk of bronchiolitis obliterans organizing pneumonia (BOOP).

Patients with BO do not present with fever, but have complaints of exercise intolerance, cough and wheezing. Chest radiograph may be normal, and PFTs will show obstructive defects. Immunosuppressant agents are usually not therapeutically helpful. Patients with bronchiolitis obliterans organizing pneumonia (BOOP) present with fever, cough, dyspnea and rales. BOOP may be present as early as one month post HSCT, but is more common after three months. In patients suffering from this condition, there is a patchy distribution of granulation tissue plugs filling the lumens of airways and extending into the alveoli [11]. BOOP is strongly associated with prior acute or chronic GVHD, as well as prior leukemia [11]. Radiographic findings may include patchy alveolar opacities and asymmetric infiltrates.

In a small study of children who received autologous HSCT, restrictive impairment was found in 20% of patients at 5–10 years [12], but there was stabilization after the first year. Obstructive impairment was rare, but diffusion impairment was found in over 50% of patients at 10 years. TBI was associated with decreased lung volumes.

17.4 Cardiac

Cardiotoxic drugs, particularly the anthracyclines, used for disease treatment prior to HSCT conditioning may increase the risk of cardiotoxicity post HSCT, although most patients are asymptomatic despite changes on ECG and echocardiograms. Factors that may increase the risk of cardiotoxicity include young age at the time of treatment, high-dose cyclophosphamide and chest irradiation. Post-transplant echocardiograms have been reported as normal in most children [25], but some studies have reported decreased systolic function [32]. Exercise testing may be a more sensitive tool for detecting changes in cardiovascular function over time; however, it is limited to patients who are old enough to perform such testing. A retrospective study of serial cardiopulmonary exercise tests noted that despite decreases in all pa-

rameters of exercise performance, both aerobic and physical working capacity increase over time [16]. This study suggests that oxygen extraction becomes more efficient with recovery, and that it may compensate for impaired cardiac ability.

17.5 Renal

Renal toxicity post HSCT may occur as a result of TBI, or as a result of nephrotoxic drugs commonly used, such as cyclosporine or tacrolimus, a history of cisplatin administration or conditioning with carboplatin. A syndrome of nephropathy post HSCT has been described and includes azotemia, anemia and hypertension. This occurs 3–12 months after HSCT and, in its most severe form, resembles hemolytic uremic syndrome.

Patients may benefit from the use of recombinant erythropoietin and anti-hypertension management, but renal dysfunction may continue to deteriorate. Many adult patients experience significant recovery over time, but there is little information regarding the timing of the dysfunction and recovery in children.

17.6 Ocular

Cataract formation and keratoconjunctivitis sicca (dry eye) syndrome are the two most common ocular complications for patients post HSCT. Risk factors for cataracts include: TBI schedule, type of transplant, development of GVHD and prolonged use of steroids. Cataracts are usually posterior subcapsular, in contrast to those seen in older adults, which appear in the central part of the lens. Cataracts are seen in up to 80% of patients who received unfractionated TBI, but are less common in patients receiving fractionated TBI, with incidences of approximately 20% [25]. They may often occur after four years (median, 98 months after fractionated TBI); annual follow-up is, therefore, extremely important. Surgical repair may be necessary for some patients, but this is not commonly required. Clinically significant cataracts are noted only occasionally in patients who received non-TBI regimens, and more often than not, this may be related to corticosteroid exposure.

The incidence of keratoconjunctivitis sicca syndrome reaches 20% fifteen years after stem cell transplantation. The ocular manifestations include reduced tear flow, conjunctivitis, corneal defects and corneal ulcerations. Chronic GVHD is the greatest risk factor, with late-onset keratoconjunctivitis occurring in 40% of patients with chronic GVHD, versus 10% of patients without GVHD. Other risk factors for late-onset keratoconjunctivitis include: female gender, age greater than 20 years, single-dose TBI and the use of methotrexate for GVHD prophylaxis [48].

17.7 Dental

Damage to dentition associated with HSCT is generally the result of irradiation. Side effects that have been reported include disruption in normal enamel development, hypoplasia and microdontia of the crowns of erupted permanent teeth, and thinning and tapering of the roots of erupted permanent molars. Cranial irradiation prior to TBI may further increase the risk of tooth agenesis [50].

Chronic GVHD may result in damage to the oral cavity and salivary glands. A significant reduction in the flow of saliva, as measured by sialometry and salivary gland scintigraphy, have been noted in patients with acute and chronic GVHD. This reduction may persist in patients who received TBI [27]. Decreased salivation and poor oral hygiene post HSCT may increase the risk of dental caries.

17.8 Ototoxicity

Children who receive platinum-based agents prior to, or as part of, the conditioning are at the highest risk for developing hearing loss after transplantation, and more than 80% may experience significant loss [30]. Depending on the chemotherapy history, local or total body irradiation can accentuate hearing loss in children with solid tumors such as neuroblastoma and brain tumors. For patients with neuroblastoma,

hearing loss prior to transplant portends significant hearing loss after a regimen containing high-dose carboplatin [30]. However, even those children who did not have a hearing loss prior to transplant developed hearing loss after receiving carboplatin as a part of the conditioning.

17.9 Bone Mineral Density

There are increasing data on the effects of HSCT upon bone mineral density. Factors that may impact BMD include prior therapy for malignancies, conditioning regimens, lack of physical activity, poor nutrition and post-HSCT therapy with calcineurin inhibitors and corticosteroids. Post-HSCT hypogonadism may also impact bone mineral density. One recent study showed nadir BMD at month 24 for total body and femoral neck [37] in patients who received allogeneic HSCT. BMD continuously declined at the femoral neck sites. Steroids and cyclosporine use, as well as loss of muscle mass, were associated with low BMD. Only very young patients were protected from bone loss. The relationship between BMD changes and fracture risk is not yet established post HSCT.

Osteochondromas are benign bone tumors that consist of projecting mature bone capped by cartilage. Radiation, including TBI, is generally believed to be the cause of osteochondromas. The pathogenesis of these bone tumors is not well understood. The mean latent time from HSCT to the development of osteochondromas was 4.6 years in one study [44], and younger patients (less than five years old) were at increased risk. Of patients less than five years old at the time of TBI, an osteochondroma occurred in 24% [44]. There is a low malignant potential for these tumors, but they do cause a great deal of anxiety when found and can be painful depending on the location.

17.10 Neuropsychologic

Conditioning regimens contain high drug doses and radiation that may be neurotoxic and result in neuropsychologic sequelae. Agents that are associated with neurotoxicity include busulfan, thiotepa and melphalan. Although much is known about the neuropsychologic effects of cranial irradiation for leukemias and brain tumors, there is relatively little known about the outcomes of children post HSCT. Doses of radiation used for central nervous system leukemia are between 1800–2400 cGy, and for brain tumors up to 6000 cGy. Although the total doses used for TBI are much lower (1000–1400 cGy) than used in other situations, the biologic effect is enhanced by the larger dose fractions. Children of different ages may be impacted by TBI in different ways; children under three years old may be at higher risk than older children, and they may experience declines in cognition and school performance [31, 42]. Other small studies have suggested that no cognitive impairment occurs even with TBI [22, 39]. Chemotherapy-only regimens rarely show a detrimental effect of upon cognitive function, although hearing loss in children with neuroblastoma may have a significant effect on verbal IQ [28].

17.11 Other Issues Post HSCT

17.11.1 Chronic GVHD

Chronic GVHD continues to be a significant problem following allogeneic HSCT. The incidence of chronic GVHD is lower in children, compared with adults. Chronic GVHD occurs in approximately 20% of children who receive matched sibling donor transplants, and 40% who received unrelated donor bone marrow. The use of mobilized peripheral stem cells increases the risk of chronic GVHD. The incidence of chronic GVHD in cord blood recipients is still being defined. The most significant risk factor is prior acute GVHD; other risk factors include older age, a female multiparous donor or an unrelated or partially-matched related donor. Chronic GVHD may be classified as progressive, evolving from acute GVHD, quiescent, following a period of resolution from acute GVHD, or de novo, in patients who had no prior acute GVHD. Chronic GVHD is associated with a decrease in leukemic relapse risk, although it comes at a price with a significant impact upon quality of life and increase in transplant-related mortality. Classification of chronic GVHD is difficult and currently undergo-

Table 17.3. Chronic GVHD: clinical features

Organ	Features	Symptoms
Skin	Dyspigmentation, lichen planus, atrophy, scleroderma Alopecia, onychodystrophy, sweat gland loss	Pruritus, erythema, inflexibility, heat insensitivity
Liver	Elevated transaminases, alkaline phosphatase, bilirubin	
Oral cavity	Lichen planus, erythema, ulcers, xerostomia, fibrosis	Pain, dry mouth
Eyes	Sicca syndrome	Dry eyes, photophobia
GI	Esophageal strictures, abnormal motility, malabsorption	Dysphagia, cramping, diarrhea, anorexia, weight loss
Pulmonary	Obstructive pattern, bronchiolitis obliterans, bronchiectasis	Cough, dyspnea, exercise intolerance
Musculoskeletal	Arthritis, joint contractures	Myalgia, stiffness
Genitourinary	Phimosis, vaginal strictures	Pain
Hematologic	Thrombocytopenia, eosinophilia	
Immunologic	Hypogammaglobulinemia, decreased T lymphocytes	Increased infectious risks, particularly strep. pneumococcus

ing revision. Most centers, however, currently classify chronic GVHD as "limited" or "extensive." Limited GVHD refers to localized skin involvement with or without hepatic test abnormalities, and extensive refers to generalized skin involvement or involvement of other organs. Poor prognostic factors include progressive onset, platelets $<100\times10^9$/ml and poor performance status.

The etiology of chronic GVHD is not well understood. Many manifestations resemble autoimmune diseases, with loss of normal T-cell regulation considered to be a possible cause.

17.11.2 Clinical Features

The manifestations of chronic GVHD usually occur after day 100 post HSCT. Almost all patients are diagnosed within the first year post HSCT. The effects of chronic GVHD vary, depending upon location and severity of involvement (Table 17.3). Skin is the most commonly affected organ, with over 50% of patients with chronic GVHD having some degree of skin involvement. Diagnosis may be confirmed with a biopsy if other diagnoses (particularly infection) are being considered.

17.11.3 Evaluation and Therapy

Most patients will be in the care of their primary oncologists when chronic GVHD is diagnosed. It is important that physicians be aware of the subtle manifestations and that particular care be taken during the physical examination of the skin, oral mucosa, nails, range of motion and lungs. Infection is the greatest risk to these patients. To control or improve the symptoms of chronic GVHD, at least two immunosuppressant drugs are necessary in order to impede the immune recovery already compromised by chronic GVHD-induced immune dysregulation. Preventive measures are listed in Table 17.4.

Therapy for chronic GVHD generally includes a regimen with prednisone and a calcineurin inhibitor, such as cyclosporine or tacrolimus. An alternate day regimen of prednisone and the calcineurin inhibitor may help decrease the side effects of both, while retaining disease control. Therapy and weaning should be done in conjunction with the transplant center, and close communication is required. For patients who do not respond to this regimen, other drugs may be added with the guidance of the transplant team.

Table 17.4. Infectious risks and prophylaxis

Pneumocystis carinii	Sulfamethoxazole/ trimethoprim or dapsone
Varicella/H. Zoster	Acyclovir
Encapsulated organisms	Daily penicillin or erythromycin, Prevnar, Pneumovax
Hypogammaglobulinemia (IgG <500 g/L)	Monthly intravenous immunoglobulin
Candida albicans	Fluconazole

17.12 Immune Reconstitution and Re-Immunization

The duration and severity of immunodeficiency post HSCT depends upon several factors, including type and manipulation of the stem cells, graft vs host disease and the age of the recipient. There are significant differences in the kinetics of immune reconstitution between autologous and allogeneic HSCT. This is also impacted by graft manipulation, such as CD34+ selection or T-lymphocyte depletion. NK cells generally recover within the first few months, and may be elevated for up to two years, but recovery of B-, and in particular, T-lymphocytes takes much longer. Children may have more active thymic tissue than adults, which may be the reason why their immune reconstitution appears to be faster than that seen in adults [41]. In general, most patients will have complete immune reconstitution by two years, unless they have chronic GVHD. Chronic GVHD has an adverse effect upon reconstitution, not only due to the effects of immune suppressive drugs required for its control, but also due to the aberrant T-cell function of the GVHD process itself. In the absence of GVHD, recipients of T- replete allogeneic or autologous grafts will have near normal CD3+ cells three months post HSCT. However, CD4+ is decreased during this period, with higher proportions of CD8+ cells. With chronic GVHD, this inverted CD4+/CD8+ ratio persists for up to a year or longer. However, even recipients of autologous HSCT may experience delayed T-cell reconstitution, and up to one-third may have sub-normal CD4+ cells at one year [20]. In the absence of GVHD, the response to mitogens usually returns to normal within several months, as does the production of IgG and IgM. IgA may take longer to recover. The delay in immune recovery may be responsible for infections, including *Pneumocystis carinii* pneumonia, varicella, CMV and EBV.

17.12.1 Reimmunization After HSCT

Most recipients of HSCT will lose their immunity to the vaccinations they have received prior to HSCT. In addition, patients with chronic GVHD are at risk for infections with streptococcus pneumoniae and H. influenzae. Therefore, re-immunization of HSCT recipients is essential. A recent guideline was published detailing the rationale for vaccination schedules [40]. In general, at 12 months post HSCT in patients without chronic GVHD, vaccinations can be given on a schedule similar to that used with normal infants; however, the 23-valent pneumococcal polysaccharide vaccine may not result in adequate antibody response, even when administration is delayed to 12 months [14]. The 7-valent pneumococcal conjugate vaccine is linked to a protein carrier and may enhance immune response. A recent study showed early immunization with this 7-valent vaccine resulted in protection in most patients. The authors of the study suggest an administration schedule of 3, 6 and 12 months [26]. Vaccines that are contraindicated include BCG, oral polio and varicella (see Table 17.5).

17.13 Secondary Malignancies

Patients are at increased risk for secondary malignancies following HSCT. This is the consequence of many factors, including conditioning with high doses of chemotherapy, radiation therapy and prior therapy. In one large study, the solid cancer risk increased to an estimated 11% at 15 years post HSCT; patients who were under 5–10 years of age at HSCT had the highest risk [9, 43]. Both chronic GVHD and irradiation may play a role in the development of secondary cancers [4]. The most common types of cancers include liver, oral cavity, thyroid and cervical. Squa-

Table 17.5. Recommended vaccinations for allogeneic and autologous hematopoietic stem cell transplant recipients[a]

Time after HSCT	
Inactivated vaccine or toxoid	
Diphtheria, tetanus, pertussis	
Children aged <7 years	DTP or DT at 12, 14, and 24 months
Children aged ≥7 years	Td at 12, 14, and 24 months
Inactivated polio	12, 14, and 24 months
Hepatitis B	12, 14, and 24 months
7-Valent pneumococcal	
23-Valent pneumococcal polysaccharide (PPV23)	12 and 24 months
Influenza	Seasonal administration ≥ 6 months after HSCT
Meningococcal	Patients at risk
Live-attenuated vaccine	
Measles–mumps–rubella	24 months
Varicella vaccine	Contraindicated for HSCT recipients

Begin immunizations when patients with chronic GVHD are off immunosuppression for minimum 6 months.
DT = diphtheria toxoid-tetanus toxoid; DTP = diphtheria toxoid-tetanus toxoid-pertussis vaccine; HSCT = hematopoietic stem cell transplant; Td = tetanus = diphtheria toxoid

mous cell cancer of the skin and oral cavity are increased in patients with chronic GVHD [9]. There are a few studies that support an increased risk of secondary cancers in children who received non-TBI regimens, but no large studies have been done.

References

1. Adan L, Lanversin M et al. (1997) Growth after bone marrow transplantation in young children conditioned with chemotherapy alone. Bone Marrow Transplant 19:253–256
2. Afify Z, Shaw P et al. (2000) Growth and endocrine function in children with acute myeloid leukaemia after bone marrow transplantation using busulfan/cyclophosphamide. Bone Marrow Transplant 25:1087–1092
3. Bakker B, Oostdijk W et al. (2004) Disturbances of growth and endocrine function after busulphan-based conditioning for hematopoietic stem cell transplantation during infancy and childhood. Bone Marrow Transplant 33:1049–1056
4. Bhatia S, Louie A et al. (2001) Solid cancers after bone marrow transplantation. J Clin Oncol 19:464–471
5. Boulad F, Bromley M et al. (1995) Thyroid dysfunction following bone marrow transplantation using hyperfractionated radiation. Bone Marrow Transplant 15:71–76
6. Brauner R, Adan L et al. (1997) Contribution of growth hormone deficiency to the growth failure that follows bone marrow transplantation. J Pediatr 130:785–792
7. Cerveri I, Fulgoni P et al. (2001) Lung function abnormalities after bone marrow transplantation in children: has the trend recently changed? Chest 120:1900–1906
8. Cohen A, Rovelli A et al. (1999) Final height of patients who underwent bone marrow transplantation for hematological disorders during childhood: a study by the Working Party for Late Effects-EBMT. Blood 93:4109–4115
9. Curtis R, Rowlings P et al. (1997) Solid cancers after bone marrow transplantation. N Engl J Med 336:897–904
10. Fletcher B, Crom D et al. (1994) Radiation-induced bone abnormalities after bone marrow transplantation for childhood leukemia. Radiology 191:231–235
11. Fredudenberger T, Madtes D et al. (2003) Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. Blood 102: 3822–3828
12. Frisk P, Arvidson J et al. (2004) Pulmonary function after autologous bone marrow transplantation in children: a long-term prospective study. Bone Marrow Transplant 33:645–650
13. Giogiani G, Bozzola M et al. (1995) Role of busulfan and total body irradiation on growth of prepubertal children receiving bone marrow transplantation and results of treatment with recombinant human growth hormone. Blood 86:825–831
14. Guinan E, Molrine D et al. (1994) Polysaccharide conjugate vaccine responses in bone marrow transplant patients. Transplant 57:677–684

15. Hoffmeister P, Storer B et al. (2004) Diabetes mellitus in long-term survivors of pediatric hematopoietic stem cell transplantation. J Pediatr Hematol Oncol 26:81–90
16. Hogarty A, Leahey A et al. (2000) Longitudinal evaluation of cardiopulmonary performance during exercise after bone marrow transplantation in children. J Pediatr 136: 311–317
17. Holm K, Nysom K et al. (1996) Growth, growth hormone and final height after BMT. Possible recovery of irradiation-induced growth hormone insufficiency. Bone Marrow Transplant 18:163–170
18. Hovi L, Saarinen-Pihkala U et al. (1999) Growth in children with poor-risk neuroblastoma after regimens with or without total body irradiation in preparation for autologous bone marrow transplantation. Bone Marrow Transplant 24:1131–1136
19. Huma Z, Boulad F et al. (1995) Growth in children after bone marrow transplantation for acute leukemia. Blood 86:819–824
20. Kamani N, Kattamis A et al. (2000) Immune reconstitution after autologous purged bone marrow transplantation in children. J Pediatr Hematol Oncol 22:13–19
21. Katsanis E, Shapiro R et al. (1990) Thyroid dysfunction following bone marrow transplantation: long term follow-up of 80 pediatric patients. Bone Marrow Transplant 5:335–340
22. Kramer J, Crittenden M et al. (1992) A prospective study of cognitive functioning following low-dose cranial radiation for bone marrow transplantation. Pediatrics 90:447–450
23. Marras T, Szalai J et al. (2002) Pulmonary function abnormalities after allogeneic marrow transplantation: a systematic review and assessment of an existing predictive instrument. Bone Marrow Transplant 30:599–607
24. Mehta J, Powles R et al. (1997) Outcome of acute leukemia relapsing after bone marrow transplantation: utility of second transplants and adoptive immunotherapy. Bone Marrow Transplant 19:709–719
25. Michel G, Societ S et al. (1997) Late effects of allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: the impact of conditioning regimen without total-body irradiation – a report from the Societe Francasie de Greffe de Moelle. J Clin Oncol 15:2238–2246
26. Molrine D, Antin J et al. (2003) Donor immunization with pneumococcal conjugate vaccine and early protective antibody responses following allogeneic hematopoietic cell transplantation. Blood 101:831–836
27. Nagler R, Marmary Y et al. (1996) Major salivary gland dysfunction in human acute and chronic graft-versus-host disease (GVHD). Bone Marrow Transplant 17:219–224
28. Notteghem P, Soler C et al. (2003) Neuropsychological outcome in long-term survivors of a childhood extracranial solid tumor who have undergone autologous bone marrow transplantation. Bone Marrow Transplant 31:599–606
29. Olshan J, Willi S et al. (1993) Growth hormone function and treatment following bone marrow transplant for neuroblastoma. Bone Marrow Transplant 12:381–385
30. Parsons S, Neault M et al. (1998) Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. Bone Marrow Transplant 22:669–674
31. Philpps S, Dunavant M et al. (2000) Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. J Clin Oncol 18:1004–1011
32. Pihkala J, Saarinen U et al. (1994) Effects of bone marrow transplantation on myocardial function in children. Bone Marrow Transplant 13:149–155
33. Rio B, Letur-Konirsch H et al. (1994) Full term pregnancy with embryos from donated oocytes in a 36=year-old woman allografted for chronic myeloid leukemia. Bone Marrow Transplant 13:487–488
34. Sanders J (1986) Growth and development following marrow transplantation for leukemia. Blood 68:1129–1135
35. Sanders J, Buckner C et al. (1988) Ovarian function following marrow transplantation for aplastic anemia or leukemia. J Clin Oncol 6:813–818
36. Sanders J, Hawley J et al. (1996) Pregnancies following high dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 87:3045–3052
37. Schulte C, Beelen D (2004) Bone loss following hematopoietic stem cell transplantation in: a long-term follow-up. Blood 103:3635–3643
38. Schultz K, Green G et al. (1994) Obstructive lung disease in children after allogeneic bone marrow transplantation. Blood 84:212–220
39. Simms S, Kazak A et al. (1998) Neuropsychological outcome of children undergoing bone marrow transplantation. Bone Marrow Transplant 22:181–184
40. Singhal S, Mehta J (1999) Reimmunization after blood or marrow stem cell transplantation. Bone Marrow Transplant 23:637–646
41. Small T, Papadopoulos E et al. (1999) Comparison of immune reconstitution after unrelated and related T-cell-depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. Blood 93:467–480
42. Smedler A, Bolme P (1995) Neuropsychological deficits in very young bone marrow transplant recipients. Acta Paediatr 84:429–433
43. Socie G, Curtis R et al. (2000) New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol 18:348–357
44. Taitaz J, Cohn R et al. (2003) Osteochondroma after total body irradiation: An age-related complication. Pediatr Blood Cancer 42:225–229
45. Taskinen M, Saarinen-Pihkala U et al. (2000) Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet 356:993–997

46. Thibaud E, Rodriguez-Macias K et al. (1998) Ovarian function after bone marrow transplantation during childhood. Bone Marrow Transplant 21:287–290
47. Thomas B et al. (1993) Endocrine function following single fraction and fractionated total body irradiation for bone marrow transplantation in childhood. Acta Endocrinol 128: 508–512
48. Ticelli et al. (1996) nnn
49. Toubert E, Socie G et al. (1997) Short-and long-term follow-up of thyroid dysfunction after allogeneic bone marrow transplantation without the use of preparative total body irradiation. Br J Haematol 98:453–457
50. Uderzo C, Fraschini D et al. (1997) Long-term effects of bone marrow transplantation on dental status in children with leukemia. Bone Marrow Transplant 20:865–869
51. Urban C, Schwingshandl J et al. (1988) Endocrine function after bone marrow transplantation without the use of preparative total body irradiation. Bone Marrow Transplant 3:291–296
52. Wingard J, Plotnick L et al. (1992) Growth in children after bone marrow transplantation: Busulfan plus cyclophosphamide versus cyclophosphamide plus total body irradiation. Blood 79:1068–1073

Second Malignancies Following Treatment for Childhood Cancer

Barbara Anne Hieb · Susan K. Ogle · Anna T. Meadows

Contents

18.1 Introduction

Survivors of pediatric cancer have a greater risk of developing a secondary cancer than age-matched individuals in the general population [42]. In order to provide focused medical follow-up care to this ever-growing population of survivors, it is important to understand the relationships between host characteristics, cancer therapy and the subsequent development of secondary malignant neoplasms (SMNs). Information regarding the influence of individual characteristics, the specific cancer diagnosis and the initial cancer therapy in the development of SMN continues to emerge in the literature, but our knowledge is constrained by the limited follow-up period of the existing cohort of survivors, namely 25–30 years. Once large enough numbers of survivors arrive at the fourth and fifth decades of life, we will begin to learn how the normal aging processes and the "natural" increase of cancer in the general population impact the development of SMNs following childhood cancer.

Large cohorts of survivors of childhood cancer have been studied during the past 30 years in an effort to estimate the incidence of, and understand the risk factors for, the development of long-term effects of disease and treatment, including SMNs. In the most recently published data from the Childhood Cancer Survivor Study (CCSS), Neglia et al. reported that 298 of approximately 13,000 five-year survivors developed 314 SMNs [42]. The estimated cumulative incidence of developing cancer following a primary cancer diagnosis was 3.2 % at 20-year follow-up. In a recent updated analysis, Friedman et al. estimated the cumulative incidence of developing cancer following a primary cancer diagnosis as 5.2 % at 20-year

follow-up [16]. Compared with an earlier LESG report, which estimated the cumulative risk to be 3% (10-fold greater than that of the general population), their data indicates that the risk for SMN continues to rise as survivors of childhood cancer age [38].

The CCSS has also analyzed the mortality of this relatively large cohort of survivors [39]. Of the 1,727 five-year survivors who subsequently died and for whom death certificates were reviewed, the leading cause of death was recurrence of primary disease in 67% of patients. Death was attributable to treatment-related causes in 21%, and, of these, the most common cause was SMNs, occurring in 12.7%. Exposure to radiation therapy was cited as the most frequent predisposing factor, with fewer cases attributable to chemotherapy or genetic predisposition. Specific types of SMNs vary with the cancer diagnosis, as well as with the treatment and time from the initial diagnosis. In this chapter, we focus on these risk factors – namely, radiation, chemotherapy, bone marrow transplantation and genetic predisposition. We will conclude with comments regarding the importance of organized, structured survivorship programs.

18.2 Radiation

Radiation therapy is a major cause of secondary cancers [23]. Eighty to ninety percent of SMNs following radiation therapy occur within the radiation field, with an overall median latency of at least 10 years, although no plateau has been reached in the published studies. Those occurring within the radiation field are considered attributable to the radiation. Others may be related to genetic risk factors, other treatment factors or chance. An increase in risk may also be attributed to an interaction between host characteristics and environmental exposure [23].

The first evidence that ionizing radiation was carcinogenic came just seven years after the discovery of X-rays, with the high incidence of skin cancer on the hands and upper extremities of radiologic workers who had been exposed to relatively high doses [26]. Since then, an increased incidence of cancer has been associated with exposure to ionizing radiation as a result of the atomic bombs dropped on Japan, scalp irradiation to treat tinea capitis in children and the treatment of cancer [25, 50].

Mutations produced by radiation primarily affect dividing cells and lead to clones of once-hit cells. Radiation can also provide a second event in those with a preexisting abnormality (or "hit"), as in the case of genetic retinoblastoma [62]. Tissues are not equally sensitive to radiation. The initial damage to individual cells caused by radiation is evidently subject to a number of additional host factors, including levels of repair enzymes, rate of cell proliferation, endocrine function and immune competence. Thus, the "second hit" needed to promote the induction of a malignancy occurs after a complex interaction between many factors. It seems logical to conclude that tissues that are actively proliferating, such as bones and soft tissues, and the breast of peripubertal females, are more likely to develop expanded mutated clones that are susceptible to additional hits along the pathway to cancer. In contrast, epithelial neoplasms, such as those of lung and gastrointestinal tract, may take many years to develop, since the majority of epithelial cells are end-stage cells without the ability to divide [40]. Cells capable of division in viscera1 organs usually divide to produce only one undifferentiated cell. SMNs from these cell types (e.g. cells of the lungs, gastrointestinal tract and genitourinary tract) in childhood cancer survivors genera1ly occur following latent periods that are longer than those of sarcomas and well into adulthood, but earlier than the usual ages at which people generally contract epithelial neoplasms [2, 5, 38]. There are still too few childhood cancer survivors who have lived long enough to estimate the excess in epithelial SMNs that is expected to occur.

Risk according to radiation schedule has not yet been quantified. However, it may be that increasing the number of fractions produces more mutations because active cells are hit more often. For a given dose of radiation, megavoltage is less oncogenic than orthovoltage because bone absorption is lower with megavoltage. Breast cancer in females previously treated with chest irradiation for Hodgkin's disease, bone or soft tissue sarcomas following radiation for Ewing's sarcoma, thyroid carcinomas following radiation in early childhood and SMNs following radia-

tion in patients with genetically determined disorders, such as genetic retinoblastoma, are the most common radiation-induced secondary malignancies. These cancers will be the focus of the remainder of this section.

18.2.1 Breast Cancer

Radiation to the breast tissue may induce secondary breast cancers. Although the risk is not isolated to those with HD, SMNs are recognized as a leading cause of death in long-term survivors of HD, with breast cancer representing the most frequent solid tumor among such women [4, 57, 60]. Radiation exposure to the breast between the ages of 10–30 years imparts the greatest risk of developing secondary breast cancer. During puberty, the breast undergoes rapid growth and differentiation secondary to a surge in pituitary hormones and the resultant increase in estrogen. Hormonal stimulation of proliferating tissue may potentiate the risk of developing subsequent breast cancer. The role of genetic predisposition is less clear. It has been speculated that genetic predisposition could accelerate the tumorigenic process by providing the initiating event, as is known to occur for renal cancer in rats that carry the tuberous sclerosis 2 gene [22].

Breast cancer was the most frequent SMN in the CCSS cohort of 13,581 long-term survivors of pediatric cancer (N=60), and 65% of the SMNs occurred in female survivors of Hodgkin's disease [42]. In another report of SMNs following treatment for Hodgkin's disease between 1955 and 1986, breast cancer was the most common of the 212 SMNs, with a standardized incidence ration (SIR) of 56.7 [5]. This report updated the results of an earlier study of 1,380 patients who were less than 16 years of age when diagnosed with HD. By extending the latent period from 11.4 years to 17 years, the number of SMNs increased from 109 to 212 in 173 individuals. Breast cancer was the most common SMN, with 42 incidences occurring in 30 women in a median time of 18 years (4.3 – 28). This represented a 57-fold risk, compared with the general population. The cumulative probability of developing breast cancer by age 40 was 14%, and the probability by age 45 was 20% [5].

Another international study of 3,817 women diagnosed with HD before age 30 reported that 105 developed breast cancer at a mean of 18 years after diagnosis and at a mean age of 40.7 years [57]. Increased risk of breast cancer was observed in patients who had received more than 40Gy to the chest, and there was a dose–response relationship. Overall, women who became menopausal before age 40, either as a result of radiation or alkylating agent chemotherapy, experienced significant reductions in risk, compared with women who retained ovarian function. Among those patients who did not become menopausal, the number of alkylating agent cycles received was inversely related to the risk of breast cancer, also implying decreased risk when ovarian function is lost. Regarding the possible role of genetic susceptibility in survivors of HD, Nichols et al. found that TP53, BRCA1 or BRCA2 were not frequently mutated in a cohort who had developed SMNs [44].

Many reports have documented that the risk of breast cancer following chest irradiation persists for more than 25 years afterward; however, more than 40% of females who were treated for Hodgkin's disease prior to the age of 30 were not aware of their increased risk [10]. This underscores the continued need for ongoing patient education and public awareness. Although there are limitations of mammography in young women, including hyper-density and radiosensitivity of a young breast, it has been shown to be technically possible and may be successful in detecting breast cancer following radiation exposure. Therefore, it is recommended that females who have received previous chest irradiation begin yearly mammograms beginning 8 years post-radiation, or at age 25 [28]. In addition, they should be instructed to perform monthly breast self-examinations and have an annual clinical breast exam starting at puberty. Lastly, because hormone replacement therapy has been shown to influence the risk of breast cancer, surveillance is especially critical when recommending HRT [28].

18.2.2 Other Radiation-Associated SMNs

18.2.2.1 Skin Cancer

Both non-melanoma (NM) and malignant melanoma skin cancer (MMSC) are known to increase following ionizing radiation, with the former being more prevalent than the latter [19, 41, 47]. Of the two histologic types of NMSC, the risk of basal cell carcinoma is increased following ionizing radiation, while that of squamous cell carcinoma is not increased [26]. To facilitate early detection and the removal of suspicious lesions, patients who have been exposed to ionizing radiation may benefit from an annual skin examination performed by a trained dermatologist.

18.2.2.2 Thyroid Cancer

The thyroid gland is one of the most sensitive organs to the carcinogenic effects of ionizing radiation. Although radiation-induced thyroid cancer is a frequently reported SMN, it is rarely fatal. Thyroid SMNs range from well-differentiated, highly curable papillary and follicular carcinomas to poorly differentiated, rapidly fatal anaplastic carcinoma, with the former being the most common [24]. Papillary carcinoma accounts for 75–90% of all radiation-induced thyroid SMNs in survivors of childhood cancer. There is a striking increased risk for young children exposed to ionizing radiation, as shown by both the atomic bomb experience and in studies of children who were less than five years of age at the time of exposure. In general, children younger than 10 years are at the greatest risk [53, 59]. This has been attributed to the known age-related changes in cell proliferation with the thyroid gland. The younger the child at the time of exposure, the more actively dividing are the thyroid cells and the greater the potential for an active growth phase following therapy. Females in the general population are three times more likely to develop a primary thyroid cancer; a gender difference that has also been shown in those previously exposed to radiation. Thyroid SMNs following radiation therapy have been shown to increase linearly with increasing doses of radiation, with a flattening of the curve at doses greater than 30Gy [53]. This finding may result from inhibition of cellular proliferation after high-dose radiation that prevents the development of an expanded malignant clone.

18.2.2.3 Sarcomas of Bone

Bone sarcomas were the most common SMN reported in a childhood cancer survivor cohort treated between 1940 and 1983 in Great Britain. The overall cumulative risk was approximately 1% within the 20-year period following the original diagnosis [21]. Patients who have survived Ewing's sarcoma appear to have a cumulative risk between 7–22% of developing a second bone tumor by 20 years, depending on the cohort studied [14]. Radiation has been implicated as the major predisposing factor, with the risk increasing substantially with increased doses, especially at doses ≥60Gy [11, 32]. Because this dose has not commonly been used during the past two decades for Ewing's sarcoma, the risk should be lower in patients treated during this period. There is also evidence that exposure to the highest doses of radiation (i.e. doses greater than 80Gy – which is not used in any current pediatric regimen) does not carry an excess risk. Presumably, this is secondary to the "cell kill" phenomenon, in which cells with a potential for malignant transformation are killed by the high dose radiation [58]. At the other end of the spectrum, patients exposed to less than 10Gy have no increased risk, or a very small increased risk. The finding by some that alkylating agents, especially cyclophosphamide, both increase the risk of a secondary bone sarcoma, independent of radiation exposure, and decrease the interval between treatment and the development of an SMN needs to be confirmed [43, 58]. The role of a genetic predisposition combined with therapeutic exposure is not yet fully understood, except in the case of heritable retinoblastoma, where the cumulative risk of SMN, most commonly bone and soft tissue sarcoma, ranges from 10–50%, – or more than 400 times that expected in the general population [62]. Since children with Neurofibromatosis 1 are prone to the development of primary and secondary sarcomas, radiation should be used only as necessary to effect cure. Careful surveillance of survivors who required radiation is indicated [34, 38].

18.2.2.4 Secondary CNS Tumors

Secondary CNS tumors following radiation therapy for children with ALL have been reported by many groups [41, 61]. In 1999, Relling et al. reported an additional relationship between these neoplasms and antimetabolite therapy. During an 8-year period, they observed a cumulative incidence of ~12.3% for patients receiving more intensive anti-metabolite therapy, i.e. mercaptopurine at 75mg/m2 before and during cranial irradiation, with a higher risk (43%) in patients with thiopurine methyltransferase (TPMT) deficiency [49]. TPMT is an enzyme that regulates the conversion of thiopurine to thioguanine nucleotides and, thus, determines its cytotoxic effect on malignant cells. Since approximately 0.33% of Caucasian individuals are completely deficient in, or have a low level of, TPMT activity, whereas approximately 10% have an intermediate level, the high incidence of tumors in Relling's report is likely attributable to the high frequency of TPMT deficiency in the cohort. In contrast, Loning et al. found a 15-year cumulative incidence of 1.3% following less intense antimetabolite therapy, i.e. mercaptopurine at 50–60mg/m2, with both groups having received similar radiation (doses ranging from 12–30Gy, with a median of 18Gy) [36]. These investigators suggest a polymorphic mechanism with respect to the enzymatic activity of TPMT on the incidence of secondary CNS neoplasms. Investigations are currently underway to evaluate the association between the variability in the activity of TPMT, antimetabolite doses during cranial irradiation and subsequent CNS tumors.

18.3 Chemotherapy and Secondary Leukemia

For more than two decades, secondary leukemia has been linked to alkylating agent therapy [13]. The risk of developing secondary leukemia following treatment with alkylating agents appears to be dose and agent-dependent. MOPP chemotherapy (mechlorethamine, vincristine, prednisone and procarbazine) has resulted in cumulative frequencies of secondary leukemia ranging from 3–5% at 7 years, and reaching a plateau of 8% at about 10 years [45]. Substituting cyclophosphamide for mechlorethamine has resulted in a reduced risk [51]. Both mechlorethamine and procarbazine are among the most potent leukemogens, with cyclophosphamide probably the least leukemogenic of the alkylators used in pediatrics [9]. Alkylating agent-related secondary leukemia is generally associated with abnormalities, usually deletions, of chromosomes 5 and 7.

Secondary leukemias are also associated with epipodophyllotoxins, which are topoisomerase II inhibitors [13, 48]. These leukemias are generally associated with a characteristic abnormality involving 11q23 at the MLL gene breakpoint. Secondary leukemia following exposure to epipodophyllotoxins has been linked to the schedule of administration, with the risk being far greater in patients receiving this drug once- or twice-weekly, compared with those receiving the more frequently-used schedules of 3–5 doses per week, given at 3–5 week intervals [54]. Perhaps the frequency of administration determines the ability of any given cell to repair DNA damage before it is subjected to further damage from another dose. Although controversy still exists regarding schedule and dose, a recent report from the French Society of Pediatric Oncology found that risk increased regularly with increasing cumulative doses, the highest risk being in those patients who received >6g/m2 [33]. This cohort was 93 times more likely to develop secondary leukemia than patients who received no epipodophyllotoxins. To further complicate risk assessment, the patients who received the higher cumulative doses were also more likely to have received the drug according to one of the following two schedules: 3 days a week for 3 weeks in a row, with one week off, or 21 consecutive days out of 28. In contrast, patients who received this therapy every 3 weeks, and who received <1.2g/m2 or between 1.2–6g/m2 had a relative risk of zero and 3.9, respectively. Although the latter schedule and doses are most commonly used today, surveillance of children who have received potentially 1eukemogenic therapy is nevertheless warranted.

18.4 Bone Marrow Transplant

As the number of survivors of hematopoietic stem cell transplant (SCT) increases, post-transplant malignancies (PTMs) are emerging as a serious long-term complication. There are three main categories of PTM, including solid tumors, hematologic malignancies and post-transplant lymphoproliferative disorder (PTLD) [4]. The etiology is thought to be multi-factorial; some of the risk factors may be similar to those associated with the development of SMNs following standard chemotherapy and radiation without transplant [1, 46]. Hypotheses regarding additional risks include immune deficiency resulting in Epstein-Barr Virus (EBV) -associated B-cell lymphoproliferative disease, total body and/or local irradiation, higher doses of chemotherapy required for myeloablation and interaction with possible genetic predisposition.

The overall cumulative incidence of developing PTM has been reported as 6.9% at 20 years, increasing by about 2% with each successive 5-year follow-up period [1]. Bhatia initially reported that patients who received a SCT have an 11-fold increased risk of developing a PTM, but in a subsequent follow-up report the number of PTMs had tripled during the 7-year period [1, 3].

Children younger than 10 years at the time of SCT appear to have the greatest risk. Socie reported a 36.6-fold excess rate of malignancy in these young children those less than 10 years of age with ALL who receive SCT have an 11% risk of a secondary solid tumor 15 years later [55]. Other studies have reported a 33-fold increased risk, with the incidence ranging from 2.2–6.7% up to 15 years post-transplant [1, 3]. The most common solid tumor following SCT in Bhatia's cohort was malignant melanoma.

In view of the conditioning therapy for SCT, it is not surprising that t- MDS/AML is the most common PTM. The incidence of hematologic PTMs has been reported to range between 3–19.8%, after a minimum follow-up of five years after SCT. This is a 300-fold increased risk, compared with that of the general population. Since 1994 when priming of stem cells with etoposide began, there has been a five-fold increase in the incidence of secondary AML/MDS, compared with the risk in patients who received stem cell transplants prior to 1994 [31].

Post-transplant lymphoproliferative disorder (PTLD) is an uncommon second neoplasm, with an incidence ranging from 1–1.6%. However, it often progresses rapidly and is frequently fatal [3, 9, 18, 55]. The two major etiologic contributors to the complication appear to be immunosuppression after prolonged periods of neutropenia and proliferation of EBV following transplant. Studies have reported an increased risk of developing PTLD in the following situations: use of unrelated or mismatched donors, T-cell depletion of donor marrow, use of antithymocyte globulin (ATG) or monoclonal anti-T cell antibodies for the prophylaxis and treatment of graft versus host disease (GVHD) [9].

18.5 Genetic Predisposition

18.5.1 Retinoblastoma

Retinoblastoma (RB) is often thought of as the paradigm for genetically inherited cancer. RB provides the basis for the two-hit hypothesis of carcinogenesis originally proposed by Knudson in 1971 [30]. Although the genetic form of RB is the most common condition predisposing to second neoplasms, other conditions should also be considered when survivors of childhood cancer are followed (see Table 1 and 2). The *RB1* gene, which was cloned in 1986, is transmitted in an autosomal dominant fashion, with more than 90% penetrance. Knudson studied both the hereditary and non-hereditary form of RB. He proposed that the development of any form of RB is caused by a complementary loss or mutation in both copies of *RB1*. In the case of the genetic form, the initial "hit" is a germinal mutation, usually in the father and, in 80% of cases, with no positive family history. In the case of non-genetic RB, this initial "hit" is sporadic and occurs in a single retinoblast. Both forms, however, require a second "hit," which is always somatic. Survivors of the genetic form of RB have been found to have an increased risk of developing second tumors. The most frequent types are bone and soft tissue sarcomas [58, 62].

Table 16.1. First and second tumours associated with specific risk factors

First tumours	Second tumours	Risk factors
Retinoblastoma	Bone and soft tissue sarcoma, pineal, melanoma, Langerhans cell histiocytosis	Genetic disease; radiation
Wilms' tumour	Bone and soft tissue sarcoma, leukaemia, brain, liver (?)	Radiation
Neuroblastoma	Thyroid, bone and soft tissue sarcoma Other sarcomas of bone and soft tissue	Radiation
Lymphoma	Leukaemia, other lymphoma, sarcoma	Alkylating agents; epipedophyliotoxins; radiation

Table 16.2. Inherited cancer syndromes and associated neoplasms[a]

Syndrome	Primary tumtour	Secondary/associated tumours	Gene
Genetic retinoblastoma	Retinoblastoma	Sarcomas, pineoblastonia, melanoma	*RBI*
Neurofibromatosis type 1	Neurofibromas	Neurofibrosarcoma, AML, JMML, glioma	*NFI*
Neurofibromatosis type 2	Vestibular schwannomas	Meningiomas, astrocytomas, ependymomas	*NF2*
Li-Fraumeni	Sarcomas, breast cancer	Adrenocortical, brain tumours, leukaemia	*p53*
Familial adenomatous polyposis	Colorectal cancer	GI cancer, hepatoblastoma, thyroid, desmoid	*APC*
Gardner's	Colorectal cancer	Hepatoblastoma	*APC*
Turcot's	Colorectal cancer	Medulloblastoma	*APC*
Hereditary nonpolyposis colorectal cancer	Colorectal cancer	Endometrial, ovarian, gastric, pancreatic Cancer	*MSH2/ MLHI*
Familial breast cancer 1	Breast cancer	Ovarian cancer	*BRCAI*
Familial breast cancer 2	Breast cancer	Pancreatic, ovarian cancer	*BRCA2*
Multiple endocrine neoplasia type 1	Pancreatic islet cancer	Parathyroid, thyroid, pituitary cancer	*MEN1*
Multiple endocrine neoplasia type 2A	Medullary thyroid	Parathyroid, pancreas, pheochromocytoma	*RET*
Multiple endocrine neoplasia type 2B	Medullary thyroid	Adrenocortical, ganglion, pheochromocytoma	*RET*
Nevoid basal cell carcinoma (Gorlin's)	Basal cell carcinoma	Medulloblastoma	*PTCH*
Beckwith–Wiedmann	Wilms' tumour	Hepatoblastoma, adrenocortical carcinoma	*?*
Von Hippel–Lindau	Renal clear cell	Brain tumours, pheochromocytoma	*VHL*
Tuberous sclerosis	Renal cancer	Brain tumours	*TSC2*

GI, gastrointestinal; JMML, acute myelogenous leukaemia; AML, acute myelogenous leukaemia
[a] Adapted from Ref. [5].

In 1985, the LESG reported that RB was the most common primary tumor in children who developed SMN [38]. Although bone and soft tissue sarcomas occur following radiation in all individuals, they are considerably more prevalent in survivors of the genetic form of RB, whether or not they have been exposed to irradiation. Osteosarcomas have been found to result from mutations at the *RB1* locus on

chromosome 13q14, a discovery that provides evidence for the claim that sarcomas following hereditary RB have a genetic etiology [17].

While approximately 15% of RB patients have a positive family history, it is known that all patients with bilateral disease, and approximately 10% with unilateral disease, have the genetic form and are, therefore, at increased risk for developing a SMN. The cumulative risk of a second tumor at 50 years of age is 50% for those patients with bilateral disease, compared with only 5% for those with unilateral disease. Furthermore, those patients with the genetic form of RB who received external beam radiation therapy (EBRT) carry an overall risk of 58% for developing a second tumor, compared with 27% of the patients with the genetic form who did not receive EBRT [62].

Children with the genetic form are also at increased risk for the development of intracranial (pineal) neoplasms. This complication, termed "trilateral RB," has been reported to occur prior to the age of 4 years in 5–15% of children with the genetic form [29]. Some investigators considered this a second cancer attributable to radiation, although many cases have occurred in the absence of radiation. [29] There is evidence for a reduction in risk when patients with bilateral disease receive chemotherapy to reduce the size of the intraretinal tumor. [52]. Trilateral RB may thus represent a primary malignancy, rather than treatment-induced malignancy.

It is now possible to offer genetic counseling to patients with bilateral disease or a positive family history, and to offer genetic testing in babies with unilateral disease without a family history who may be carriers of new germline mutations. Newer approaches to the treatment of bilateral disease that use chemotherapy successfully have reduced the need for EBRT and could reduce the long-term complications of therapy [15].

18.5.2 Neurofibromatosis

Neurofibromatosis, Type 1 is an autosomal dominant disorder that primarily affects the development and growth of neural tissues. The gene responsible for NF1 is located on chromosome 17q11.2 [27]. NF is the most common gene predisposing to childhood cancer and is second to RB as the most frequent genetic condition predisposing to SMN. NF patients often develop benign neurofibromas, as well as optic pathway gliomas, astrocytomas, ependymomas, spinal cord tumors, childhood MDS, juvenile chronic myelogenous leukemia, neurofibrosarcomas, rhabdomyosarcomas, hepatocellular cancer and pheochromocytomas [20]. Radiation has been thought to play a role in the etiology of SMNs following therapy for a primary cancer in patients with NF1.

18.5.3 LiFraumeni Syndrome

Li–Fraumeni Syndrome (LFS) is a rare, autosomal-dominant, familial cancer syndrome initially described in 1969 by Li and Fraumeni, who incidentally discovered five pedigrees with a variety of cancer types, including soft tissue sarcomas, early onset breast cancer, acute leukemia, brain tumor and adrenocortical carcinoma [35]. It was 20 years later when Friend et al. identified *p53* mutations in family members with the syndrome, and when Malkin et al. reported that individual members in these LF families developed multiple malignancies, that the *p53* was implicated in the etiology of SMN [17, 37]. TP53 is a transcription factor that regulates growth by exerting anti-proliferative effects via control at G1/S and G2/M checkpoints. In addition, it plays a role in apoptosis and the cellular response to DNA damage.

The family history can be instructive in permitting the clinician to recognize the syndrome when following survivors of childhood cancer for SMN. The classic LFS is one of multiple cancers occurring in several generations of family members, meeting the following criteria: 1) a proband who developed a bone or soft tissue sarcoma before the age of 45, 2) a first degree relative of a proband with a specific cancer before the age of 45, 3) a first or second degree relative of the proband diagnosed with any cancer before the age of 45 years or 4) a first or second degree relative of the proband diagnosed with a sarcoma at any age. Fifty to seventy percent of LFS families will have a germline *p53* mutation, leaving the remaining 30–50% unexplained [56]. Birch et al. have defined a Li–Fraumeni-like (LFL) syndrome in fami-

lies with the above criteria and any first- or second-degree relative with any cancer under the age of 60 years [6]. A negative family history does not rule out this syndrome since individuals can acquire the gene as a new germline mutation. Individuals whose family history is compatible with the LFS require counseling and careful follow-up for SMN.

18.5.4 Other Predisposing Conditions

Children with the genetic forms of embryonal tumors, such as Wilms' tumor and neuroblastoma, including those with a positive family history of bilateral or multifocal disease, may also be at greater risk for the development of SMNs [38]. Multiple neoplasms are also features of the phakomatoses, such as von Hippel–Lindau disease, tuberous sclerosis, the nevoid basal cell carcinoma syndrome, Cowden disease and DNA repair disorders such as familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, Bloom syndrome, Fanconi syndrome and ataxia teleangiectasia [7, 12].

18.6 Summary

Although childhood and adolescent cancers comprise only 2–3% of all cancers, as survival rates continue to increase, now approaching approximately 70–80%, the number of individuals at risk for new neoplasms over an extended lifetime continues to grow. With approximately 12,400 children and adolescents or one in 300 persons under the age of 20 years diagnosed with cancer each year in the U.S., it is estimated that 1 in 450 young adults is a survivor of childhood cancer. One of the most well-recognized obstacles to continued survival for these individuals is the development of SMNs. The challenge for oncologists today is to determine the least toxic therapy, as well as the least amount of therapy, necessary to cure specific types of childhood cancer. In addition to mitigating other long-term toxicities, this effort may reduce the number of SMNs. The recognition that certain survivors – owing to their initial diagnosis, treatment or other factors – are at increased risk for the development of SMNs should prompt practitioners to institute educational practices and specialized surveillance that might lead to early detection, interventions and a more favorable outcome. For education and counseling to be effective it must be ongoing, and it needs to encompass knowledge of risk factors directly related to cancer and its therapy, as well as those that are known to increase cancer risk in the general population. Education focused on good preventive health, such as the importance of eating well, exercising, not smoking and avoiding other risk-taking behaviors, may encourage good follow-up care without needlessly increasing anxiety.

Most adult survivors of childhood cancer will receive healthcare from providers who may not have the knowledge or the understanding of the risks imposed by childhood cancer therapy. Survivors could become their own best advocates, able to convey these risks to providers after they have been appropriately counseled by those knowledgeable of the long-term effects of cancer therapy.

References

1. Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL (2003) New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol 21:1352–1358
2. Bassal M, Kadan-Lottick NS, Neglia JP, Taylor L, Yasui Y, Friedman DL, Mertens AC, Robison LL, Meadows AT (2004) Risk of rare adult-type carcinomas as a subsequent malignant neoplasm in survivors of childhood cancer: the Childhood Cancer Survivor Study. Paper presented at the ASCO, New Orleans, Louisiana, abstr. 8530
3. Bhatia S, Ramsay NK, Steinbuch M, Dusenbery KE, Shapiro RS, Weisdorf DJ, Robison LL, Miller JS, Neglia JP (1996a) Malignant neoplasms following bone marrow transplantation. Blood 87:3633–3639
4. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, Meadows AT (1996b) Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 334:745–751
5. Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, DeLaat C, Fossati-Bellani F, Morgan E, Oberlin O, Reaman G, Ruymann FB, Tersak J, Meadows AT (2003) High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 21:4386–4394

6. Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, Harris M, Jones PH, Binchy A, Crowther D et al (1994) Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 54: 1298–1304
7. Bishop DT, Kolodner RD (1999) DNA repair disorders and multiple primary cancers. In: Neugut AI, Meadows AT, Robinson E (eds) Multiple primary cancers. Lippincott Williams and Wilkins, Philadelphia, pp 197–212
8. Curtis RE, Boice JD Jr, Stovall M, Bernstein L, Greenberg RS, Flannery JT, Schwartz AG, Weyer P, Moloney WC, Hoover RN (1992) Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med 326:1745–1751
9. Curtis RE, Travis LB, Rowlings PA, Socie G, Kingma DW, Banks PM, Jaffe ES, Sale GE, Horowitz MM, Witherspoon RP, Shriner DA, Weisdorf DJ, Kolb HJ, Sullivan KM, Sobocinski KA, Gale RP, Hoover RN, Fraumeni JF Jr, Deeg HJ (1999) Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood 94:2208–2216
10. Diller L, Medeiros Nancarrow C, Shaffer K, Matulonis U, Mauch P, Neuberg D, Tarbell NJ, Litman H, Garber J (2002) Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. J Clin Oncol 20:2085–2091
11. Dunst J, Ahrens S, Paulussen M, Rube C, Winkelmann W, Zoubek A, Harms D, Jurgens H (1998) Second malignancies after treatment for Ewing's sarcoma: a report of the CESS-studies. Int J Radiat Oncol Biol Phys 42:379–384
12. Eng C, Maher ER (1999) Dominant genes and phakomatoses associated with multiple primary cancers. In: Neugut AI, Meadows AT, Robinson E (eds) Multiple primary cancers. Lippincott Williams and Wilkins, Philadelphia, pp 165–195
13. Felix CA (1999) Chemotherapy-related second cancers. In: Neugut AI, Meadows AT, Robinson E (eds) Multiple primary cancers. Lippincott Williams and Wilkins, Philadelphia, Lippincott Williams and Wilkins, Philadelphia, p. 137–164
14. Friedman DL, Meadows AT (1999) Pediatric tumors. p. 235–256
15. Friedman DL, Himelstein B, Shields CL, Shields JA, Needle M, Miller D, Bunin GR, Meadows AT (2000) Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol 18:12–17
16. Friedman DJ, Whitton JA, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL, Neglia JP (2004) Second malignant neoplasms in five-year survivors of childhood cancer: an update from the Childhood Cancer Survivor Study. Paper presented at the ASCO, New Orleans, Louisiana, abstr. 8530
17. Friend SH, Bernards R, Rogelj S, Weinberg RA, Rapaport JM, Albert DM, Dryja TP (1986) A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 323:643–646
18. Gross TG, Steinbuch M, DeFor T, Shapiro RS, McGlave P, Ramsay NK, Wagner JE, Filipovich AH (1999) B cell lymphoproliferative disorders following hematopoietic stem cell transplantation: risk factors, treatment and outcome. Bone Marrow Transplant 23:251–258
19. Guerin S, Dupuy A, Anderson H, Shamsaldin A, Svahn-Tapper G, Moller T, Quiniou E, Garwicz S, Hawkins M, Avril MF, Oberlin O, Chavaudra J, de Vathaire F (2003) Radiation dose as a risk factor for malignant melanoma following childhood cancer. Eur J Cancer 39:2379–2386
20. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278:51–57
21. Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, Marsden HB, Stovall MA (1996) Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst 88:270–278
22. Hino O, Kobayashi E, Hirayama Y, Kobayashi T, Kubo Y, Tsuchiya H, Kikuchi Y, Mitani H (1995) Molecular genetic basis of renal carcinogenesis in the Eker rat model of tuberous sclerosis (Tsc2). Mol Carcinog 14:23–27
23. Inskip PD (1999) Second cancers following radiotherapy. In: Neugut AI, Meadows AT, Robinson E (eds) Multiple primary cancers. Lippincott Williams and Wilkins, Philadelphia, pp 91–136
24. Inskip PD (2001) Thyroid cancer after radiotherapy for childhood cancer. Med Pediatr Oncol 36:568–573
25. Jablon S, Kato H (1970) Childhood cancer in relation to prenatal exposure to atomic-bomb radiation. Lancet 2:1000–1003
26. Karagas MR, McDonald JA, Greenberg ER, Stukel TA, Weiss JE, Baron JA, Stevens MM (1996) Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. J Natl Cancer Inst 88:1848–1853
27. Karnes PS (1998) Neurofibromatosis: a common neurocutaneous disorder. Mayo Clin Proc 73:1071–1076
28. Kaste SC, Hudson MM, Jones DJ, Fryrear R, Greenwald CA, Fleming ID, Pratt CB (1998) Breast masses in women treated for childhood cancer: incidence and screening guidelines. Cancer 82:784–792
29. Kivela T (1999) Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. J Clin Oncol 17:1829–1837
30. Knudson AG, Jr. (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 68: 820–823
31. Krishnan A, Bhatia S, Slovak ML, Arber DA, Niland JC, Nademanee A, Fung H, Bhatia R, Kashyap A, Molina A, O'Donnell MR, Parker PA, Sniecinski I, Snyder DS, Spielberger R, Stein A, Forman SJ (2000) Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood 95:1588–1593

32. Kuttesch JF Jr, Wexler LH, Marcus RB, Fairclough D, Weaver-McClure L, White M, Mao L, Delaney TF, Pratt CB, Horowitz ME, Kun LE (1996) Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas. J Clin Oncol 14:2818–2825
33. Le Deley MC, Leblanc T, Shamsaldin A, Raquin MA, Lacour B, Sommelet D, Chompret A, Cayuela JM, Bayle C, Bernheim A, de Vathaire F, Vassal G, Hill C (2003) Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Societe Francaise d'Oncologie Pediatrique. J Clin Oncol 21:1074–1081
34. Lefkowitz IB, Obringer AC, Meadows AT (1990) Neurofibromatosis and cancer: incidence and management. In: Rubenstein AE, Korf BR (eds) Neurofibromatosis: a handbook for patients, families and health care professionals. Thieme Medical, New York, pp 99–110
35. Li FP, Fraumeni JF J. (1969) Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 71:747–752
36. Loning L, Kaatsch P, Riehm H, Schrappe M (1998) Secondary neoplasms subsequent to acute lymphoblastic leukemia in childhood: experience of the BFM study group. Blood 92:679a
37. Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA et al (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233–1238
38. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RD, Marsden B, Nesbit M, Newton W, Oberlin O, Sallan SG et al (1985) Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol 3:532–538
39. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, Smithson WA, Robison LL (2001) Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 19:3163–3172
40. Moolgavkar SH, Knudson AG Jr (1981) Mutation and cancer: a model for human carcinogenesis. J Natl Cancer Inst 66:1037–1052
41. Neglia JP, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, Sather HN, Hammond GD (1991) Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 325:1330–1336
42. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL (2001) Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 93:618–629
43. Newton WA Jr, Meadows AT, Shimada H, Bunin GR, Vawter GF (1991) Bone sarcomas as second malignant neoplasms following childhood cancer. Cancer 67:193–201
44. Nichols KE, Heath JA, Friedman D, Biegel JA, Ganguly A, Mauch P, Diller L (2003) TP53, BRCA1, and BRCA2 tumor suppressor genes are not commonly mutated in survivors of Hodgkin's disease with second primary neoplasms. J Clin Oncol 21:4505–4509
45. Pedersen-Bjergaard J, Larsen SO (1982) Incidence of acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. N Engl J Med 307:965–971
46. Pedersen-Bjergaard J, Andersen MK, Christiansen DH (2000) Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood 95:3273–3279
47. Perkins JL, Liu Y, Mitby PA, Neglia JP, Hammond S, Stovall M, Meadows AT, Hutchinson R, Dreyer Z, Robison LL, Mertens AC (2003) Non-melanoma skin cancer in survivors of childhood and adolescent cancer: a report from the Childhood cancer Survivor Study. Paper presented at the ASCO, New Orleans, Louisiana, abstr. 8530
48. Pui CH, Ribeiro RC, Hancock ML, Rivera GK, Evans WE, Raimondi SC, Head DR, Behm FG, Mahmoud MH, Sandlund JT et al (1991) Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 325:1682–1687
49. Relling MV, Rubnitz JE, Rivera GK, Boyett JM, Hancock ML, Felix CA, Kun LE, Walter AW, Evans WE, Pui CH (1999) High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet 354:34–39
50. Ron E, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, Katz L (1988) Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 319:1033–1039
51. Schellong G, Riepenhausen M, Creutzig U, Ritter J, Harbott J, Mann G, Gadner H (1997) Low risk of secondary leukemias after chemotherapy without mechlorethamine in childhood Hodgkin's disease. German-Austrian Pediatric Hodgkin's Disease Group. J Clin Oncol 15:2247–2253
52. Shields CL, Meadows AT, Shields JA, Carvalho C, Smith AF (2001) Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). Arch Ophthalmol 119:1269–1272
53. Sigurdson A, Ronckers CM, Mertens AC et al (2004) Second Primary Thyroid Cancer After First Childhood Malignancy: a report from the Childhood Cancer Survivor Study. Paper presented at the Epidemiologisch Congress, Leiden
54. Smith MA, Rubinstein L, Anderson JR, Arthur D, Catalano PJ, Freidlin B, Heyn R, Khayat A, Krailo M, Land VJ, Miser J, Shuster J, Vena D (1999) Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. J Clin Oncol 17:569–577
55. Socie G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, Sullivan KM, Rowlings PA, Kingma DW, Banks PM, Travis WD, Witherspoon RP, Sanders J, Jaffe ES, Horowitz MM (2000) New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol 18:348–357

56. Toguchida J, Yamaguchi T, Dayton SH, Beauchamp RL, Herrera GE, Ishizaki K, Yamamuro T, Meyers PA, Little JB, Sasaki MS et al (1992) Prevalence and spectrum of germline mutations of the p53 gene among patients with sarcoma. N Engl J Med 326:1301–1308
57. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer MB, Glimelius I, Storm H, Pukkala E, Stovall M, Curtis R, Boice JD Jr, Gilbert E (2003) Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 290: 465–475
58. Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W et al (1987) Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 317:588–593
59. Tucker MA, Jones PH, Boice JD Jr, Robison LL, Stone BJ, Stovall M, Jenkin RD, Lubin JH, Baum ES, Siegel SE, Merdons AT, Hoover RN, Kaumeni JF (1991) Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res 51:2885–2888
60. Van Leeuwen FE, Klokman WJ, Veer MB, Hagenbeek A, Krol AD, Vetter UA, Schaapveld M, van Heerde P, Burgers JM, Somers R, Aleman BM (2000) Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 18: 487–497
61. Walter AW, Hancock ML, Pui CH, Hudson MM, Ochs JS, Rivera GK, Pratt CB, Boyett JM, Kun LE (1998) Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. J Clin Oncol 16:3761–3767
62. Wong FL, Boice JD Jr, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF Jr, Li FP (1997) Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278:1262–1267

Psychological Aspects of Long-Term Survivorship

Mary T. Rourke · Anne E. Kazak

Contents

It can come as a surprise to survivors and their families that cancer does not end when treatment ends, and that life does not automatically return to normal. Instead, as families manage the many transitions that accompany the end of treatment, they find that cancer survivorship has its own set of medical and psychological issues. Medical screening continues – first, for disease recurrence and, later, for the emergence of medical late effects and longer-term psychological reactions. For this reason, it may be more accurate to conceive of cancer survivorship as a stage in a lifelong chronic illness, rather than as an acute illness that ends with "cure" or some other arbitrary end point [45]. The goal of this chapter is to summarize psychological aspects of cancer survivorship. Specifically, we will present an overview of what is known about psychological late effects of childhood cancer, as well as some guidelines for managing these effects.

We use the phrase, "psychological late effects," to refer to the influence of cancer, treatment and survivorship on survivors' and their family members' feelings, thoughts, behaviors and relationships. Like medical late effects, psychological late effects can occur a year or two after treatment, but they may not even begin to emerge until many years after treatment ends. The breadth of this definition implies that psychological late effects can appear in many aspects of a survivor's life. Much research to date on psychological late effects has focused on the neurocognitive sequelae of treatment (see Chapter 4 for an excellent review of this work). Here, we will focus on the broader array of areas in which psychological late effects have been examined: the development of psychological symptoms (e.g. depression, behavior disorders, posttraumatic stress), the abd functional im-

pact of cancer/quality of life and peer relationships/social skills. In addition, because childhood cancer is a powerful experience – not only for the diagnosed child, but also for those closely involved with him or her – we will explore psychological late effects that survivors' family members may experience.

19.1 Psychological Symptoms in Childhood Cancer Survivors

19.1.1 Depression and Behavioral Disorders

Although many healthcare providers may believe that high rates of depression or behavioral disorders are common in cancer survivors, there is little evidence that this is the case. While parents tend to see higher than average levels of somatic symptoms in children (e.g. headaches, stomachaches, toileting issues [39, 43]), most research indicates no unusual levels of psychological symptoms in survivors during childhood and adolescence. Across a number of studies, overall rates of depression [42], behavioral disorders [41, 43] and other general psychological symptoms [9, 31, 55] reported by children and their parents have been comparable to rates reported by children who have never had cancer. Similarly, survivors appear to have no more social anxiety, loneliness or body image concerns than do their never-ill peers [46], and they may even have a more positive self-image than their peers [3, 35].

Similar results have been found with older survivors of childhood cancer. In general, young adult survivors' rates of depressive symptoms are comparable to those of peers [34] or norms [52]. Although the large multi-site Childhood Cancer Survivors Study (CCSS) identified higher levels of depressive and somatic symptoms in survivors than in their siblings, survivors' rates of depressive and somatic symptoms were still in the normal range [63]. Similarly, in a large study of Danish survivors, overall rates of depression and other psychiatric disorders in survivors of childhood cancers other than brain tumor were consistent with national norms. Only brain tumor survivors evidenced higher levels of depression and other presumably organic disorders (e.g. psychoses, schizophrenia), as well as a higher rate of psychiatric hospitalization [52]. Aggression and antisocial behavior in young adult survivors occur at rates comparable to those in never-ill peers, while survivors' use of illegal drugs may be less frequent than that of peers [61].

Although most survivors are not depressed and report that they are doing well overall, a significant minority may experience some form of significant psychological distress. One-quarter to one-third of young adult survivors report higher-than-average levels of global psychological distress [14, 31, 49], with a concerning percentage reporting that they have experienced suicidal thoughts [49]. It is important to note that these high levels of psychological distress are evident even in groups of survivors that also report good overall functioning, with high rates of employment and high scores on quality of life measures [54].

The relatively high rates of global distress, coupled with the lack of evidence for any one clear psychological diagnosis, has led recent researchers to speculate that more traditional or general measures of psychopathology and well-being may not capture the specific experiences of childhood cancer survivors [22]. One alternative is to view cancer (and, potentially, aspects of the cancer survivorship period) as traumatic events, which may in turn lead to the experience of posttraumatic stress in the survivorship years [22, 53, 56].

19.1.2 Posttraumatic Stress

It is easy to see the ways in which childhood cancer can be traumatic. At diagnosis, parents are told explicitly that their child may die. Survivors may hear this information, or may interpret life threat from their parents' urgency and intense emotional reactions, their own physical reactions to treatment and the abrupt changes in their family routine. Cancer treatment can be experienced as a horrifying, scary and painful series of events for everyone involved, ranging from events like losing hair to feeling nauseous to experiencing repeated and painful invasive procedures. Patients and their families may watch other children, with whom they have developed relationships, die of the same disease they are fighting.

Likewise, survivorship can offer its own set of traumatic events. Just when survivors are reaching a stage of development at which they are becoming more independent, they may be faced with significant late effects – such as cardiovascular disease, infertility or cognitive disabilities – that limit or otherwise affect the life choices available to them. Further, it is not uncommon for survivors to know fellow survivors who have died of a recurrence or medical late effect.

Posttraumatic stress reactions to these distressing events can begin soon after the initial traumatic event and continue for many years. Three kinds of posttraumatic stress symptoms may emerge: persistent re-experiencing of the traumatic parts of cancer/survivorship (including intrusive thoughts, nightmares or strong negative feelings triggered by reminders), actual or considered avoidance of cancer- or survivorship-related situations and strong physiological responses when reminded about cancer or survivorship [2, 29]. Survivors may experience only a few of these posttraumatic stress symptoms (PTSS), or they may develop several symptoms from all three categories. If this happens, and if the symptoms significantly interfere with their normal activities, the diagnosis of posttraumatic stress disorder (PTSD) is warranted.

Research has, indeed, documented higher levels of both PTSS and PTSD in cancer survivors and their family members. Rates of PTSD for adolescent survivors are generally low and roughly comparable to rates in non-ill adolescents (ranging from 5–10% [5, 11, 26]. Most adolescent survivors, however, do report at least some symptoms of PTSD [4, 11]. In one study, 50% of adolescent survivors reported re-experiencing symptoms, and 29% reported increased physiological responses when reminded of cancer/survivorship [26].

Developmentally, PTSD and PTSS appear to be even more prominent for childhood cancer survivors during young adulthood, where 15–21% of young adult survivors report experiencing PTSD. In addition, more than 75% of young adult survivors report re-experiencing difficult moments of treatment/survivorship, while nearly half report increased physiological reactions when reminded of cancer/survivorship and one-quarter attempt to or want to avoid cancer-related discussions or situations [54]. Data indicate that for child and adolescent survivors, traumatic reactions are associated with concrete events, such as losing hair or experiencing painful procedures. For young adult survivors, these reactions to concrete events persist, but are accompanied by two kinds of additional distress: distress over the retrospective realization of the life threat that they experienced and worry over medical late-effects that exist or may occur [26].

Although PTSS is often subclinical, symptoms can significantly impede development for survivors. For example, an adolescent who is very upset when reminded of her treatment experience may do everything she can to avoid talking or thinking about her cancer. She may not feel comfortable socializing with friends or dating, even though she would like to do these things. A child or adolescent might become so distracted by a high level of worry or vigilance about his health that his ability to focus at school suffers, resulting in lower or inconsistent grades. For young adult survivors, worries about infertility and other medical late-effects can interfere with intimate relationships and family planning, and concerns related to cognitive or physical limitations may prevent the establishment of independence. Because survivors may report no other significant areas of difficulty, it may be difficult to discern that they are experiencing posttraumatic stress.

As mentioned above, cancer and survivorship can be traumatic not only for the survivor, but also for family members, and data do indicate that parents and siblings also experience PTSS and PTSD. Although rates of PTSD in mothers and fathers range across studies from 5–20% [26, 27, 36, 37], at least one-third of families of adolescent survivors have at least one member who has had cancer-related PTSD. In addition, subclinical rates of PTSS in family members are common. Mothers and fathers of survivors report significantly more PTSS than do parents of never-ill children [23, 27]. Nearly all families (99%) have at least one family member who struggles with re-experiencing symptoms, over 80% have at least one member with increased physiological reactions when reminded of cancer and nearly half have at least one member who avoids reminders of cancer [28].

Adolescent siblings, too, appear to have mild to moderate levels of PTSS in response to a brother or sister's cancer [1]. Common sibling reactions include persistent worries about the survivor's health and distress when reminded of the cancer experience. Like adolescent survivors, adolescent siblings may be functioning well overall, and the posttraumatic stress may not be apparent at first glance.

The factors that predispose some survivors and family members to develop PTSD or PTSS are not completely clear. It makes sense to expect that survivors who endured more difficult treatments, or whose diagnoses had worse prognoses, would be more likely to develop PTSD or some symptoms of posttraumatic stress. This does not seem to be the case, however. The more objective factors of treatment intensity, diagnosis and age at time of treatment do not appear to be related to posttraumatic stress for most survivors and their family members. What *is* related are the beliefs of survivors about their treatment intensity and their current and past life threat [17, 24]. The one exception appears to involve medical late effects. There are some indications that for young adult survivors, medical team ratings of medical late-effect severity are related to higher levels of posttraumatic stress [54].

19.2 Quality of Life and Functional Impact of Cancer

A number of studies have looked at the more global construct of "quality of life" in order to assess psychological late-effects and overall functioning in the years after childhood cancer. These studies agree that adolescent and young adult survivors of childhood cancer report very good overall functioning in physical and general psychosocial domains [6, 8, 32, 62]. In some studies, quality of life scores are even better than norms for peers with other chronic illnesses or those who have never been ill [54]. Only two quality of life issues appear to emerge as consistent areas of difficulty for survivors: the experience of ongoing fatigue or aches and pains, and worry over medical late-effects or the possibility of a second cancer [6, 32, 62]. Mothers report more negative quality of life for their adolescent survivors than survivors report themselves [8], suggesting the importance of asking both children and their mothers, independently, about quality-of-life issues. Brain tumor survivors report a lower physical quality of life than survivors of other cancers, while there is some evidence that ALL survivors, who report good physical quality of life, may have more psychosocial issues [8]. Overall, however, average levels of quality of life across studies indicate that survivors have a positive outlook, are satisfied with their lives, feel a sense of purpose and have the same opportunities in daily living as do their never-ill peers.

Studies documenting the impact of childhood cancer on educational and employment achievements, as well as on the achievement of developmental milestones, are largely consistent with these generally high levels of quality of life. Overall, survivors tend to enter gifted programs, finish high school and earn bachelors degrees at rates comparable to those of their siblings [15, 33, 34]. Some survivors, however, appear to be at greater risk for difficulties in these areas. Those treated before the age of 6 who survived a brain tumor, or who received intrathecal methotrexate and/or cranial radiation (especially at doses higher than 24Gy), are more at risk for learning disabilities and special education placements, and are less likely to finish high school and complete a bachelors degree [15, 33, 38, 40]. Receiving special education may increase survivors' educational attainment levels to more closely parallel those of siblings [38].

Later differences in employment may also be evident in some survivors, despite overall high rates of employment in survivors generally. Survivors appear to be employed less frequently than their siblings [40], although more survivors than siblings report being students or homemakers [33]. As many as one-third of all survivors report problems obtaining health insurance [40], a potentially significant problem in this medically-vulnerable population. Rates of marriage are also generally high, although there is evidence that survivors marry at rates lower than those of their siblings or population norms. Those with CNS tumors appear to have lower marriage rates and, when they do marry, higher divorce rates [33, 48].

19.3 Effects on Social Development

Developing social relationships is a primary task of childhood and adolescence. It also provides children with the contextual experience necessary for building an understanding of who they are and developing a sense of competence. Because cancer and treatment at least partially remove children from the normal everyday activities in which most children build relationships, it seems likely that social development is an area at risk for difficulties.

19.3.1 Social Consequences for Survivors of Non-CNS Malignancies

While childhood cancer survivors do show some social developmental differences, it is not clear that these differences represent deficits. Overall, survivors of childhood cancer are rated as more socially isolated and they have fewer best friends than do other children [60]. Survivors participate in fewer than half as many normative peer activities (e.g. going to a friend's house, going out with friends, playing sports) as their never-ill peers [46]. Children whose physical appearance and athletic ability were affected by their treatment may be at higher risk for some of these social challenges [50, 60].

For survivors of non-CNS malignancies, there seem to be few immediate consequences of these social differences. Despite being identified as more socially isolated and having fewer best friends, childhood cancer survivors are as well liked as their classmates. Teachers rate survivors as less aggressive than other children and, in some studies, as more sociable [13]. Furthermore, as mentioned above, survivors themselves generally do not report feeling lonely or depressed.

The potential for longer-term problems associated with social developmental differences exists, however, and has not yet been well researched. Being less involved with peers may not give survivors the social practice they will need as young adults. These kinds of difficulties are likely to emerge slowly over time, and they might not be evident until several years after treatment ends. Indeed, one study suggests that in adulthood, childhood cancer survivors have more difficulty with close friendships and romantic relationships, reporting shorter intimate relationships and relationships characterized by a lack of confiding or personal involvement [34]. While there are no other empirical studies of this issue, the lower marriage rates cited by some studies (see above) are consistent with this possibility. More work in this area is necessary to better understand the long-term social implications for survivors.

19.3.2 Social Consequences for Survivors of CNS Malignancies

As reviewed above, CNS malignancies appear to present a specific vulnerability for psychological late effects, above and beyond the cognitive changes that are usually associated with CNS disease and treatment [50]. This vulnerability appears to be particularly associated with deficits in the area of social development. Several studies of children who were treated for brain tumors identify difficulties in social competence and communication with peers; they also cite reports of social isolation [12, 18, 47, 59]. In one study, classmates continued to see brain tumor survivors as "sick," even many years after treatment had ended [59]. It is likely that compromises in social competence are related to the cognitive changes that many brain tumor survivors experience as a result of their disease and treatment. Cognitive impairments may impede a child's ability to understand and respond appropriately to social cues. Indeed, in one study of brain tumor survivors, verbal memory and learning problems accounted for much of the social withdrawal seen in the children, while difficulties in verbal fluency and decreased IQ were significantly related to difficulties with attention, inhibition and social functioning [18]. Over time, these survivors are at higher risk psychologically. For example, in a large Danish study of long-term childhood cancer survivors, brain tumor survivors (but not survivors of non-CNS malignancies) were significantly more likely to experience psychiatric hospitalization and to demonstrate a higher risk of psychotic illness after physical illness [52].

19.3.3 Social Consequences for Survivors' Family Members

There is very little research on the social consequences of childhood cancer for members of a survivor's family. Some research suggests that parents may feel lonely or isolated after treatment ends [58]. During the survivorship period, parents may have continued concerns about their child's health and fewer people available to hear and respond to those concerns. Medical teams are seen less frequently, while friends and family members – relieved by the victory of survival – may not understand a parent's continued medical concerns. Being aware that these feelings can emerge, and finding new ways to talk to supportive people in their lives about the stage of cancer survivorship, can help parents feel more connected and less isolated. Increasingly, parents are also turning to books, on-line support groups, websites, list-serves and other media to reduce feelings of isolation (see [30] for a particularly good resource for parents and others close to long-term survivors).

19.4 Implications for the Provision of Follow-Up Care

Participation in regular follow-up care is strongly recommended for long-term survivors in order to provide prevention and/or early detection of medical late effects [16, 44, 51]. Because childhood cancer survivors are doing well overall and, as a group, demonstrate relatively low levels of psychological symptoms, it is easy to overlook the ways in which psychosocial issues can interfere in survivors' medical care. However, even low-to-moderate levels of posttraumatic stress, like that evident in a majority of survivors and their parents, can have very significant medical consequences. For example, avoidance of reminders of the traumatic illness experience – a common symptom of posttraumatic stress – puts survivors at risk for avoiding medical care, a potentially disastrous behavior in this medically-vulnerable population. The distress and arousal that accompany cancer reminders – also hallmark symptoms of posttraumatic stress – are likely to be high during cancer follow-up visits and may impede the abilities of survivors to comprehend or attend to the cancer-related education and information being delivered. Participating in follow-up care itself may affect distress. For example, survivors may become more upset and even be re-traumatized as they hear about medical complications associated with their treatment. While there are no data that explicitly demonstrate a link between follow-up care and distress in childhood cancer survivors, long-term survivors and their family members report follow-up visits to be among some of the most frightening moments they experience [26].

Developmental issues may make participating in long-term follow-up care particularly important, and frightening, for young adult survivors. Childhood cancer survivors may not have had full access to information during their treatments, and, as a result, often learn of their long-term medical risks for the first time during a follow-up visit [21]. Furthermore, as childhood cancer survivors reach adulthood, they take on the direct responsibility for managing their own healthcare – a complex task, formerly handled by parents, that can be overwhelming and frightening.

Thus, recent urgings for the development of widely-available follow-up care have appropriately argued for the integration of medical and psychosocial evaluation throughout the lifespan of childhood cancer survivors [16, 44]. There is some evidence that survivors are receptive to psychosocial screening and interventions in the context of their follow-up care (e.g. [10, 49]) and that even brief educational interventions can be effective in changing survivors' understanding of their medical vulnerability, as well as their perceptions about the importance of follow-up care [7]. There is a lack of clarity, however, in exactly what form specific interventions should take. For example, although survivors may endorse their willingness to participate in interventions that target modifications of health-risk behaviors (e.g. [10]), it is often difficult to demonstrate the effectiveness of these very-targeted interventions [19].

Increasingly, professionals are advocating that follow-up care explicitly attend to the broader array of psychosocial issues that can emerge during survivor-

ship [17, 20, 22, 44, 57]. Recommendations include instituting comprehensive, but brief, psychosocial screening into every follow-up visit for every patient [49]. Such assessments will best inform subsequent referrals and care if they include assessments of issues specific to the cancer experience (rather than assessments of global distress). Although healthcare providers may be able to accomplish some level of assessment through the use of standardized questionnaires, there are some indications that interviews may elicit more information than questionnaires about cancer-specific symptoms [54]. In the context of the medical exam, then, it is important for healthcare providers to ask specific questions about survivors' achievement of appropriate developmental milestones (e.g. education, employment, relationships), emotional distress and, in particular, specific symptoms of posttraumatic stress (i.e. re-experiencing, avoidance and arousal; for examples of specific questions, see [53]). Knowing a survivor's strengths, as well as the specific symptoms s/he experiences, enables healthcare providers to direct the survivor to the most appropriate and effective psychosocial care. The process may not be easy, however, due to issues related to availability and access. For example, pediatric cancer programs may have difficulty identifying appropriate adult mental healthcare services, while survivors' lack of insurance coverage can complicate access to such services even when they are identified. While there are no easy answers, it is recommended that follow-up program personnel draw on social work or psychology expertise to identify the most appropriate referral sources or policies that may be available in their region.

It is also critical to develop ways of responsibly educating survivors on their medical risk while minimizing the anxiety that such education may provoke [20]. Providers should be attuned to the potential psychological impact of the information they are delivering, and they should be sensitive to the fact that many survivors may be hearing the information directly for the first time or feel independently responsible for managing this health-related issue for the first time. Being careful to ask about and listen to survivors' perceptions, and then carefully correcting misperceptions, can minimize anxiety-provoking misunderstandings that can impede participation in future medical care. Providing anticipatory guidance about psychosocial symptoms that are normative for many survivors (e.g. anxiety and worry about medical late effects or distress when reminded of cancer and late effects) can also minimize worry. Helping survivors recognize aspects of the situation that they control (e.g. participating in regular preventive care) and identifying their areas of strength in managing their own health may also decrease the chances that posttraumatic reactions could undermine their involvement in future medical care. For example, practitioners can help survivors identify modifiable risk factors and can emphasize their control over maintaining their health [20]. Finally, while it is recommended that all patients receive this standard level of psychosocial care integrated into each follow-up visit, some survivors will demonstrate specific, and possibly intensive, psychological needs. It is, therefore, important to maintain a referral list of care providers who can deliver more intensive care, including psychotherapists and neuropsychologists.

19.5 Research and Practice: Developing Interventions Targeting Psychological Late Effects

A critical piece of providing comprehensive follow-up care involves interdisciplinary research that aims to develop and demonstrate the effectiveness of psychosocial interventions as part of the follow-up care. Cancer centers across the country are now beginning to develop and test such interventions, spanning a broad range of psychosocial needs. Such interventions range from targeted behavioral efforts for modifying health risk behaviors (e.g. [10, 20]), to more general programs that, during follow-up visits, aim to educate survivors on their medical vulnerability and the need for continued participation in follow-up care (e.g. [7]).

As an example, building on the research related to PTSS across members of the family, an intervention for adolescent survivors and their families has been developed and tested in a randomized clinical trial of 150 families. The intervention, Surviving Cancer

Competently Intervention Program (SCCIP [25]) integrates cognitive behavioral approaches to distressing symptoms of posttraumatic stress within a family systems intervention model. SCCIP has been shown to reduce PTSS in survivors and in their fathers [28].

19.6 Conclusion

Overall, survivors of childhood cancer report doing very well and demonstrate low rates of traditional psychological issues. Though most do well, a significant minority may experience PTSD, and most survivors and their family members experience at least some symptoms of posttraumatic stress related to cancer, treatment or survivorship experiences. The large majority of these reactions – although they can pose significant impediments to individual and family development – are normal reactions to the unusual stress of childhood cancer that are likely to emerge unpredictably and to wax and wane over the course of time. Social and relationship differences may also affect childhood cancer survivors, though it is unclear whether these differences contribute to ongoing distress. It is essential during any comprehensive follow-up care program that there be a sensitive assessment of these issues and that the development of interventions to combat psychological late effects be part of ongoing efforts.

Finally, it is important to emphasize that the experience of psychological late effects does not rule out the possibility that survivors may have positive experiences or outcomes that they ascribe to the childhood cancer experience. There is little formal research on this topic, but many psychologists working with survivors have qualitative or anecdotal reports that parents and survivors grow to appreciate at least some parts of the cancer experience. Parents and survivors frequently explain that childhood cancer taught them to put things in perspective in ways that other people do not do, that they are not as materialistic and that they are more empathic. Survivors frequently feel that they are more mature than others their age, and that they value their family relationships more. Family members and survivors may feel grateful to the medical professionals who worked with them, and proud of their ability to manage – and survive – challenges like childhood cancer and survivorship [26]. Drawing on these strengths and the positive contributions of the cancer experience can help survivors and their family members weather future challenges they may face.

References

1. Alderfer M, Labay L, Kazak A (2003) Brief report: does posttraumatic stress apply to siblings of childhood cancer survivors? J Pediatr Psychol 28:281–286
2. American Psychiatric Association (1994) Diagnostic and statistical manual of the American Psychiatric Association, 4th edn. American Psychiatric Press, Washington DC
3. Anholt UV, Fritz GK, Keener M (1993) Self-concept in survivors of childhood and adolescent cancer. J Psychosoc Oncol 11:1–16
4. Brown R, Madan-Swain A, Lambert R (2003) Posttraumatic stress symptoms in adolescent survivors of childhood cancer and their mothers. J Traum Stress 16:309–318
5. Butler R, Rizzi L, Handwerger B (1996) Brief report: the assessment of posttraumatic stress disorder in pediatric cancer patients and survivors. J Pediatr Psychol 21:499–504
6. Crom DB, Chathaway DK, Tolley EA, Mulhern RA, Hudson MM (1999) Health status and health-related quality of life in long-term adult survivors of pediatric solid tumors. Int J Cancer 12:25–31
7. Eiser C, Hill JJ, Blacklay A (2000) Surviving cancer: what does it mean for you? An evaluation of a clinic-based intervention for survivors of childhood cancer. Psycho Onco 9:214–220
8. Eiser C, Vance YH, Glaser A, Galvin H (2003) The value of the PedsQTLM in assessing quality of life in survivors of childhood cancer. Child Care Health Dev 29:95–102
9. Elkin TD, Phipps S, Mulhern RK, Fairclough D (1997) Psychological functioning of adolescent and young adult survivors of pediatric malignancy. Med Pediatr Oncol 29: 582–588
10. Emmons KM, Butterfied RM, Puleo E, Park ER, Mertens A, Gritz ER, Lahti M, Li FP (2003) Smoking among participants in the Childhood Cancer Survivors cohort: the Partnership for Health Study. J Clin Oncol 21:189–196
11. Erickson S, Steiner H (2001) Trauma and personality correlates in long term pediatric cancer survivors. Child Psychiatr Hum Dev 31:195–213
12. Fuemmeler BF, Elkin TD, Mullins LL (2001) Survivors of childhood brain tumors: behavioral, emotional, and social adjustment. Clin Psychol Rev 22:547–585
13. Gartstein MA, Noll RB, Vannatta K (2000) Childhood aggression and chronic illness: Possible protective mechanisms. J Appl Dev Psychol 21:315–333

14. Glover DA, Byrne J, Mills JL, Robison LL, Nicholson HS, Meadows A, Zeltzer LK (2003) Impact of CNS treatment on mood in adult survivors of childhood leukemia: a report from the Children's Cancer Group. J Clin Oncol 21:4395–4401
15. Haupt R, Fears TR, Robison LL, Mills JL, Nicholson S, Zeltzer LK, Meadows AT, Byrne J (1994) Educational attainment in long-term survivors of childhood Acute Lymphoblastic Leukemia. JAMA 272:1427–1432
16. Hobbie W, Ogle S (2001) Transitional care for young adult survivors of childhood cancer. Semin Oncol Nursing 17:268–273
17. Hobbie W, Stuber M, Meeske K, Wissler K, Rourke M, Ruccione K, Hinkle A, Kazak A (2000) Symptoms of posttraumatic stress in young adult survivors of childhood cancer. J Clin Oncol 18:4060–4066
18. Holmquist LA, Scott J (2002) Treatment, age, and time-related predictors of behavioral outcome in pediatric brain tumor survivors. J Clin Psychol Med Sett 9:315–321
19. Hudson MM, Tyc VL, Srivastava DK, Gattuso J, Quargnenti A, Crom DB, Hinds P (2002) Multi-component behavioral intervention to promote health protective behaviors in childhood cancer survivors: the protect study. Med Pediatr Oncol 39:2–11
20. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, Yeazel M, Recklitis CJ, Marina N, Robison LR, Oeffinger KC (2003) Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA 290:1583–1592
21. Kadan-Lottick NS, Robison L, Gurney JG, Neglia JP, Yasui Y, Hayashi R, Hudson M, Greenberg M, Mertens A (2002) Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. JAMA 287:1832–1839
22. Kazak A Evidence-based interventions for survivors of childhood cancer. J Pediatr Psychol (in press)
23. Kazak A, Barakat L, Meeske K, Christakis D, Meadows A, Casey R, Penati B, Stuber M (1997) Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 65:120–129
24. Kazak A, Stuber M, Barakat L, Meeske K, Guthrie D, Meadows A (1998) Predicting posttraumatic stress symptoms in mothers and fathers of survivors of childhood cancer. J Am Acad Child Adoles Psychiatry 37:823–831
25. Kazak A, Simms S, Barakat L, Hobbie W, Foley B, Golomb V, Best M (1999) Surviving Cancer Competently Intervention Program (SCCIP): a cognitive-behavioral and family therapy intervention for adolescent survivors of childhood cancer and their families. Family Proc 38:175–191
26. Kazak A, Barakat L, Alderfer M, Rourke M, Meeske K, Gallagher P Cnaan A, Stuber M (2001) Posttraumatic stress in survivors of childhood cancer and their mothers: development and validation of the Impact of Traumatic Stressors Interview Schedule (ITSS). J Clin Psychol Med Sett 8:307–323
27. Kazak A, Alderfer M, Rourke M, Simms S, Streisand R, Grossman J Posttraumatic stress symptoms (PTSS) and Posttraumatic stress disorder (PTSD) in families of adolescent cancer survivors. J Pediatr Psychol (in press)
28. Kazak A, Alderfer M, Streisand R, Simms S, Rourke M, Barakat L, Gallagher P. A Treatment of posttraumatic stress symptoms in adolescent survivors of childhood cancer and their families: a randomized clinical trial (submitted)
29. Kazak AE, Kassam-Adams N, Alderfer M, Rourke MT, Schneider S, Zelikovsky N A model for understanding pediatric medical traumatic stress (in preparation)
30. Keene N, Hobbie W, Ruccione K (2000) Childhood cancer survivors: a practical guide to your future. O'Reilly, Cambridge
31. Kupst MJ, Natta M, Richardson C, Schulman J, Lavigne J, Das L (1995) Family coping with pediatric leukemia: Ten years after treatment. J Pediatr Psychol 20:601–617
32. Langeveld NE, Stam H, Grootenhuis MA, Last BF (2002) Quality of life in young adult survivors of childhood cancer. Supp Care Cancer 10:579–600
33. Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voute PA, DeHaan RJ (2003) Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psycho Oncol 12:213–225
34. Mackie E, Hill J, Kondryn H, McNally R (2000) Adult psychosocial outcomes in long-term survivors of acute lymphoblastic leukaemia and Wilms' tumour: a controlled study. Lancet 355:1310–1314
35. Maggiolini A, Grassi R, Adamoli L, Corbetta A, Charmet GP, Provantini K, Fraschini D, Jankovic M, Lia R, Spinetta J, Masera G (2000) Self-image of adolescent survivors of long-term childhood leukemia. J Pediatr Hematol Oncol 22:417–421
36. Manne S, DuHamel K, Gallelli K, Sorgen K, Redd W (1998) Posttraumatic stress disorder among mothers of pediatric cancer survivors: diagnosis, comorbidity, and utility of the PTSD Checklists as a screening instrument. J Pediatr Psychol 23:357–366
37. Manne S, DuHamel K, Nereo N, Ostroff J, Parsons S, Martini R, Williams S, Mee L, Sexson S, Wu L, Difede J, Redd W (2002) Predictors of PTSD in mothers of children undergoing bone marrow transplantation: the role of cognitive and social processes. J Pediatr Psychol 27:607–617
38. Mitby PA, Robison LL, Whitton JA, Zevon MA, Gibbs IC, Tersak JM, Meadows AT, Stovall M, Zeltzer LK, Mertens AC (2003) Utilization of special education services and educational attainment among long-term survivors of childhood cancer. Cancer 97:1115–1126
39. Mulhern R, Wasserman AL, Friedman AG, Fairclough D (1989) Social, competence and behavioral adjustment of children who are long-term survivors of cancer. Pediatrics 83:18–25

40. Nagarajan R, Neglia JP, Clohisy DR, Yasui Y, Greenberg M, Hudson M, Zevon MA, Tersak JM, Ablin A, Robison LL (2003) Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors: a report of the Childhood Cancer Survivor Study. Cancer 97:2554–2564
41. Newby WL, Brown RT, Pawletko TM, Gold SH, Whitt JK (2000) Social skills and psychological adjustment of child and adolescent cancer survivors. Psycho Oncol 9:113–126
42. Noll R, Bukowski W, Davies W, Koontz K, Kularkrni R (1993) Adjustment in the peer system of children with cancer: a two-year follow-up study. J Pediatr Psychol 18:351–364
43. Noll RB, MacLean WE, Whitt JK, Kaleita TA, Stehbens JA, Waskerwitz MJ, Ruymann FB, Hammond GD (1997) Behavioral adjustment and social functioning of long-term survivors of childhood leukemia: parent and teacher reports. J Pediatr Psychol 22:827–841
44. Oeffinger KC (2003) Longitudinal risk-based health care for adult survivors of childhood cancer. Curr Prob Cancer 27:143–167
45. Patenaude AF, Last B (2001) Editorial. Cancer and children: Where are we coming from? Where are we going? Psycho Oncol 10:281–283
46. Pendley JS, Dahlquist LM, Dreyer Z (1997) Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 22:29–43
47. Radcliffe J, Bennett D, Kazak AE, Foley B, Phillips PC (1996) Adjustment in childhood brain tumor survival: child, mother, and teacher report. J Pediatr Psychol 21:529–539
48. Rauck AM, Green DM, Yasui Y, Mertens A, Robison LL (1999) Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study. Med Pediatr Oncol 33:60–63
49. Recklitis C, O'Leary T, Diller L (2003) Utility of routine psychological screening in the childhood cancer survivor clinic. J Clin Oncol 21:787–792
50. Reiter-Purtill J, Noll R (2003) Peer relationships of children with chronic illness. In: Roberts M (ed) Handbook of pediatric psychology, 3rd edn. Guilford, New York
51. Richardson RC, Nelson MB, Meeske K (1999) Young adult survivors of childhood cancer: attending to emerging medical and psychosocial needs. J Pediatr Oncol Nurs 16: 136–144
52. Ross L, Johansen C, Dalton S O, Mellemkjaer L, Thornassen LH, Mortensen PB, Olsen JH (2003) Psychiatric hospitalizations among survivors of cancer in childhood or adolescence. N Engl J Med 349:650–657
53. Rourke M, Stuber M, Hobbie W, Kazak A (1999) Posttraumatic stress disorder: Understanding the psychosocial impact of surviving childhood cancer into young adulthood. J Pediatr Oncol Nurs 16:126–135
54. Rourke M, Hobbie W, Kazak A (2002) Posttraumatic stress in young adult survivors of childhood cancer. 7th international conference on long-term complications of treatment of children and adolescents for cancer, Niagara on the Lake, Ontario, Canada
55. Sawyer M, Antoniou G, Toogood I, Rice M, Baghurst P (2000) Childhood cancer: a 4-year prospective study of the psychological adjustment of children and parents. J Pediatr Hematol Oncol 22:214–220
56. Stuber M, Kazak A, Meeske K, Barakat L (1998) Is posttraumatic stress a viable model for understanding responses to childhood cancer? Psychiatr Clin North Am 7:169–182
57. Van Dongen-Melman JE (2000) Developing psychosocial aftercare for children surviving cancer and their families. Acta Oncol 39:23–31
58. Van Dongen-Melman JE, Pruyn JFA, DeGroot A, Koot HM, Hahlen K, Verhulst FC (1995) Late psychosocial consequences for parents of children who survived cancer. J Pediatr Psychol 20:567–586
59. Vannatta K, Gartstein MA, Short A, Noll RB (1998) A controlled study of peer relations of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 23:279–287
60. Vannatta K, Zeller M, Noll RB, Koontz K (1998) Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 23:169–178
61. Verrill JR, Schafer J, Vannatta K, Noll RB (2000) Aggression, antisocial behavior, and substance abuse in survivors of pediatric cancer: possible protective effects of cancer and its treatment. J Pediatr Psychol 25:493–502
62. Zebrack BJ, Chesler M (2001) Health-related worries, self-image, and life outlooks of long-term survivors of childhood cancer. Health Soc Work 26:245–256
63. Zebrack BJ, Zeltzer LK, Whitton J Mertens AC, Odom L, Berkow R, Robison LL (2002) Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. Pediatrics 110:42–52

Legal Issues

Barbara Hoffman

Contents

20.1 Introduction

A growing number of children in the United States are being diagnosed with and successfully treated for cancer. Approximately 80 % of all children diagnosed with cancer can expect to become long-term survivors [3]. Unlike adult survivors, whose average age of diagnosis is near the retirement ages of 60–65, most childhood survivors offer decades of productive employment after cancer [3]. Young adult survivors entering the job market for the first time are a rapidly growing population. By 2010, approximately one of every 450 young adults will be a childhood cancer survivor [17]. Although a significant number of survivors from the previous generation could expect to encounter cancer-related barriers to employment, improvements in medical treatment and legal rights have reduced these barriers considerably.

This chapter reviews current studies of employment problems reported by cancer survivors, describes why survivors encounter discrimination not faced by workers with other medical histories, lists legal resources available for those whose rights have been violated and provides suggestions for how to avoid and address these problems. This chapter also discusses childhood cancer survivors' rights to health insurance and education.

20.2 The Scope of Cancer-Based Employment Problems

The work issues of childhood cancer survivors differ somewhat from those of adult cancer survivors. Because childhood survivors must first enter the work-

place, they are often more concerned with how to obtain a job than with how to keep a job. Although many childhood survivors do not enter the job market for years or even decades after their diagnoses, some may find that their cancer histories affect their employability at any stage of their careers.

Most employers treat cancer survivors fairly and legally. Some employers, however, erect unnecessary and sometimes illegal barriers to job opportunities. Most personnel decisions are driven by economic factors, not by charitable or personal consideration. Increased costs due to insurance expenses and lost productivity are of concern to employers, as is the potential psychological impact of a survivor's cancer history on other employees. Some employers fail to revise their personnel policies to comply with new laws. Even those who have updated personnel policies may not properly train their personnel managers to comply with these laws.

20.2.1 The Types of Employment Problems Encountered by Cancer Survivors

The employment problems of cancer survivors take many forms. A cancer diagnosis may affect any type of job action, including dismissal, failure to hire, demotion, denial of promotion, undesirable transfer, denial of benefits and hostility in the workplace. Disparate treatments, such as blanket hiring bans against all individuals with a cancer history, are irrational and blatant. Other employment decisions, especially actions by legally sophisticated employers, are far more subtle.

In her 1986 study of 403 Hodgkin's disease survivors, Fobair reported a variety of job problems, including denial of insurance(11%), denial of other benefits(6%), denial of a job offer (12%), termination of employment following therapy (6%), conflict with supervisors or coworkers (12%) and rejection by the military (8%) [7]. Survivors interviewed by Koocher and O'Malley in the early 1980s reported job refusals (17%), denied benefits (5%) and conflicts with supervisors (5%) [14].

20.2.2 The Numbers of Cancer Survivors Who Encounter Employment Problems

Unlike many years ago, when cancer was a literal death sentence, today, most working-age survivors return to work [6]. Helen Crothers' summary of several studies from the 1970s and 1980s concluded that 80% of employees returned to work after being diagnosed with cancer [6]. Physicians are now more aware of cancer survivors' employment problems [16] and offer more flexible outpatient treatment programs to accommodate survivors' work schedules [5]. They also have an improved medical arsenal with which to combat the side effects of cancer, such as the risk of infection, nausea and hair loss [8].

One 1996 survey questioned 500 cancer patients who were employed at the time of their treatment, 100 supervisors and 100 coworkers [23]. The results showed that workers with cancer reported being fired or laid off at five times the rate of other workers in the United States (7 vs 1.3%) [23]. A follow-up survey of 662 employed adult Americans who had not been diagnosed with cancer found that 41% worried about losing their job if they were diagnosed with cancer, and 14% said they would be very worried [1]. Their fear of discrimination was so great that 18% of survivors would not disclose their diagnosis to anyone at work [1]. An earlier survey of people with Hodgkin's disease and leukemia survivors found that more than one-third attributed at least one negative vocational problem (employment, income or education) to their cancer [15].

One reason survivors legitimately fear discrimination at work is because their supervisors and coworkers have misconceptions about survivors' abilities to work during and after cancer treatment. Of the 200 supervisors questioned in the 1996 survey, 33% believed that the employee could not handle the job and cancer, and 31% thought that the employee needed to be replaced [23]. After working with a person who has cancer, 34% of supervisors and 43% of coworkers said that they would be less concerned about this in the future [23]. A 1992 survey of 200 supervisors found that 66% were concerned that employees with cancer could no longer perform their jobs adequately [24]. Nearly one-half said that a cur-

rent cancer diagnosis would affect their decision to hire a qualified applicant [24]. Of 500 employees surveyed, 13% believed that co-workers with cancer probably would not be able to do their job. One in four believed they would have to work harder to pick up the slack [24].

Survivors of childhood cancer have experienced employment problems similar to those encountered by adult cancer patients. Studies conducted prior to the passage of comprehensive employment discrimination laws suggest that survivors encountered substantial employment obstacles. A Stanford study found that 43% of 403 Hodgkin's disease survivors experienced difficulties at work that they attributed to their cancer history [7]. Eight of the 40 survivors of childhood/adolescent Hodgkin's disease surveyed by Wasserman reported job problems [22]. Koocher and O'Malley studied 60 survivors of childhood cancer and found that 25% reported job discrimination (10 persons were refused a job at least once, three were denied benefits, three experienced illness-related conflict with a supervisor, four reported job task problems and 11 were rejected by the military) [14]. Greenleigh Associates found that younger cancer survivors who were either employed or active in the labor market were more concerned than were older survivors about revealing their cancer history when searching for another job [10].

Teta compared childhood cancer survivors with their siblings [20]. Eighty percent of the male survivors were rejected from the military vs 18% of their siblings, and 32% were rejected from job opportunities vs 19% of their siblings. Although female survivors faced disproportionate rejection from the military (75% vs 13% for siblings), the percentage of women rejected from employment was the same for survivors as for their siblings (19%).

More recent studies suggest a trend towards fewer problems. Hays surveyed 219 childhood survivors and matched controls who were treated between 1945 and 1975 and were at least 30 years old at the time of the survey [11]. He found that childhood survivors, with the exception of survivors of central nervous system tumors, experienced relatively the same employment history as the controls [11]. The controls, however, reported somewhat more annual income than did the survivors [11]. Hays' results suggest that as the length of time between diagnosis and initial employment increases, the incidence of employment problems may decrease.

Only those survivors who sought entry into the military faced increased rates of discrimination (15.2% of survivors at one institute and 20.7% at another, versus 7.7% and 1.8%, respectively, of the controls). Although the Department of Defense presumes cancer survivors to be unfit for military service, it considers waivers on a case-by-case basis for childhood survivors who have been out of treatment and cancer-free for five years (two years for Wilms tumor and germ cell tumors of the testes).

20.3 Why Cancer Survivors Face Employment Problems

Cancer survivors can face employment problems arising from limitations on their abilities to perform particular job functions resulting from their cancer treatment [4]. Diminished physical strength, stamina or cognitive skills can reduce a survivor's job opportunities. Additionally, the negative reactions of others, especially those based on stereotypes of cancer survivors, can cause job problems, including illegal discrimination. The work experiences of cancer survivors suggest that some disparate treatment is rooted in myths about cancer, three of which impact survivors' employment opportunities.

One myth is that cancer is a death sentence. Dr. Susan Mellette has found that, in informal word association tests, one of the most common thoughts associated with "cancer" is "death" [18]. The impact of the death sentence myth is that employers are hesitant to invest in an individual they believe will die imminently, insurance companies increase rates or refuse to insure at all and society disallows long-term planning on the assumption of a short-term life.

The second myth is that cancer is contagious. For example, one man in Wasserman's study reported that he "was transferred from his job in a hotel kitchen for fear that he might 'contaminate' the food" [22]. The impact of the contagious myth is that fellow workers physically and emotionally isolate those

with cancer and employers succumb to co-workers' demands to fire or transfer cancer patients. Fortunately, the belief that cancer is contagious is no longer very prevalent.

The third myth is that cancer survivors are an unproductive drain on the economy. The impact of the unproductive worker myth is that the employed are fired, demoted and denied benefits, while the unemployed are faced with remaining so or considering lying about their medical history to obtain a new job and the underemployed are drained of their self-esteem. Cancer survivors, however, have relatively the same productivity rates as other workers [6].

20.4 How to Combat Cancer-Based Discrimination

20.4.1 When Cancer-Based Discrimination is Illegal

Under federal law and most state laws, an employer cannot treat a survivor differently from other workers in job-related activities because of his or her cancer history, provided the survivor is qualified for the job. Individuals are protected by these laws only if:

1. They can do the major duties of the job in question.
2. Their employer treated them differently from other workers in job-related activities *because* of their cancer history.

20.4.1.1 Americans with Disabilities Act

The Americans with Disabilities Act (ADA) prohibits some types of job discrimination by employers, employment agencies and labor unions against people who have or have had cancer. All private employers with 15 or more employees, state and local governments, the legislative branch of the federal government, employment agencies and labor unions are covered by the ADA.

A "qualified individual with a disability" is protected by the ADA if he or she can perform the "essential functions" of the job. The ADA prohibits employment discrimination against individuals with a "disability," a "record" of a "disability," or who are "regarded" as having a "disability." A "disability" is a major health "impairment" that substantially limits the ability to do everyday activities, such as drive a car or go to work.

Cancer is an "impairment" as defined by law. In most circumstances, cancer survivors, regardless of whether they are in treatment, in remission or cured, are protected as persons with a disability because their cancer substantially limited a major life activity. Indeed, many federal courts and the Equal Employment Opportunities Commission (EEOC) consider cancer under most circumstances to be a disability under the ADA. Whether a cancer survivor is covered by the ADA is determined, however, on a case-by-case basis.

The ADA prohibits discrimination in most job-related activities such as hiring, firing and benefits. In most cases, a prospective employer may not ask applicants if they have ever had cancer. An employer has the right to know only if an applicant is able to perform the essential functions of the job. A job offer may be contingent upon passing a relevant medical exam, provided that all prospective employees are subject to the same exam. An employer may ask detailed questions about health only after making a job offer.

Cancer survivors who need extra time or help to work are entitled to a "reasonable accommodation." Common accommodations for survivors include changes in work hours or duties to accommodate medical appointments and treatment side effects. An employer does not have to make changes that would impose an "undue hardship" on the business or other workers. "Undue hardship" refers to any accommodation that would be unduly costly, extensive, substantial or disruptive, or that would fundamentally alter the nature or operation of the business. For example, an employer may replace a survivor who has to miss six months of work that cannot be performed by a temporary employee.

The ADA does not prohibit an employer from ever firing or refusing to hire a cancer survivor. Because the law requires employers to treat all employees similarly, regardless of disability, an employer may fire a cancer survivor who would have been terminated even if he or she were not a survivor.

Most employment discrimination laws protect only the employee. The ADA offers protection more responsive to survivors' needs because it prohibits discrimination against family members, too. Employers may not discriminate against workers because of their relationship or association with a "disabled" person. Employers may not assume that an employee's job performance will be affected by the need to care for a family member who has cancer.

20.4.1.2 Family and Medical Leave Act

The Family and Medical Leave Act requires employers with at least 50 workers to provide employees up to 12 weeks of unpaid leave for serious medical illness, including cancer, to care for themselves or dependents. The statute provides a number of benefits to people with cancer:

- Requires employers to continue to provide benefits, including health insurance coverage, during the leave period.
- Provides 12 weeks of unpaid leave during any 12 month period.
- Requires employers to restore employees to the same or equivalent position at the end of the leave period.
- Allows leave to care for a spouse, child or parent who has a serious health conditions such as cancer.
- Allows leave because a serious health condition renders the employee unable to perform the functions of the position.
- Allows an intermittent or reduced work schedule when medically necessary. Under some circumstances, an employer may transfer the employee to a position with equivalent pay and benefits to accommodate the new work schedule.
- Allows employees to stack leave under the FMLA with leave allowable under the state medical leave law.

The FMLA reasonably balances the needs of the employer and employee:

- Requires employees to make reasonable efforts to schedule foreseeable medical care to minimize workplace disruption.
- Requires employees to give employers 30 days notice of foreseeable medical leave or as much notice as is practicable.
- Allows employers to require employees to provide certification of medical needs and allows employers to seek a second opinion, at the employer's expense, to corroborate medical need.
- Permits employers to provide leave provisions more generous than those required by the FMLA.

20.4.1.3 Employee Retirement and Income Security Act

The Employee Retirement and Income Security Act (ERISA) may provide a remedy to an employee who has been denied full participation in an employee benefit plan because of a cancer history. ERISA prohibits an employer from discriminating against an employee for the purpose of preventing him or her from collecting benefits under an employee benefit plan. For example, some employers fear that the participation of a cancer survivor in a group medical plan will drain benefit funds or increase the employer's insurance premiums. An employer may violate ERISA if, upon learning of a worker's cancer history, it dismisses that worker for the purpose of excluding him or her from a group health plan. All employers who offer benefit packages to their employees are subject to ERISA.

20.4.1.4 Federal Executive Order on Genetic Information

Unlike most private and state employees, federal employees are protected from genetic-based discrimination. An Executive Order issued by President Clinton in 2000 prohibits federal departments and agencies from making employment decisions about civilian federal employees based on protected genetic information. The Order also prohibits federal em-

ployers from requiring genetic tests as a condition of being hired or receiving benefits.

20.4.1.5 State Employment Rights Laws

All states except Alabama and Mississippi have laws that prohibit discrimination against people with disabilities in public and private employment [12]. Alabama and Mississippi laws, which have not been amended since the 1970s, cover only state employees [12]. Several states, such as New Jersey, cover all employers regardless of the number of employees [12]. The laws in most states, however, cover only employers with a minimum number of employees [12]. A small number of states, such as California, Florida, Vermont and West Virginia, expressly prohibit discrimination based on cancer history [12]. Many state laws protect individuals with real or perceived disabilities, and therefore, cover most cases of cancer-based discrimination [12]. The rights of cancer survivors who are not handicapped are unclear in those states where courts have not addressed the issue and where one must have a physical or mental impairment to bring a claim.

Many states have leave laws similar to the federal Family and Medical Leave Act in that they guarantee employees in the private sector unpaid leave for pregnancy, childbirth and the adoption of a child. Some state laws provide employees with medical leave to address a serious illness, such as cancer. Several states provide coverage more extensive than the federal law.

State medical leave laws vary widely as to:

- how long an employee may take leave;
- which employees may take leave (most states require an employee to have worked for a minimum period of time);
- which employers must provide leave (a few states have leave laws that apply to employers of fewer than 50 employees);
- the definition of "family member" for whose illness an employee may take family medical leave;
- the type of illness that entitles an employee to medical leave;
- how much notice an employee must give prior to taking leave;
- whether an employee continues to receive benefits while on leave and who pays for them; and
- how the law is enforced (by state agency or through private lawsuit).

20.4.2 How to Avoid Becoming a Victim of Discrimination

Lawsuits are neither the only nor best way to fight employment discrimination against cancer survivors. State and federal anti-discrimination laws help cancer survivors in two ways. First, they discourage discrimination. Second, they offer remedies when discrimination does occur. These laws, however, should be used as a *last resort* because they can be costly, time-consuming, and they do not necessarily result in a fair solution. The first step is to try to avoid discrimination. If that fails, the next step is to attempt a reasonable settlement with the employer. If informal efforts fail, however, a lawsuit may be the most effective next step.

When seeking employment, survivors can take several steps to lessen the chance they will face cancer-based discrimination:

- Do not volunteer that you have or have had cancer, unless it directly affects your qualifications for the job. An employer has the right – under accepted business practices and most state and federal laws – to know only if you can perform the major duties of the job.
- Do not lie on a job or insurance application. If you are hired and your employer later learns that you lied, you may be fired for your dishonesty. Insurance companies may refuse to pay benefits or cancel your coverage.
- If a job questionnaire asks "have you ever had cancer?" or "have you had surgery in the past five years; if so, for what?", answer truthfully and then explain your current health and prognosis.
- Apply only for jobs that you are able to do. It is not illegal for an employer to reject you for a job if you are not qualified for it, regardless of your medical history.

- If you have to explain an educational gap or a long period of unemployment during cancer treatment, if possible, explain it in a way that shows your illness is past, and that you are in good health and expected to remain healthy. One way to de-emphasize a gap in your school or work history because of cancer treatment is to organize your resume by experience and skills, instead of by date.
- Offer your employer a letter from your doctor that explains your current health status, prognosis and ability to work. Be prepared to educate the interviewer about your cancer and why cancer often does not result in death or disability.
- Seek help from a job counselor with resume preparation and job interviewing skills. Practice answers to expected questions such as "why did you miss a year of school?" or "why did you leave your last job?" Answers to these questions must be honest, but should stress your current qualifications for the job and not past problems, if any, resulting from your cancer experience.
- If you are interviewing for a job, do not ask about health insurance until after you have been given a job offer. Then ask to see the "benefits package." Prior to accepting the job, review it to make sure it meets your needs.
- If possible, look for jobs with large employers because they are less likely to discriminate.
- Do not discriminate against yourself by assuming you are handicapped. Although cancer treatment leaves some survivors with real physical or mental disabilities, many survivors are capable of performing the same duties and activities as they did prior to diagnosis. With the help or your medical team, make an honest assessment of your abilities in relation to the mental and physical demands of the job.

20.4.3 Fighting Back Against Discrimination

Survivors who suspect that they are being treated differently at work because of their cancer history should consider an informal solution before filing a lawsuit. Survivors who face discrimination may consider the following suggestions:

- Consider using your employer's policies and procedures for resolving employment issues informally. First, let your employer know that you are aware of your legal rights and would rather resolve the issues openly and honestly than file a lawsuit. Be careful of what you say during discussions to avoid saying something that could be used to hurt your claim, should your discussions fail to resolve the problem.
- If you need some kind of accommodation to help you work, such as flexible working hours to accommodate doctors' appointments for follow-up or late-effects treatment, suggest several alternatives to your employer. If your employer offers you accommodations, do not turn them down lightly. Such an offer may be in the employer's favor if the case ends up before a judge. The Job Accommodation Network, a free service of the President's Committee on Employment of the Handicapped, helps employers to fashion accommodations for disabled employees. Call 1-800-ADA-WORK for more information.
- Educate employers and co-workers who might believe that people cannot survive cancer and remain productive workers. For example, you could give your employer a letter from your doctor explaining the type of cancer you have, or have had, and why you are able to work. More than 9,000,000 Americans are cancer survivors, so there is a good chance that some of your co-workers may have had cancer and are now valued employees.
- Ask a member of your healthcare team to write or call your supervisor to offer to mediate the conflict and suggest accommodations.
- Consider seeking support from your co-workers. They have an interest in protecting themselves from future discrimination.

Survivors who are considering a lawsuit should take several precautions to protect their rights:

- *Keep carefully written records of all job actions, both good and bad.* Good actions, such as positive performance evaluations, may help in a lawsuit to show that you were qualified for the job. Bad actions, such as being moved from a job that has

much public interaction to a job that has little interaction with the public after your cancer history is disclosed, may be used against your employer to show illegal acts. Keep complete notes of telephone calls and meetings (including dates, times and attendees), letters and the names and addresses of witnesses. Make written notes as events occur, instead of trying to recall the events weeks or months later.

- *Pause before you sue.* Carefully evaluate your goals. For example, do you want your job back, a change in working conditions, certain benefits, a written apology or something else? Consider the positive and negative aspects of a lawsuit. Potential positive aspects include getting a job and monetary damages, protecting your rights and tearing down barriers for other survivors. Potential negative aspects include long court battles with no guarantee of victory, legal fees and expenses, stress, a hostile relationship between you and the people you sue and a reputation in your field as a troublemaker.
- *Consider an informal settlement of your complaint.* Someone, such as a union representative, human resources employee or social worker, may be able to assist as a mediator. Your state or federal representative or local media may help persuade your employer to treat you fairly. Keep in mind that the first step most government agencies and companies take when they receive a complaint is to try to resolve the dispute without a costly trial.
- *Be aware of filing deadlines so you do not lose your option to file a complaint under state or federal law.* You have 180 days from the date of the action against you to file a complaint with a federal agency. If you work for the federal government, you have only 45 days to begin counseling with an equal employment opportunity counselor. In most states, you have 180 days to file a complaint with the state agency. If you file a complaint and later change your mind, you can drop the lawsuit at any time.

If an informal solution does not work, a lawsuit may be the most appropriate next step for some survivors. To enforce a complaint under the Americans with Disabilities Act, the survivor must file a complaint with the Equal Employment Opportunities Commission (EEOC). The EEOC will attempt to settle the dispute. If no settlement is reached, the EEOC may appoint an investigator to evaluate the claim. If the EEOC determines that your rights may have been violated, the EEOC may sue on your behalf or may grant you the right to file a lawsuit in federal court.

The complaint should be filed with the closest regional EEOC office. To obtain the location of your regional EEOC office, call the EEOC Public Information System in Washington, DC, at 1-800-669-4000. The EEOC also offers publications that explain the Americans with Disabilities Act and how to enforce your rights under the law (call 1-800-669-EEOC).

If the survivor proves that he or she was qualified for a job but treated differently because of a cancer history, he or she may be entitled to back pay, injunctive relief, such as reinstatement, and attorney's fees. The Americans with Disabilities Act does not, however, permit an award for compensatory or punitive damages, except for cases of intentional discrimination.

Under the Federal Rehabilitation Act, employees of recipients of federal financial assistance have up to 180 days from the action against them to file a complaint with the federal government. Employees of the federal government, however, have only 30 days.

Survivors must file a complaint with the federal agency that provided federal funds to their employer. Individuals who do not know the name of that agency or would like more information can contact: the Coordination and Review Section, Civil Rights Division, Department of Justice, P.O. Box 66118, Washington, DC 20530.

Remedies under the Federal Rehabilitation Act include, but are not limited to, back pay and reinstatement and attorney's fees. Punitive damages are not included.

Most states have a state agency that enforces the law. Some states permit people to file a lawsuit in state court to enforce their rights. Under most state laws, employees have up to 180 days from the action against them to file a complaint with the state enforcement agency.

For more information about the laws in your state, contact your state division on civil or human rights commission, or contact an attorney who is experi-

enced in job discrimination cases. The EEOC Public Information System at 1-800-669-4000 can help you locate the appropriate state enforcement agency. Also check your local telephone book under "state government."

In some situations, a single act may support a claim of discrimination under more than one law. For example, a cancer survivor who is denied a job by an employer in New York City may have a claim under the New York Human Rights Law (state), the New York City Law on Human Rights (city) and the Americans with Disabilities Act (federal).

Survivors who have a choice of remedies may file a complaint with each relevant enforcement agency. One agency may "stay" (not act on) the claim until another agency issues a decision. A survivor may always drop a complaint at any time once he or she determines which agency is most responsive. Factors to consider when choosing a resource include the types of remedies available, how quickly the agency responds to complaints (ask them how long the process usually takes) and which office is most convenient.

Survivors do not have to have a lawyer to represent them before an enforcement agency or court. However, someone who is represented by a lawyer experienced in job discrimination is more likely to meet with success.

20.5 Health Insurance

20.5.1 The Impact of Cancer on Health Insurance

Employment rights and health insurance rights are closely related because most adult Americans receive health insurance through an employer's group plan. Cancer survivors experience two types of barriers to health insurance. First, many survivors are unable to purchase affordable, effective coverage. Because most adults obtain health insurance through their own or their spouse's employment [6], many insurance problems are related to loss of employment and employment discrimination. Those who are not covered by group policies are the most vulnerable to insurance problems.

Studies report a variety of barriers to insurance, including refusal of new applications, policy cancellations or reductions, higher premiums, waived or excluded pre-existing conditions and extended waiting periods [6]. Approximately 25% of the 940 cancer patients surveyed by the Mayo Clinic Rehabilitation Program reported insurance "discrimination" [6]. Hays found that the more years that have passed since treatment, the better the chance for obtaining health insurance on the same terms as the general population [11]. In her study, Kornblith found that nearly one-half of Hodgkin's disease and leukemia survivors reported insurance problems due to cancer [15]. These problems included the denial of health insurance, increased insurance rates, problems changing from a group to an individual plan and the loss of health insurance [15].

Survivors of childhood cancer also experience problems obtaining health insurance. Like adult cancer survivors, the more years that have passed since treatment, the better the chances that childhood cancer survivors can obtain health insurance on the same terms as non-survivors. Vann found that young adult survivors of childhood cancer in North Carolina were more likely to be denied health insurance than their siblings [21]. Hays found that 81–91.9% of long-term childhood survivors were covered as adults by health insurance policies without cancer-related restrictions (compared with 82.3–94.6% of the controls) [11]. Among survivors, 6.9–14.3% described difficulties experienced by their parents in obtaining affordable health insurance for the entire family group during or after the survivor's illness (compared with 5.1–9.7% of the controls) [11]. Teta found that 14% of male childhood survivors and 9% of female childhood survivors were rejected for health insurance (compared with 1% and 0%, respectively, among controls) [20].

Barriers to adequate health insurance can have a detrimental impact on survivors' physical, emotional, financial, social and occupational health [9]. For example, one study found that breast cancer patients who have inadequate health insurance receive fewer medical services, lower quality hospital care, fewer major procedures and less state-of-the-art cancer treatment [2]. Survivors who have private health in-

surance and higher income experience better cancer screening, treatment and access to medical care [9]. This discrepancy is so great that survivors who have no or inadequate health insurance experience poorer health and higher mortality risks [9]. With the growth of managed care, survivors are increasingly forced to make decisions regarding their choice of type of treatment, treatment site and provider, based on whether their insurance plan will cover treatment, rather than on whether their choices satisfy their medical and personal needs [9].

20.5.2 Cancer Patients' Health Insurance Rights

Cancer patients who have health insurance are entitled to all of the rights described in their policies. Insurers who fail to pay for treatment in accordance with the terms of the policies may be sued for violating the contract between the survivor and the insurer. State and federal laws offer cancer survivors very limited remedies to barriers to securing adequate health insurance.

20.5.2.1 Federal Health Insurance Laws

Four federal laws provide survivors some opportunities to keep health insurance that they obtain through work.

Americans with Disabilities Act

First, the ADA prohibits employers from denying health insurance to cancer patients, if other employees with similar jobs receive insurance. The ADA does not require employers to provide health insurance, but when they choose to provide health insurance, they must do so fairly. An employer who does not provide a person with cancer or a history of cancer the same health insurance provided to employees with similar jobs must prove that the failure to provide insurance is based on legitimate actuarial data or that the insurance plan would become bankrupt or suffer a drastic increase in premiums, co-payments or deductibles. An employer, such as a small business, that can prove that it is unable to obtain an insurance policy to cover the survivor, may not have to provide him or her with the same health benefits provided to other employees. Because the ADA protects employees from discrimination based on their association with a person with a disability, an employer may not refuse to provide a family health policy solely because one of the employee's dependents has cancer.

Health Insurance Portability and Accountability Act

Second, the Health Insurance Portability and Accountability Act (HIPAA) alleviates job-lock by allowing individuals who have been insured for at least 12 months to change jobs without losing coverage, even if they previously have been diagnosed with cancer. Additionally, for previously uninsured individuals, group plans cannot impose preexisting condition exclusions of more than 12 months for conditions for which medical advice was received, or for which a diagnosis or treatment was received or recommended, within the previous six months. HIPAA prevents group health plans from denying coverage based on health status factors such as current and past health, claims experience, medical history and genetic information. Insurers may, however, uniformly exclude coverage for specific conditions and place lifetime caps on benefits.

HIPAA specifically helps cancer survivors retain their health insurance by:

- Alleviating job-lock by allowing individuals who have been insured for at least 12 months to change to a new job without losing coverage, even if they previously have been diagnosed with cancer. In addition, for previously uninsured individuals, group plans cannot impose preexisting condition exclusions of more than 12 months for conditions for which medical advice was received, or for which a diagnosis or treatment was received or recommended, within the previous six months.
- Preventing group health plans from denying coverage based on health status factors such as current and past health, claims experience, medical history and genetic information. Insurers, however, may uniformly exclude coverage for specific conditions and place lifetime caps on benefits.
- Increasing insurance portability for people changing from a group policy to an individual one.

- Requiring insurers of small groups to cover all interested small employers and to accept every eligible individual under the employer's plan who applies for coverage when first eligible.
- Requiring health plans to renew coverage for groups and individuals in most cases.
- Increasing the tax deduction for health insurance expenses available to self-employed individuals.

Comprehensive Omnibus Budget Reconciliation Act

Third, the Comprehensive Omnibus Budget Reconciliation Act (COBRA) requires employers to offer group medical coverage to employees and their dependents who otherwise would have lost their group coverage due to individual circumstances. Public and private employers with more than 20 employees are required to make continued insurance coverage available to employees who quit, are terminated or work reduced hours. Coverage must extend to surviving, divorced or separated spouses, and to dependent children.

By allowing survivors to keep group insurance coverage for a limited time, COBRA provides valuable time to shop for long-term coverage. Although the survivor, and not the former employer, must pay for the continued coverage, the rate may not exceed by more than two percent the rate set for the former co-workers.

Eligibility for the employee, spouse and dependent child varies under COBRA. The employee becomes eligible if he or she loses group health coverage because of a reduction in hours or because of termination due to reasons other than gross employee misconduct. The spouse of an employee becomes eligible for any of four reasons:

1. Death of spouse.
2. Termination of spouse's employment (for reasons other than gross misconduct) or reduction in spouse's hours of employment.
3. Divorce or legal separation from spouse.
4. Spouse becomes eligible for Medicare.

The dependant child of an employee becomes eligible for any of five reasons:

1. Death of parent.
2. Termination of parent's employment or reduction in parent's hours.
3. Parent's divorce or legal separation.
4. Parent becomes eligible for Medicare.
5. Dependent ceases to be a dependent child under a specific group plan.

The continued coverage under COBRA must be identical to that offered to the families of the employee's former co-workers. If employment is terminated for any reason other than gross misconduct, the employee and his or her dependents can continue receiving coverage for up to 18 months. A qualified beneficiary who is determined to be disabled for Social Security purposes at the time of the termination of employment or reduction in employment hours can continue COBRA coverage for a total of 29 months. Dependents can continue coverage for up to 36 months if their previous coverage will end because of any of the above reasons.

Continued coverage may be cut short if:

1. The employer no longer provides group health insurance to any of its employees.
2. The continuation coverage premium is not paid.
3. The survivor becomes covered under another group health plan.
4. The survivor becomes eligible for Medicare.

Employee Retirement and Income Security Act

Fourth, the Employee Retirement and Income Security Act (ERISA) regulates employee-benefit or self-insured plans. ERISA prohibits an employer from discriminating against an employee for the purpose of preventing him or her from collecting benefits under an employee benefit plan. Employee benefit plans are defined broadly, and include any plan whose purpose is to provide medical, surgical or hospital care benefits or benefits in the event of sickness, accident, disability, death or unemployment.

Unlike commercial insurance plans that employers purchase to provide health insurance as a benefit for their employees, self-insured plans are funds set

aside by employers to reimburse employees for their allowable medical expenses. The claims employees file to obtain their reimbursement through these plans are likely to be administered by commercial insurance companies, so most people covered through self-insured plans do not even realize their health insurance is somewhat different from insurance purchased by an insurance company. Generally, large employer groups or unions find it to their benefit to self-insure, while smaller employer groups choose to finance employee health benefits through commercial insurers. Employee-benefit plans are regulated by federal law only and are not subject to state insurance laws and regulations.

ERISA may provide a remedy to an employee who has been denied full participation in an employee benefit plan because of a cancer history. ERISA prohibits an employer from discriminating against an employee for the purpose of preventing him or her from collecting benefits under an employee benefit plan. Some employers fear that the participation of a cancer survivor in a group medical plan will drain benefit funds or increase the employer's insurance premiums. A violation of ERISA may occur when an employer, upon learning of a worker's cancer history, dismisses that worker for the purpose of excluding him or her from a group health plan.

If an employer fires an employee for the purpose of cutting off the employee's benefits, regardless of whether the employee is considered disabled under the statute, the employer may be liable for a violation of ERISA. An employer also may violate ERISA by encouraging a person with a cancer history to retire as a disabled employee. Most benefit plans define disability narrowly to include only the most debilitating conditions. Individuals with a cancer history often do not fit under such a definition and should not be compelled to so label themselves.

Under certain circumstances, ERISA may provide grounds for a lawsuit to workers with a cancer history. ERISA covers both participants (employees) and beneficiaries (spouses and children). Thus, if the employee is fired because his or her child has cancer, the employee may be entitled to file a claim. ERISA, however, is inapplicable to many victims of employment discrimination, including individuals who are denied a new job because of their medical status, employees who are subjected to differential treatment that does not affect their benefits, and employees whose compensation does not include benefits.

20.5.2.2 State Insurance Laws

Additionally, every state regulates policies sold by insurance companies in the state. These laws vary significantly. Some states require insurance policies to cover off-label chemotherapy, minimum hospital stays for cancer surgery, and benefits for certain types of cancer treatment and screening. Most states provide the right to convert a group health insurance policy to an individual policy. The specific rules of open enrollment periods vary from state to state. Many states guarantee the right to purchase health insurance to individuals who are barred from the marketplace due to their medical history. Some states provide group health insurance through high-risk pools.

20.5.3 How to Challenge a Denied Claim

Cancer treatment often involves numerous bills from different parties: hospital, physicians (surgeon, anesthesiologist, oncologist, radiologist, etc.), support services (nurse, social worker, nutritionist, therapist, etc.), radiology group, pharmacy (drugs and medical supplies) and consumer businesses (wigs, breast inserts, special clothing, etc.). Insurance companies will pay some of these parties directly, in part or in whole. The survivor must pay other bills and submit copies to the company for reimbursement.

Keeping track of dozens of expenses, often amounting to tens of thousands of dollars, can be confusing and exhausting. The key to collecting the maximum benefits covered by the insurance policy is to keep accurate records of all medical expenses by:

- Making photocopies of everything you send to your insurance company, including letters, claim forms and bills.
- Keeping all correspondence you receive from your insurance company.
- Submitting a bill, even if you are unsure whether a particular expense is covered by your policy.

- Keeping accurate records of your expenses, claim submissions and payment vouchers.

A policyholder has a right to appeal a claim that is denied by a public or private insurer. Because claims are frequently delayed or rejected in part or in full because of errors in filling out the claims forms, care should be taken in accurately providing all the information requested by the insurance company. The following steps could help survivors who are having trouble collecting on their claims:

- Contact your insurance company in writing and insist that they reply in writing. Send copies of all documents and keep the originals for your files.
- Keep a record of your contacts with the insurance company (copies of all letters you send and notes from every telephone call). Write down everything you do, the names of people you talk to, dates and other facts.
- Contact the state or federal agency that regulates your insurance provider if you do not receive a satisfactory and timely answer from your insurer. Most state insurance departments or commissions help consumers with complaints. Look under State Government in the telephone directory.
- Contact cancer support organizations in your community. Some, such as the Candlelighters Childhood Cancer Foundation, offer ombudsman programs to help survivors and their families maximize insurance reimbursement.
- If your claim is still not settled, consider filing a complaint in small claims court or hiring a lawyer to sue your insurance company.

20.6 Right to Education

Some survivors of childhood cancer grow up with long-term and late effects of treatment that affect their ability to receive an education and obtain gainful employment. Late effects of radiation, chemotherapy and surgery can include physical and mental limitations, such as neuro-cognitive deficits, growth retardation, cardiac dysfunction, second malignancies and fatigue. Two federal laws protect survivors who have such disabilities from barriers to education, which in turn, help expand their employment opportunities.

20.6.1 Individuals with Disabilities Education Act

The Individuals with Disabilities Education Act (IDEA) requires states to provide children with disabilities with a free appropriate public education from the age of three to 21. A child with a disability includes a child with developmental disabilities, a hearing, speech, visual, or orthopedic impairment, a serious emotional disturbance, brain injury, autism, learning disability or other similar health impairment.

The purpose of the IDEA is to ensure that children with disabilities receive a public education that emphasizes special education and related services designed to address their individual needs. Thus, every child is entitled to an individualized education plan (IEP), which is crafted by a team of professionals who are familiar with the child's specific limitations, needs and abilities. Where possible, school districts are required to provide children with disabilities an education in the regular classroom setting. Schools must provide whatever services are necessary to help a child benefit from his or her education. These services may include a special education teacher, speech or sign-language interpreter, large-print texts, placement in private school, testing accommodations, tutor, special transportation, occupational therapy, physical therapy, speech therapy or psychotherapy. Although schools are not required to provide all medical services, they must provide certain medical services that are necessary to implement the IEP. For example, a child who uses a catheter is entitled to the services of a school nurse or other trained professional to help keep the catheter clean during the school day.

20.6.2 Americans with Disabilities Act

Students who are older than 21, and thus no longer protected by the IDEA, can turn to the Americans with Disabilities Act for protection from discrimination in higher education. The ADA mandates that no

individual with a disability shall be excluded from participation in public services or programs, such as higher education. Educational institutions are required to provide disabled students who can meet the academic standards of the school with reasonable accommodations. For example, a university may be required to provide a sign-language interpreter to a cancer survivor who has a hearing loss as a result of treatment. Additionally, the institution may not discriminate on the basis of the student's disability. For example, a survivor who has respiratory fibrosis may not be required to complete the same physical educational standards required of other students.

20.7 Conclusion

Survivors of childhood cancer diagnosed in the Twenty-First Century can expect fewer legal and economic barriers than those encountered by previous survivors. Although the barriers to adequate health insurance still remain, the majority of childhood cancer survivors today will enter schools and the job market with a decreasing chance of facing discrimination and an increasing array of legal rights and remedies.

Acknowledgements. This chapter is adapted in part from Hoffman B (ed) (2004) A cancer survivor's almanac: charting your journey. JWiley, New York, Chaps. 12 and 13.

Appendix

Tables 1, 2, 3 and 4 give details of some useful resources, outline the main provisions of the Americans with Disabilities Act and the Family and Medical Leave Act, and summarize advice on avoidance and handling of workplace discrimination.

Table 1. Resources

Organization	Contact	Service
The National Coalition for Cancer Survivorship	1010 Wayne Avenue, 7th Floor, Silver Spring, MD 20910; (888) YES-NCCS (937-6227); www.canceradvocacy.org	Provides publications, answers to questions about employment rights and assistance locating legal resources. Publications include: "Working It Out: Your Employment Rights as a Cancer Survivor" [12] (booklet), "What Cancer Survivors Need to Know About Health Insurance" (booklet) and "A Cancer Survivors' Almanac: Charting Your Journey" [12] (paperback book available from NCCS and most bookstores).
Cancer Care, Inc.	275 Seventh Avenue, New York, NY 10001; (800) 813-HOPE or (212) 302–2400; www.cancercare.org	Provides assistance by oncology social workers, including answers to questions about employment, insurance and finances. Provides help in locating local resources.
Equal Employment Opportunities Commission	(800) 669–4000 (to obtain the location of regional EEOC office); (800) 669-EEOC (to obtain free publications about the ADA); www.eeoc.gov	Federal agency that enforces the ADA. Individuals must file a complaint with the EEOC within 180 days of the discriminatory act. The EEOC will attempt to settle the dispute. If no settlement is reached, the EEOC may appoint an investigator to evaluate the claim, sue on the claimant's behalf or grant the right to file an individual lawsuit in federal court.
Medicare Hotline	800-633-4227; www.medicare.gov	

Table 2. Americans with Disabilities Act

What the ADA prohibits
Discrimination based on actual disability, perceived disability or history of disability
Which employers are covered by the ADA
Employers with at least 15 employees
What the ADA requires
Reasonable accommodations
Employer may ask only job-related medical questions
Employer may not discriminate because a family member is ill
Does not require employer to provide health insurance
How the ADA is enforced
Enforced by the EEOC: (800) 669-4000 (local EEOC office); (800) 669-EEOC (enforcement information)

Table 3. Family and Medical Leave Act

Applies to employers with 50+ employees
Provides 12 weeks of unpaid leave during any 12-month period to care for seriously ill self, spouse, child or parent
Requires employer to continue to provide benefits – including health insurance – during the leave period
Requires employer to restore employee to the same or equivalent position at the end of the leave period
Requires employee to make reasonable efforts to schedule foreseeable medical care so as not to disrupt the workplace
Enforced by private lawsuit

Table 4. Discrimination

How to avoid employment discrimination
Do not volunteer cancer history
Do not lie about medical history
Keep focus on current health and ability
Be prepared with letter from physician
Seek employment with large employers
Do not ask about health benefits prior to job offer
Steps to take if confronted with discrimination
Consider resolving problem informally
Suggest accommodations
Seek support from health care providers, co-workers, legal resources and other survivors
Keep written records of actions
Be aware of filing deadlines
Carefully evaluate goals

References

1. Amgen (1997) Cancer in the workplace survey (random telephone survey of 662 employed adult Americans interviewed from June 13 to June 15, 1997)
2. Ayanian JZ et al. (1993) The relation between health insurance coverage and clinical outcomes among women with breast cancer. N Engl J Med 329:326–331
3. Bleyer WA (1990) The impact of childhood cancer on the United States and the world. CA 40:355–367
4. Bradley C, Bednarek H (2002) Employment patterns of long-term cancer survivors. Psycho Oncol II:188–198
5. Clark EJ, Stovall EL (1996) Advocacy: the cornerstone of cancer survivorship 4. Cancer Pract 239:243
6. Crothers HM (1987) Health insurance: problems and solutions for people with cancer histories. Proceedings of the 5th national conference on human values and cancer. American Cancer Society, San Francisco, California Division of the American Cancer Society, pp 100–109. Available from the American Cancer Society
7. Fobair P, Hoppe RT, Bloom J, Cox J, Varghese A, Spiegel D (1986) Psychosocial problems among survivors of Hodgkin's disease. J Clin Oncol 4:805–814
8. Ganz P (2004) Understanding cancer, its treatment, and the side effects of treatment. In: Hoffman B (ed) A cancer survivors' almanac: charting your journey. Wiley, New York
9. Glajchen M (1994) Psychosocial consequences of inadequate health insurance for patients with cancer. Cancer Pract 2:115–120
10. Greenleigh Associates (1982) Report on the social, economic and psychological needs of cancer patients in California. Report of American Cancer Society, San Francisco, CA Division, 1982. (Also in) Proceedings of Western States Conference on Cancer Rehabilitation. San Francisco, 1982
11. Hays DM et al. (1992) Educational, occupational, and insurance status of childhood cancer survivors in their fourth and fifth decades of life. J Clin Oncol 10:1397–1406
12. Hoffman B (2004) Working it out: your employment rights, chap 13. In: Hoffman B (ed) A cancer survivors' almanac: charting your journey. Wiley, New York
13. Keene N, Hobbie H, Ruccione K (2002) Childhood cancer survivors: a practical guide to your future. O'Reilly, Sebastopol, p xvii
14. Koocher GP, O'Malley JE (1982) The Damocles syndrome: psychosocial consequences of surviving childhood cancer. McGraw-Hill, New York
15. Kornblith AB et al. (1998) Comparison of psychosocial adaptation of advanced stage Hodgkin's disease and acute leukemia survivors. Ann Oncol 9:297–306
16. Meadows A (1998) Cancer survivors: future clinical and research issues. Am Soc Clin Oncol Educ Book 115:116
17. Meadows A, Green D, Oeffinger K (2003) Pediatric cancer survivors: past history and future challenges. Curr Prob Cancer 27:105–168

18. Mellette S (1986) The semantics of cancer and disability. Proceedings of the workshop on employment, insurance and the patient with cancer. American Cancer Society, New Orleans, pp 24–26
19. Mor V, Guadognoli E, Wool M (1988) The role of concrete services in cancer care. Adv Psychosom Med 18:102–118
20. Teta MJ, del Po MC, Kasl SV, Meigs JW, Myers MH, Mulvihill JJ (1986) Psychosocial consequences of childhood and adolescent cancer survival. J Chron Dis 39:751–759
21. Vann JC et al. (1995) Health insurance access to young adult survivors of childhood cancer in North Carolina. Med Pediatr Oncol 25:389–95
22. Wasserman AL, Thompson ET, Wilmas JA, Fairclough DL, (1987) The psychosocial status of survivors of childhood/adolescent Hodgkin's disease. Am J Dis Child 141:626–631
23. Working Woman/Amgen, Cancer in the Workplace Survey (conducted by CBD Research & Consulting; random telephone survey of 500 survivors employed at time of their treatment, 100 supervisors, and 100 co-workers in May 1996; published September 1996)
24. Yankelovich Clancy Shulman (1992) Cerenex survey on cancer patients in the workplace; breaking down discrimination barriers (unpubl)

Methodological Issues in the Study of Survivors of Childhood Cancer

Ann C. Mertens · Yutaka Yasui

Contents

21.1 Introduction

Numerous reports and reviews have been published about the late effects of chemotherapy and radiation among childhood cancer survivors [11, 13, 17, 23]. This literature describes the sequelae present at, or shortly following, the end of therapy, as well as the occurrence of selected late complications. Most studies of late sequelae focus on medical outcomes. These studies have shown that both the type and intensity of therapy, as well as the age of the patient at therapy, are important factors influencing both overall survival and the occurrence of late effects. Children who are younger at diagnosis and treatment are more severely affected than older children, particularly if treatment is administered at a time of significant development and growth. However, specific treatment exposures and outcomes remain to be investigated in depth. Well-designed epidemiologic investigations of these subjects can provide strong and reliable evidence on which to base both clinical practice and health policy. The objectives of this chapter are to present an overview of methodological issues important in the proper conduct and analysis of late-effect studies, using the Childhood Cancer Survivor Study as an illustration, and to outline briefly several types of study design that are useful in the research of childhood cancer survivors hip research.

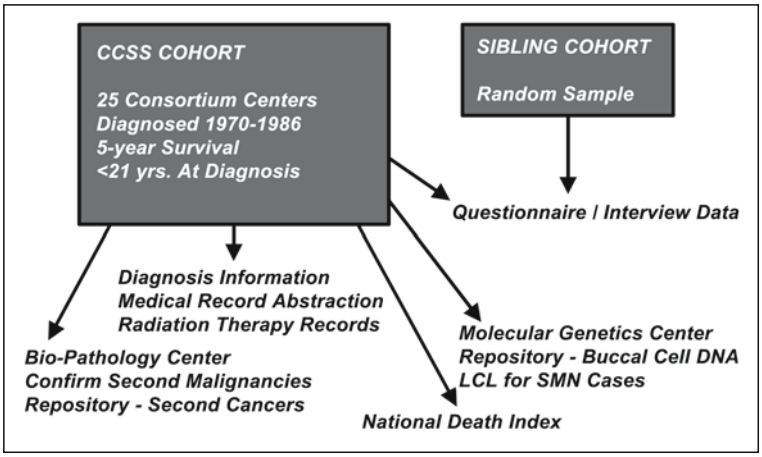


Figure 21.1
Childhood Cancer Survivor Study

21.1.1 Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) (NIH study # U01-CA-55727) is a multi-institutional collaboration, established in 1994, to assess late, adverse events following treatment for childhood or adolescent cancer (see Fig. 21.1). Each participating institution identified patients who fulfilled the following eligibility criteria: a) diagnosis of leukemia, CNS tumors (all histologies), Hodgkin's disease, non-Hodgkin's lymphoma, malignant kidney tumor (Wilms), neuroblastoma, soft tissue sarcoma or bone tumor (list of eligible ICD-O codes can be found at www.cancer.umn.edu/ccss); b) diagnosis and initial treatment at one of the 25 collaborating CCSS institutions; c) diagnosis date between January 1, 1970 and December 31, 1986; d) age less than 21 years at diagnosis; e) survival five years from diagnosis.

Information on the characteristics of the original cancer diagnosis and treatment was obtained for 20,276 eligible cases from the treating institution [21]. Baseline data were collected for members of the study cohort using a 24-page, self-administered questionnaire. Treatment information was obtained for participants who gave permission to abstract information from their medical records. The data collection surveys are available for review at www.cancer.umn.edu/ccss.

21.2 Methodological Issues Relevant to Survivor Studies

21.2.1 Selection of Study Subjects

Studies of late effects begin with the conjecture that a particular factor or exposure may influence the occurrence of a disease. A study is then designed to test the conjecture or hypothesis. The first, and perhaps the most important, task in the study design is the definition and selection of the population to be tested and the definition and selection of the comparison group, i.e. the group that will appropriately determine whether a statistical association exists between the factor or exposure of interest and the outcome or disease of interest. The study population must be defined in such a way that it is as representative as possible of the wider population of interest (i.e. the entire population of childhood cancer survivors). Care must be exercised in selecting cases and controls to minimize the possibility of differential selection on the basis of exposure. The first step in case selection is to define the disease/outcome of interest and to establish strict diagnostic criteria to keep the disease entity well defined. Participants can be obtained from a population-based source, such as a disease registry, from hospital or clinic records over a specified period of time, or they can be members of a defined study cohort assembled from a consortium of treating institutions, such as the CCSS. Each source from which

potential study subjects can be drawn will present both drawbacks and benefits. Studies that recruit their subjects from single institutions generally suffer from small sample sizes and findings may be less generalizable. There are advantages to institution studies, particularly if outcomes of interest include clinic follow-up. Clinical trial groups, such as the Children's Oncology Group, have the advantage of being able to ascertain approximately 93 percent of all newly diagnosed children with cancer [22]. A drawback, however, is that cases not enrolled in the study are generally not followed by the cooperative groups, which may lead to an ascertainment bias. Consortia such as the CCSS allow for complete case ascertainment from each participating institution, but can suffer from low participation rates or from subjects being lost to follow-up.

An important rule of thumb for the selection of the comparison group is that it should represent a population with the potential to develop the disease or condition being studied. In the CCSS, siblings of survivors were selected to serve as the study's comparison group, on the assumption that these individuals shared many of the same genetic and environmental factors, with the exception of treatment exposures, and, as a result, that their risk for developing diseases/conditions was comparable to that of their sibling who had had cancer.

21.2.2 Protection of Human Subjects

Research projects involving human subjects must be approved by the Human Subjects Committee at each participating institution. Approval is conditional upon ensuring that subjects are not placed at undue risk during the research, and that subjects (both cases and controls) give informed consent to their participation. Research in late effects entails the collection of treatment-related exposure information and validation of health-related outcomes from medical records. In addition, in the United States, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) sets forth minimum standards for protecting the privacy of this type of information. Access to medical information can be granted only after written permission is obtained from study subjects using a HIPAA authorization document which describes the uses to which the information will be put and informs subjects of any anticipated disclosures of their protected health information (PHI).

21.2.3 Bias, Confounding, Matching

Once a well-defined study population has been assembled, it is then necessary to assess the study hypothesis with considerations of possible alternative explanations. Finally, a conclusion is drawn as to whether the statistical association under investigation represents a cause-effect relationship between exposure and disease.

To determine whether a statistical association is valid, possible sources of bias must be considered and, if possible, eliminated. Bias refers to any element of the study design, data collection, or data analysis that introduces a systematic error into the results. It can occur when individuals are selected into a study, or through the manner in which information is obtained or reported. Bias is minimized by ensuring that subject selection, exposure assessment and methods of collecting information are all identical between the two groups being compared.

Confounding is an alternative explanation for an observed association between an outcome and an exposure. Confounding occurs when unmeasured or uncontrolled factors associated both with the exposure and with the outcome explain the observed association. A confounder variable cannot be a step in the causal pathway between the exposure and the outcome. One can control for known confounders either in the study design or analysis phase. To address confounding in the study design, matching can be performed. Matching is the selection of a comparison group that is identical to the group of interest with respect to the distribution of one or more confounders. Often, one matches on known major risk factors, such as age for chronic diseases, in order to remove their effect so that the effect of variables under study can be more clearly discerned.

21.2.4 Exposure Assessment

In assessing the risk of late effects by therapeutic exposure, one must obtain accurate and detailed information on all cancer therapies received by the patients. The assessment process must be unbiased with respect to patients' characteristics, including the types of cancer, the treating institution, whether the patient has experienced any late effects and the length of follow-up. Specifically, the information must be equally available and of equal quality across all institutions participating in the study. Furthermore, it should include all relevant exposures prior to development of the condition under study, including treatment for any recurrence of the individual's original diagnosis and for any subsequent primary cancer. Potential obstacles to the accurate assessment of therapeutic exposures include incomplete or lost medical records. To ensure accuracy and minimize bias, a detailed, clear protocol for therapeutic exposure assessment must be prepared and followed. Such a protocol includes the development of a structured, medical record abstraction form, as well as consistent training of personnel to abstract the medical records.

In the CCSS, data managers at each participating institution were trained centrally to abstract all treatment data for the primary diagnosis, including initial treatment, treatment for relapse and myoablative therapy preparatory to bone marrow transplant for the original diagnosis. Chemotherapy information entered on the abstraction form included beginning and end dates of therapy, standard protocols used, all chemotherapy drugs received, whether any drug was permanently discontinued due to toxicity and the route of administration for each drug. Additionally, detailed dose information was collected on 22 specific chemotherapeutic agents.

Information was also collected on all surgical procedures performed under general anesthesia from the time of diagnosis. This information included the ICD-9 code assigned to each procedure, the surgery date and the name of the institution where surgery was performed.

Information on radiation treatment that was collected on the CCSS medical-record abstraction form included beginning and end dates of treatment and the name and address of the radiation therapy facility. Retrieved therapeutic radiation records were copied and forwarded to the CCSS Radiation Dosimetry Center at the MD Anderson Cancer Center, where dosimetry was performed.

21.2.5 Outcome Assessment

While medical records can be used to ascertain outcome data, such records have significant limitations in the study of long-term outcomes in childhood cancer survivors. As survivors grow into adults, the medical facilities at which they receive care will likely shift from the institutions where they were treated for their primary diagnosis to adult care facilities. Because of the large number of adult care facilities involved, requesting copies of records can be costly, as well as inefficient. Direct communication with study subjects – in person, by telephone or by mail – using standardized interview protocols or questionnaires, is a more practical method of preliminary outcome ascertainment in late effects research. Data on outcomes for which self-reporting is unreliable can then be supplemented/validated by a focused collection of medical records.

A well-constructed survey instrument capable of eliciting reliable and valid medical information from study subjects is crucial to success in late-effect research. Questions must be phrased in such a way as to obtain the most accurate information possible while encouraging high response rates. Both closed and open-ended questions can be useful in late-effect studies. Closed questions require subjects to respond with a limited number of set responses (e.g. a list of drugs); open-ended questions require respondents to recall information and give explanations of events. All questionnaires and other data capture forms must be piloted before first use to determine whether questions are properly phrased and unambiguous, and to ensure that the contents of the questionnaire and the length of time required to complete it are acceptable to respondents.

21.2.5.1 Confirmation of Key Medical Events

Data on key medical events collected by interview or questionnaire can often be validated by medical records. Information about hospitalizations for recurrent or new primary neoplasms, for example, can be validated by obtaining the pathology report from the diagnosing hospital. Review of the pathology report can then confirm the diagnosis reported on the questionnaire.

Medical records can also be used to validate other key events of interest that have been diagnosed by a physician. Outcomes that are self-reported on a study questionnaire can be followed-up with a telephone script to elucidate whether and where the participant received treatment for the reported outcomes. A request for the subject's medical records for the time period of the diagnosis of the selected outcome can then be made to the appropriate institution. Common late effects that can be validated in this fashion include congestive heart failure, myocardial infarction, stroke and lung fibrosis.

Medical records are useful for identifying false-positive, self-reported outcomes; however, it is difficult to identify false-negative outcome events that are not reported by the respondent. To remedy this, a fraction of the study subjects who do not self-report a selected outcome can be chosen randomly for assessment by medical records. For the analysis of potentially misclassified outcome data with a validation subset such as this, see references [18, 19].

21.2.6 Need for External Comparisons

A comparison group outside of the survivor population of interest is needed to evaluate the extent of the excess risk of a selected outcome experienced by survivors. For example, it is expected that chronic disease frequencies increase as survivors age: the question is whether, and to what extent, survivors are experiencing excess risk beyond that seen in the general population. An external control cohort, whose members have not been exposed to the therapy-related risk factors under investigation, such as survivors' close-age siblings or friends, can provide a convenient comparison group, as in the CCSS. To avoid potential bias, assessments of exposures and outcomes in such an external comparison cohort must be done in an equal manner as in the survivor cohort. Survivor cohorts can also be compared to available population data, such as mortality from vital statistics, the US SEER registry cancer incidence data or health behaviors reported in the National Health Interview Survey. To assure comparability of study data with external population data, it is necessary to use the same definitions of outcomes (e.g. specific types of cancer as defined by SEER) or the same questionnaire items (e.g. smoking question items used in the National Health Interview Survey) as those used by the population registry or survey to which study participants are being compared.

21.2.7 Importance of Thorough Recruitment and Follow-up

Significant loss of eligible cases in any study can compromise the validity of study findings, since it will be difficult to determine if exposures or outcomes of interest are in some way related to the loss. Non-participation in case-control studies can cause bias if response rates differ between cases and controls and are somehow related to exposure. Loss to follow-up from either cases not found at the initiation of the study or those lost after entry into the cohort introduces another potential source of bias. For example, individuals who remain in the study might be healthier than those who drop out, or those who participate may not be truly representative of the population in terms of rates of disease or risk factors.

21.2.7.1 Tracing Techniques

In late-effect research it is particularly important to achieve maximum ascertainment, enrollment and follow-up of the eligible study population in order to minimize the potential introduction of bias. One challenge is to locate subjects who may have moved since they became eligible for membership in the cohort [12, 14]. Hospital records are commonly used for assembling a cohort. Because most of the information contained in such records is not collected with the objective of long-term follow-up, key pieces of

information that would facilitate tracing and successful location of eligible subjects are often missing. Moreover, subjects who have ongoing medical conditions, which might include the research outcomes of interest, may be more likely to have been seen in follow-up visits and to have had their addresses updated in their medical records. This increases the potential for enrolling a selected and possibly biased study population.

In attempting to contact a cohort by mail, correspondence can be sent to subjects (or their parents) at the last known address per medical records, via envelopes marked "Address Service Requested." Common tracing techniques for non-respondents include directory assistance and Internet searches (people-finder websites). If these methods fail, commercial survey research firms can be employed for more intensive tracing.

In the United States information provided to commercial tracing firms should include the study subject's full name, date of birth, social security number (when available), last known address and parents' address(es). The sources such firms might pursue can include telephone directory assistance, reverse telephone directories, Polk's directories, voter registration records, post offices, Department of Motor Vehicles and commercial credit bureaus. Study subjects who are not successfully traced by these methods can be processed through the National Death Index (NDI) to determine vital status.

21.2.8 Use of Molecular Tools

While an increased risk of late effects is often associated with treatment-related factors, individual susceptibility to a particular outcome is clearly variable, with the majority of patients treated for cancer not affected. A possible explanation for unequal susceptibility is variability in the genetic make-up of survivors. Biologic specimens can be collected to evaluate genetic influence on the risk of late effects. Collection of genomic DNA samples, however, is a challenge in a survivor study population that is large, highly mobile and geographically dispersed.

Several studies have reported success in collecting buccal cell samples by mailing mouthwash to participants and requesting return by mail [5, 9, 15]. This method was employed in the CCSS. Participants were mailed a specimen collection kit that contained a cover letter describing the DNA study, a consent form, an instruction sheet, a 45-ml bottle of mouthwash, a specimen collection container, return mail labels and postage. They were instructed to repeatedly rinse the mouth with mouthwash, and to return the used mouthwash to the laboratory in the sterile container provided with the kit. The buccal cell samples thus collected were centrifuged, and the cells pelleted and washed. DNA was extracted, quantified, aliquoted and stored in a hydration solution at –20 °C until used for genotyping. The quality and volume of the material obtained were excellent, with a median of 64μg (range 1–9,000 μg) DNA obtained per sample.

Other materials that can be collected for use in genetic or proteomic research are tumor tissue from subsequent cancers and blood specimens. A limitation on the collection of tumor specimens is that many community hospitals store tumor tissues only for a limited time after surgery. Blood specimens can be requested and collected during a participant's regularly scheduled doctor's appointment, although this can be expensive and logistically complex. Another possibility is to contract with a company, such as those that perform insurance physicals, to arrange for a phlebotomist to visit the participant's home or office (or other convenient location) to take the blood specimen.

In addition to genetic susceptibility analyses, the biologic specimens can potentially be used for other research purposes, such as the identification of high-risk groups and for genetic/proteomic screening for late effects.

21.3 Types of Epidemiologic Study Designs

Two basic types of study design are employed in epidemiologic research of late effects: descriptive studies and analytic studies. Features of both the exposure (usually treatment-related) and the outcome will influence the choice of study design, as will the amount of time needed to collect the data and the resources available to conduct the study. Results of

previous research and gaps in knowledge that remain to be filled must also be taken into account. A given hypothesis can be, and often is, the subject of a progression of different types of studies, each building on a previous study, as researchers attempt to gain increasing precision in their understanding of particular late effects.

21.3.1 Descriptive Studies

Descriptive studies are essentially concerned with the distribution of the late effect or disease outcome of interest. These types of studies are primarily used to generate hypotheses. They generally use existing data and are, therefore, relatively inexpensive to conduct. However, they cannot cause-and-effect relationships between exposure and outcome. The three principal types of descriptive study are case reports, case series and cross-sectional studies.

Case reports and case series describe the characteristics of one or more subjects with a given disease. These types of reports can lead to the formulation of hypotheses for testing in analytic studies. An example of a case series report is an early review of retinoblastoma patients treated with radiation who subsequently presented with osteogenic sarcoma as a second primary diagnosis [24]. Because these tumors occurred in the radiation field at sites that were uncharacteristic of spontaneously occurring sarcomas, the investigators suggested a strong role for radiation in their etiology. The link between retinoblastoma and subsequent sarcomas has been confirmed in several follow-up studies.

Cross-sectional studies, also referred to as prevalence studies, are descriptive studies used to assess the presence (or absence) of both exposure and disease at the same point in time. Results from these studies are useful in generating hypotheses regarding possible associations between exposure and disease. As with other descriptive studies, they represent a feasible and affordable strategy for developing etiologic hypotheses. There are many examples of cross-sectional studies in the late-effect literature that have led to further research. For example, Sklar et al. conducted a study of final adult height attainment in long-term survivors of acute lymphoblastic leukemia [25]. This was one of the first studies to track changes in height through adulthood, and to associate these findings with different treatment regimens (no cranial radiation, 1800cGY cranial radiation, 2400cGY cranial radiation). It led to subsequent studies that have confirmed the significance of the association between cranial radiation dosage and final height attainment.

21.3.2 Analytic Studies

Analytic studies focus on determinants of a disease and are often set up to test hypotheses generated from previous descriptive studies. Analytic studies are designed to determine whether certain exposures cause (or prevent) a disease of interest. The general approach for analytic studies is first to define the outcome (disease) of interest, then to identify the exposed and unexposed groups. The choice of analytic design depends on the features of the exposure and the disease, the current state of knowledge regarding the hypothesis of interest and, finally, the available time and financial resources. The methodological issues discussed in the first section of this chapter pertain to the design and conduct of all types of analytic studies of the late effects discussed below.

21.3.2.1 Case-Control Study

The case control study is the most common type of epidemiologic study design. It is often used to determine preliminary information about the etiology of a disease. In this type of study, cases and controls are selected on the basis of the outcome status of interest and the frequency and/or dosage of the exposure in question is compared between the groups. In late-effect studies, the case-control design is somewhat uncommon because the exposure of interest (specific cancer treatment) is already known. However, case-control studies nested within cohort studies are often employed in late-effect research (see description of nested case-control studies, below).

21.3.2.2 Cohort Study

The cohort study is perhaps the most effective study design for late-effect research. A cohort study compares a group of subjects who share a common characteristic (such as being treated for childhood cancer) within a defined time period. Subjects within the cohort are categorized according to exposures of interest. The groups are followed over time and their outcomes are compared. Cohort studies typically enroll large numbers of individuals and follow them for many years. Because of the study population selected, cohort studies allow the assessment of rare exposures (e.g. cranial radiation). They also allow the assessment of multiple outcomes from a single exposure (e.g. development of subsequent CNS tumors, neurocognitive problems). Cohort studies are very expensive to mount. They are also subject to certain types of bias, notably attrition bias resulting from either dropout or loss to follow-up.

A principal benefit of cohort studies is that they make possible the calculation of both the absolute risk and the relative risk of an outcome of interest. Absolute risk is a measure of the occurrence of a disease in a population, divided by the number at risk for the disease. Relative risk is defined as the ratio of the incidence of disease in those exposed, divided by the incidence of disease in those not exposed. It estimates the magnitude of the risk in the exposed group relative to that in the unexposed group.

Many long-term survivor studies have used the cohort design. In the Five-Center Study, for instance, Byrne et al. studied effects of treatment on fertility in 2,283 childhood/adolescent cancer survivors, compared with 3,270 subjects selected from the survivors' siblings [3]. They found that chemotherapy with alkylating agents was associated with a fertility deficit in men, while in women, it was associated with only a moderate fertility deficit when administered with radiation below the diaphragm. An example of a larger-scale investigation is the cohort study by Boivin et al., who examined the risk of second cancers by treatment modalities in 10,472 Hodgkin's disease long-term survivors [2]. Mitby et al., in the CCSS cohort, investigated nonclinical outcomes – the use of special education services and educational attainment [16].

21.3.2.4 Nested Case-Control Design

Large, well-defined survivor cohorts can provide an ideal setting for smaller analytic studies focusing on rare outcomes. A nested case-control study [10] is a case-control study conducted within a defined cohort. The advantage of a nested case-control study is that it avoids the potential selection bias inherent in standard case-control designs. Nested case-control designs are useful especially when the assessment of exposure is resource-intensive (e.g. radiation dosimetry). Cases are those cohort members who have developed the disease/outcome of interest. Potential controls are all other cohort members who are at risk but have not yet developed the disease. Controls are selected by matching them to cases on potential confounding variables that may be associated with both exposure and outcome, such as age at cancer diagnosis and sex. This technique ensures that potential confounders are distributed in an identical manner among cases and controls. For example, the risk of secondary breast cancer is strongly associated with age at follow-up. Without a proper adjustment for age at follow-up, the risk may appear elevated for those diagnosed with childhood cancer at an older age [29].

After controls have been matched to cases according to potential confounding variables, cases are compared to controls with respect to the exposure of interest. The sources and quality of exposure information (e.g. medical records or biologic specimen) should not differ by case/control status, and it is preferable to have the abstraction of exposure information done with the case/control status blinded. This study design leads to resource savings because the exposure assessment is required only for those cases and sampled controls selected, and not for the entire cohort.

A major disadvantage of this type of design is the retrospective assessment of prior exposures. If the exposure assessment relies on self-report, for example, a survivor's recall of exposures may be biased by knowledge of his or her outcome status, or it may be difficult for the subject to assess exposure retrospectively. Also, since the real frequency/rate of outcome in the full study population is not reflected in the

case-control sets, one cannot determine the absolute risk of the outcome; only the odds ratio (an estimate) can be determined.

A nested case-control design was used in a long-term cancer-survivor study by Hawkins et al. to investigate second primary bone cancer after childhood cancer [6]. Based on a cohort of 13,175 three-year survivors of childhood cancer in Britain, the analysis comprised 59 cases of second primary bone cancer and 220 controls. The use of the nested case-control design permitted the collection of detailed exposure measurements, such as the site-specific radiation dose and cumulative dose of alkylating agents. The resources needed to collect these measurements would have been about 50 times greater if the study had used a cohort design employing all 13,175 survivors.

21.3.2.5 Case-Cohort Design

The case-cohort study [20] is a relatively new study design that is similar to the nested case-control design, except that the selection of controls is performed without any reference to the specific time of the occurrence of each case's outcome of interest. Case-cohort studies share many of the advantages and disadvantages of nested case-control studies. A key additional advantage of the case-cohort design, compared with the nested case-control design, is the ability to use the same controls for multiple outcomes of interest [8, 26]. This can be particularly relevant to long-term survivor studies, since there may be multiple outcomes of interest, such as mortality from different causes and second cancers at different sites or of different types. External comparisons of the study cohort with a general/reference population are simple with the case-cohort design, and standardized mortality or morbidity ratios, a familiar tool in epidemiology, can be computed [27].

The use of the case-cohort design (although it was not explicitly identified as such) in cancer-survivor studies goes back to Hutchison who studied long-term leukemia risk following radiotherapy for cervical cancer [7]. Boice and Hutchison later discussed the incompleteness of the follow-up in Hutchison's earlier analysis and re-analyzed the data with a greatly extended follow-up of the same cohort [1]. They conducted external comparisons by computing the expected number of leukemia cases in the cohort, based on rates from population cancer registries. In the computation of the expected number, only a 10% random sample of all patients was used to estimate total person-years in the entire cohort. This greatly minimized the time required for detailed record abstraction and computer analysis.

21.3.2.6 Intervention Studies

In contradistinction to the above described *observational* analytic studies, which test etiologic hypotheses, the purpose of *intervention* studies (also referred to as *randomized controlled trials* or *clinical trials*) is to test the efficacy of a preventive or therapeutic measure, while assessing its potential negative effects (i.e. side effects). In this type of study, investigators have control over the scheme for assigning individuals to groups with different "exposures" of interest (i.e. interventions and control). These types of studies are generally considered the strongest design for establishing causal relationships. Therapeutic trials and chemoprevention trials are examples of intervention studies.

Therapeutic trials are conducted on individuals with a disease to determine whether a drug or modified condition of therapy is efficacious as a treatment of the disease without serious toxicity. The therapeutic trials often used in the Children's Oncology Group are designed to test whether modifications in treatment will increase disease-free survival and minimize the occurrence of late effects.

Chemoprevention trials are designed to evaluate whether an agent or procedure can reduce the risk of developing a disease in individuals free of the condition at enrollment. An example of such a trial in late-effect research is a randomized clinical trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin [28].

Other randomizal intervention trials endeavor to modify behavior and minimize late effects. An example is the smoking cessation trial performed within the CCSS, using peer counseling to increase smoking cessation [4].

The advantage of intervention studies is that investigators can create exposure groups with a high degree of comparability (the groups differ only with respect to the interventions of interest) and follow them for differential risk of outcomes, thereby minimizing confounding and increasing the validity of causal inferences. Major drawbacks to intervention studies are the extensive resource requirements, the length of follow-up needed to ascertain outcomes and, lastly, the inability to achieve high compliance to protocols. Other, equally important, drawbacks are possible contaminations across experimental arms and loss to follow-up.

21.4 Conclusion

Current knowledge regarding late effects in childhood cancer survivors can be attributed to the diligence of investigators who performed the initial studies and to the wisdom of succeeding researchers in building on work previously completed. The establishment of large, well-characterized cohorts of long-term survivors, such as the CCSS and others (including the National Wilms' Tumor Study and the Late Effects Study Group), has created a framework that allows for both the continued surveillance of childhood cancer survivor populations as they age, and the dissemination of the information that has been gained to survivors and clinicians. Future steps in late-effect research include the conduct of intervention trials that will determine the most appropriate methods for communicating information about the risk of particular late effects to those who are at risk of experiencing them, as well as the most effective methods for modifying behaviors to maximize survivors' future health.

Acknowledgements. We would like to thank Catherine Moen for her assistance in compiling this chapter.

References

1. Boice JD, Hutchison GB (1980) Leukemia in women following radiotherapy for cervical cancer: ten-year follow-up of an international study. J Natl Cancer Inst 65:115–129
2. Boivin JF, Hutchison GB, Zauber AG, Bernstein L, Davis FG, Michel RP, Zanke B, Tan CTC, Fuller LM, Mauch P, Ultmann JE (1995) Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 87:732–741
3. Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K, Holmes GF, Holmes FF, Latourette HB, Weyer PJ, Meigs JW, Teta MJ, Cook JW, Strong LC (1987) Effects of treatment of fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 317:1315–1321
4. Emmons K, Butterfield RM, Puleo E, Park ER, Mertens A, Gritz ER, Lahti M, Li F (2003) Smoking among participants in the childhood cancer survivors cohort: the partnership for health study. J Clin Oncol 21:189–196
5. Feigelson HS, Rodrigeuz C, Robertson AS, Jacobs EJ, Calle EE, Reid YA, Thun MJ (2001) Determinants of DNA yield and quality from buccal cell samples collected with mouthwash. Cancer Epidemiol Biomarkers Prev 10:1005–1008
6. Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, Marsden HB, Stovall MA (1996) Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst 88:270–278
7. Hutchison GB (1968) Leukemia in patients with cancer of the cervix uteri treated with radiation. A report covering the first 5 years of an international study. J Natl Cancer Inst 40:951–982
8. Langholz B, Thomas DC (1990) Nested case-control and case-cohort methods of sampling from a cohort: a critical comparison. Am J Epidemiol 131:169–176
9. Le Marchand L, Lum-Jones A, Saltzman B, Visaya V, Normua AM, Kolonel LN (2001) Feasibility of collecting buccal cell DNA by mail in a cohort study. Cancer Epidemiol Biomarkers Prev 10:701–703
10. Liddell FDK, McDonald JC, Thomas DC (1977) Methods of cohort analysis: appraisal by application to asbestos mining. J R Statist Soc A 140:469–491
11. Marina N (1997) Long-term survivors of childhood cancer. Pediatr Clin North Am 44:1021–1042
12. McCormick MC, Baker J, Brooks-Gunn J et al. (1991) Cohort reconstruction: which infants can be restudied at school age? Paediatr Perinat Epidemiol 5:410–422
13. Meadows AT, Hobbie WL (1986) The medical consequences of cure. Cancer 58:524–528
14. Mertens AC, Potter JD, Neglia JP, Robison LL (1997) Methods for tracing, contacting, and recruiting a cohort of survivors of childhood cancer. J Pediatr Hematol Oncol 19:212–219

15. Mertens AC, Mitby PA, Perentesis JP, Radloff G, Kiffmeyer WR, Neglia JP, Meadows A, Jones I, Potter JD, Friedman D, Yasui Y, Robison LL, Davies SM (2004) XRCC1 and Glutathione S-Transferase Polymorphism and Susceptibility to Therapy-Related Cancer in Hodgkin's Disease Survivors: A Report from the Childhood Cancer Survivor Study. Cancer 101:1463–1472
16. Mitby PA, Robison LL, Whitton JA, Zevon MA, Gibbs IC, Tersak JM, Meadows AT, Stovall M, Zeltzer LK, Mertens AC (2003) Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 97:1115–1126
17. Neglia JP (1994) Childhood cancer survivors: past, present, and future. Cancer 73:2883–2885
18. Pepe MS (1992) Inference using surrogate outcome data and a validation sample. Biometrika 79:355–365
19. Pepe MS, Reilly M, Fleming TR (1994) Auxiliary outcome data and the mean score method. J Stat Plann Infer 42:137–160
20. Prentice L (1986)A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 73:1–11
21. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SE, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit NE, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK. (2002) Study design and cohort characteristics of the childhood cancer survivor study: a multi-institutional collaborative project. Med Pediatr Oncol 38:229–239
22. Ross JA, Severson RK, Pollock BH, Robison LL. (1996) Childhood cancer in the United States: a geographical analysis of cases from the Pediatric Cooperative Clinical Trials Groups. Cancer 77:201–207
23. Schwartz CL (1995) Late effects of treatment in long-term survivors of cancer. Cancer Treat Rev 21:355–366
24. Schwarz MB, Burgess LP, Fee WE, Donaldson SS (1988) Postirradiation sarcoma in retinoblastoma, induction or predisposition? Arch Otolaryngol Head Neck Surg 114: 640–644
25. Sklar C, Mertens A, Walter A, Mitchell D, Nesbit M, O'Leary M, Hutchinson R, Meadows A, Robison L (1993) Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. J Pediatr 123:59–64
26. Wacholder S (1991) Practical considerations in choosing between the case-cohort and nested case-control designs. Epidemiology 2:155–158
27. Wacholder S, Boivin JF (1987) External comparisons with the case-cohort design. Am J Epidemiol 126:1198–209
28. Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, Dilsizian V, Avila N, Jarosinski P, Balis FM, Poplack DG, Horowitz ME (1996) Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 14:362–372
29. Yasui Y, Liu Y, Neglia J, Friedman D, Bhatia S, Meadows A, Diller L, Mertens A, Whitton J, Robison LL (2003) A methodological issue in the analysis of second cancer incidence in long-term survivors of childhood cancers. Am J Epidemiol 158:1108–1113

Transition Issues

Kevin C. Oeffinger · Debra A. Eshelman

Contents

22.1 Risk-Based Healthcare for Survivors

The preceding chapters have described the long-term outcomes and the potential late effects associated with chemotherapy, radiation therapy and surgery for cancer. The goal of caring for survivors is to maximize their health and quality of life while minimizing morbidity and mortality associated with these previous exposures. To accomplish this goal and provide optimum healthcare for survivors, it is essential to develop a systematic plan for healthcare that extends not just through childhood, but also through the lifetime of the survivor. There are significant barriers that must be faced and overcome to achieve this goal. Most notable are the barriers associated with two critical transition periods in the life of a survivor: (a) transitioning from acute cancer care to long-term follow-up and (b) transitioning from the pediatric/adolescent years to young adulthood. Prior to addressing these two transition periods, it is important to understand the meaning and rationale of risk-based healthcare.

22.1.1 Risk-Based Healthcare: Definition and Rationale

To understand the concept of risk-based healthcare, it is important to recognize three principles that influence the long-term health and well being of survivors. First, the incidence of most late effects increases with age, generally becoming clinically apparent decades after therapy [3, 9, 20]. Second, through cellular changes and alterations in mechanisms of cellular and tissue repair, chemotherapy and radiation therapy administered to a developing child

Table 22.1. Models of care for pediatric and young adult survivors of childhood cancer

Follow-up during pediatric years	Follow-up during young adult years
1. Long-term follow-up (LTFU) program Provide risk-based healthcare Surveillance for late effects of therapy Evaluation and management of psychosocial problems related to the cancer experience Targeted education on methods to reduce long-term risk Approximately 50% of treating institutions have an LTFU program	**1. Children's hospital-based LTFU** Extension of care for survivors into their young adult years Limited access to specialists in adult medicine May have limitations in services offered
2. Primary care physician Pediatrician or family medicine physician Most primary care physicians are unfamiliar with the risks and healthcare needs of childhood cancer survivors Generally, do not have an established method of communication between the cancer center and the primary care physician Medical summary provided to survivor for record and for primary care physician	**2. One-time transition visit** Single visit in young adult years Based at children's hospital Risks discussed
	3. Young adult program Based in an adult patient setting Involvement of primary care physicians or medical oncologists Access to specialists in adult medicine Require significant resources and committed personnel
	4. Community physician Medical oncologist or primary care physician (general internist or family medicine physician) Most community physicians are unfamiliar with the risks and healthcare needs of childhood cancer survivors Specialists in adult medicine are also unfamiliar with risks of this population, influencing the process and outcomes of referrals Generally, there is no established method of communication between the cancer center and the primary care physician

or adolescent will eventually result in a loss of reserve and a premature aging of various organ systems. And, finally, as a survivor ages and develops diseases common to the middle adult years, such as hypertension, diabetes and dyslipidemia, these new processes will compound the previous cellular/tissue damage and hasten the further loss of reserve or premature organ failure.

Fortunately, there is a window of opportunity to modify the severity of health outcomes by prevention or early intervention. Early diagnosis and intervention or preventive care targeted at reducing risk for late effects can benefit the health and quality of life of survivors [12]. The outcomes of the following late effects can be influenced by early diagnosis and early intervention: second malignant neoplasms following radiation therapy (breast, thyroid and skin), altered bone metabolism and osteoporosis, obesity-related health problems (dyslipidemia, hypertension, diabetes mellitus, cardiovascular disease), liver failure secondary to chronic hepatitis C following blood transfusion and endocrine dysfunction following chest/mantle or cranial radiotherapy. Primary, secondary and tertiary prevention, including tobacco avoidance/cessation, physical activity, low-fat diet and adequate calcium intake, can modify risk. Longitudinal care addressing other late effects, such as infertility, musculoskeletal problems, cognitive dysfunction and psychosocial issues, may also improve survivors' health outcomes and quality of life.

Founded on these concepts, the recently published Institute of Medicine report, Childhood Cancer Sur-

Table 22.2. Barriers to risk-based healthcare of childhood cancer survivors by transition period, and methods to facilitate transition

First transition period: from acute cancer care to long-term follow-up (LTFU) program	Second transition period: from LTFU program to young adult care
Barriers Lack of adequate number of LTFU programs Fear of continued care Financial or distance constraints Lack of understanding of the need for continued surveillance	Barriers Survivor-specific barriers Lack of understanding or knowledge of risks Fears of transitioning Healthcare professional-specific barriers Few programs for young adult survivors Community healthcare physicians unfamiliar with the risks and problems of the population Lack of communication between cancer center and community physicians Medical system-specific barriers Difficulty finding affordable insurance, especially for survivors in rural settings or self-employed survivors Limitations on medical insurance coverage of some screening tests in young adults Restrictions of managed care organizations
Methods to facilitate transition Clearly explain purpose of risk-based care Discuss long-term plans for follow-up through the survivor continuum Address emotional issues of survivorship Provide a summary of the cancer diagnosis and treatment Educate regarding risks and methods to reduce risk Foster self-care practices Promote positive decision-making skills for healthy lifestyles	Methods to facilitate transition Survivor in an LTFU program Develop a policy for the process of transition Identify qualified and committed healthcare providers Involve the survivor and the family in the process Assess the expectations and healthcare beliefs of the survivor and the family Emphasize the goals of risk-based healthcare Highlight the importance of the survivor/family as the key providers of healthcare information Focus on the survivor as self-advocate Stress the ongoing communication between the LTFU team and new providers Discuss the transfer of medical records and the oncology medical summary Survivors in general (and not in an LTFU Program) LTFU community as activists for survivorship Raise public awareness Educate insurance companies and managed care organizations Communicate with state and federal legislators

vivorship: Improving Care and Quality of Life, strongly encourages life-long follow-up of all cancer survivors [4]. Risk-based healthcare, defined as care of the survivor that includes a systematic plan for screening, surveillance and prevention, incorporating a survivor's risks based on the previous cancer/cancer therapy, genetic predispositions, lifestyle behaviors and comorbid health conditions, is recommended for all survivors of pediatric cancer.

The concepts and practice of risk-based healthcare have gradually evolved over the past two decades. In the following two sections, the two critical transition periods of risk-based healthcare are discussed. Each section includes a description,

specific to the age and needs of the survivor, of (a) models of care, (b) current status of care, (c) barriers to transitioning and (d) methods to facilitate transition. A synopsis of this information is provided in Tables 22.1 and 22.2.

22.2 First Transition Period: From Acute Cancer Care to Long-Term Follow-up

The concept of transitioning moves the survivor and her family across the continuum of pediatric oncology care from the acute phase of cancer diagnosis and treatment, through a maintenance phase and then, finally, to survivor status. Ideally, when a survivor is off therapy and through the time period of highest rate of relapse (generally 24 months off therapy), she is transitioned from the primary treating oncologist to a longitudinal program focused on her long-term healthcare needs, in addition to the acute care needs. Longitudinal programs, based at cancer centers or children's hospitals and generally referred to as "long-term follow-up" (LTFU) programs.

Throughout the course of her illness, the survivor and her family have likely developed significant relationships, expectations and a high level of trust and comfort with the people involved in their care. The depth of this type of relationship contributes to the feeling of the children's hospital and the employees as a second home or "adopted" family. Transitioning to the LTFU or survivor program – albeit a milestone for the cancer survivor – may cause a wide range of emotions. Survivors and their families often deal with new fears when follow-up care intervals become extended, testing becomes less frequent and new healthcare providers are introduced. Still, however, care in traditional LTFU settings is within the confines of the pediatric hospital, where a level of comfort has already been established, expectations are known and processes are familiar.

22.2.1 Models of Care for Follow-up During Childhood

The primary and recommended model of care for survivors in childhood is through an LTFU program. In addition to monitoring for recurrence or relapse of the primary cancer in the early years of follow-up, the focus gradually shifts to providing risk-based care that includes surveillance for late effects of therapy, evaluation and management of psychosocial problems related to the cancer experience and targeted education on methods to reduce long-term risk. In North America, care provided through LTFU programs is relatively homogenous. Most programs evaluate survivors on an annual basis. During this visit, the history and physical examination should be targeted for the particular risks associated with the treatment exposures of the survivor. Based upon the findings of the history and physical examination, the previous-treatment exposures and modifying factors of risk (genetic predisposition, lifestyle behaviors), screening tests are generally obtained to assess for asymptomatic and symptomatic late effects.

The second model of care is follow-up by a primary care physician in the community. Although there may be program or individual-specific success stories of collaboration between cancer centers and community physicians, there is generally a lack of communication or a systematic method of enhancing follow up of the survivor. Because of the time demands of risk-based healthcare and the necessary multidisciplinary approach, optimum care is generally not delivered through this second model [8, 11, 22].

In recent years, some programs have begun to experiment with a hybrid of the two models. Using a shared management approach, LTFU programs seek to formalize their collaboration with primary care physicians in the community. The impetus for this approach is the recognition that many LTFU programs do not have adequate resources to follow their burgeoning population of survivors. With a focus on continuity of care, the survivor is formally transitioned to a primary care physician. Continued two-

way communication is an essential component of this approach, not just at the time of transition but through the life of the survivor.

22.2.2 Current Status of Risk-Based Healthcare During Childhood

Although there is general agreement that risk-based healthcare provided through LTFU programs is important to the health and well-being of survivors, there is a paucity of such programs in North America. In 1997, only 53 % of the centers that treat children and adolescents for cancer had an LTFU program [13]. Since that time, this number has slowly increased. However, because of the limited resources and available trained personnel, a significant percent of centers still lack a LTFU program. Compounding this, many programs exist within the acute care environment, without dedicated space, time or staffing for long-term care. The problem is illustrated by the fact that 10 years after cancer diagnosis, not even one-third of the 12,871 survivor participants in the Childhood Cancer Survivor Study reported a visit to a cancer center or children's hospital during the previous two years.

22.2.3 Barriers to Transitioning Survivors to Childhood Follow-up

In addition to the lack of LTFU programs, there are other barriers to the risk-based care of survivors during childhood that should be considered. Even when an LTFU program exists at the treating institution, survivors and their families may elect not to return because of financial or distance constraints, fear of the hospital (and reminders of the cancer experience) or a lack of understanding of the need for continued surveillance. Fortunately, lack of health insurance is generally not a problem during the childhood years, as most state-supported programs continue to provide healthcare insurance for survivors throughout their childhood.

Although this has not been formally studied, many directors and coordinators of LTFU programs with dedicated staff and time anecdotally report high follow-up rates of their survivor population. This leads one to conclude that the primary barrier to the risk-based healthcare of survivors in this age group may, indeed, simply be the scarcity of such programs.

22.2.4 Methods to Facilitate Transition and Risk-Based Healthcare of Survivors in Their Childhood Years

To date, there has been little published specifically about the preparation of the cancer survivor for transition. The principles of transition published for other chronically ill children may be applied [16, 18]. Transition is a process, not an event, and, as such, it should be available to the survivor/family at various intervals during their long-term follow-up.

During the initial introductory visit to the LTFU clinic, the purpose of risk-based healthcare should be clearly explained, with the overall global plans for follow-up during the pediatric years as fully as possible delineated. Providers should introduce the oncology medical summary or treatment history and emphasize the importance of knowing what is included in this document and how to provide the information it contains to subsequent healthcare providers. Although, at this point, the parents are the primary keepers of information, every opportunity to include the child in the educational process in an age-appropriate manner should be capitalized upon. The pediatric healthcare provider must continually foster self-care practices and promote positive decision-making skills for healthy lifestyles. This can be accomplished by simple strategies, such as allowing adolescent survivors to provide medical history, fill out demographic forms and be examined privately.

This is also a transition period for the parent(s). Having gone through the traumatic experience of the cancer diagnosis and therapy, the parent is often very involved in the care of the survivor and may be overprotective. It is important, over time, to assist the parent in facilitating the survivor's growth in self-care skills. The parent(s) need to be supported in their willingness to have the adolescent survivor seen privately. Providing the parent(s) with an opportunity to express their fears, concerns and frustrations

through this period promotes a healthy relationship between the survivor, the parent and the healthcare professionals.

22.3 Second Transition Period: Young Adulthood

As the survivor enters late adolescence and young adulthood, she and her family embark upon the second critical transition period [7]. This is a developmentally important time in the life of the survivor, as she begins exerting her independence and becomes responsible for her own healthcare. How the cancer experience influences the health practices and behaviors of the parent of an adolescent with cancer (e.g. preventive periodic health examination, completion of cancer screening tests, tobacco use and physical activity) is not well understood. Likewise, how the health-seeking practices of the parent(s) and the survivor/family cancer experience affect the development of a survivor's health beliefs and practices, and how these are modified as the survivor progresses through adolescence into young adulthood, have not been explored in a systematic, theory-based manner. This developmentally vulnerable period overlaps with the optimum window of opportunity for prevention and early detection/intervention for many late effects. Thus, risk-based care is vital during this period of the survivor's life [5, 12].

22.3.1 Models of Care for Young Adult Survivors

There are four models of care for young adult survivors: (1) continued follow-up at the childhood cancer center; (2) one-time evaluation of adult survivors at a childhood cancer center, with a planned transition to a primary care physician; (3) young adult programs at academic centers; and (4) care provided by a medical oncologist or a primary care physician in the community [11]. Each of these models is briefly described below.

A few LTFU programs follow survivors into their young adulthood, generally to around age 25–30, but sometimes older. These programs are focused on educating survivors about long-term risks and delivering preventive healthcare. Without the involvement of medical professionals trained in providing care for young adults, the pediatric providers in these programs have generally acquired additional skills over time. Anecdotally, the directors of these programs generally have had difficulty finding medical professionals with adult healthcare experience. Many express the sentiment that if they did not continue seeing the survivor, risk-based care would not be delivered.

As a second model of care, the Children's Hospital of Philadelphia (CHOP) developed a novel and successful transition program several years ago. Adult survivors, generally over the age of 25 years, are seen for a one-time evaluation by a pediatric oncology nurse practitioner and physician from the survivorship team. At this visit, potential risks based on previous treatments are discussed and a medical summary with recommendations is provided to the survivor and sent to their primary care physician.

The "young adult survivor program," as it is referred to, is a relatively new model of care. Two variations of this model have evolved. In one, primary care physicians in an academic setting are involved in or direct the program, and survivors are seen in a practice setting that includes adults. As an example, the author of this chapter directs a multi-disciplinary program for young adult survivors, which is called the After the Cancer Experience (ACE) Young Adult Program [14]. This program, developed in 1994, is a collaborative effort between the Center for Cancer and Blood Disorders at the Children's Medical Center of Dallas and the Departments of Family Practice & Community Medicine and Pediatrics at the University of Texas, Southwestern Medical Center at Dallas. In mid to late-adolescence, survivors are transitioned from the ACE Program at the Children's Medical Center of Dallas to the Family Practice clinic. The co-author of this chapter, a pediatric oncology nurse practitioner, coordinates both the ACE and ACE Young Adult Programs and is the primary patient educator, providing the key bridge of continuity between the two institutions. In addition, a multi-disciplinary network of pediatric and adult specialists, including

cardiologists, hepatologists, reproductive endocrinologists and psychologists, has been developed to serve for the special needs of survivors.

Through collaborative efforts between pediatric and adult oncologists in cancer centers or academic settings, another type of young adult program has also evolved over the past few years. Childhood cancer survivors are transitioned to the adult oncologist at or around the age of 18 for long-term follow-up. The pediatric oncologist generally continues involvement for an extended period of time. A few programs of this type also provide healthcare for survivors of young adult cancers, such as testicular cancer. Both types of program for young adults require significant resources and committed personnel, which tends to impede their adoption in most settings.

Medical oncologists in the community provide healthcare for a small percentage of young adult survivors. However, most adult oncologists are not particularly cognizant of the special long-term risks of childhood cancer survivors and care often resembles prolonged acute care, with a focus on late recurrence or relapse of the primary cancer, rather than on the potential for late-effects of therapy.

Finally, many, if not most, young adult survivors seek a primary care physician for some aspect of their healthcare and, as with medical oncologists, most primary care physicians are unfamiliar with the risks of this population, a state of affairs which should not be surprising [12]. There is no primary, widely used, care-specific textbook that describes the risk-based care of survivors. Nationally recommended curricula for instruction of medical students and primary care residents do not include the topic of healthcare for childhood cancer survivors. Little has been written in primary, care-based journals or general, non-cancer specific journals regarding childhood cancer survivors and their long-term healthcare. Compounding this general lack of readily available information, there has not been a national effort to link childhood cancer centers with primary care physicians in the transitioning process. Although, on occasion, an LTFU program identifies a primary care physician in the community who is interested in providing care for survivors and a collaborative relationship develops, this is the exception. Moreover, because of constant changes in insurance plans, long-term continuity with the same primary care physician is infrequent, necessitating that most LTFU programs continually re-establish ties with the survivor's physician.

As a result of these difficulties, there can be a protracted interval in initiating the transition to long-term care – and the longer the interval, the less likely it is to occur at all.

For the primary care physician, who sees a survivor and attempts to navigate the complexities of a cancer center to find and communicate with the individual(s) involved in long-term survivor care, frustration is often the outcome. Compounding the problem is that the fact that a typical family physician generally has only two to three young adult survivors in her practice [10]. Recognizing that these survivors are heterogeneous, with a variety of different cancers diagnosed at different age periods in different treatment eras, and that the recommendations for screening and surveillance are constantly evolving, it is understandable that primary care-initiated, risk-based healthcare for survivors is infrequent.

22.3.2 Current Status of Risk-Based Healthcare for Young Adult Survivors

In a recent analysis of 9,434 young adult survivors of childhood cancer (age range 18–48 years; mean: 27 years), 19% of the cohort reported a medical visit to a cancer center within the previous two years [15]. Only 42% reported a healthcare visit in the previous two years that addressed their previous cancer or cancer therapy. The older the survivor or the greater the time interval from cancer diagnosis, the less likely s/he was to report a visit to a cancer center or a medical visit that addressed prior cancer or cancer therapy. This trend was also apparent for those treated with therapies associated with substantial risk for cardiovascular disease or breast cancer.

22.3.3 Barriers to Transitioning Survivors to Young Adult Follow-up

For the past four years, the authors of this chapter have led a multi-institutional study identifying and describing barriers to transitioning young adult survivors to risk-based healthcare. These barriers can be categorized in three groups: survivor-specific, healthcare professional-specific and medical system-specific. Each is briefly described in the following paragraphs.

The primary barrier specific to survivors is a lack of knowledge or understanding about the risks associated with previous cancer therapy. Highlighting the lack of awareness of their health risks, Kadan-Lottick and colleagues surveyed 635 long-term survivors of childhood cancer and reported that while most (91%) survivors had a fair knowledge of their general diagnosis and whether they received chemotherapy (94%) or radiation therapy (89%), the depth of their knowledge was generally minimal [6]. Only 15% responded that they had ever received a summary of their cancer diagnosis and treatment. To better understand this problem, it is important to study the relationship of the age-appropriate delivery of information to the survivor and her family and their healthcare practices. If, when a survivor becomes an independent on her own behalf, she is unaware of the details of her cancer and of the long-term risks, the likelihood of her seeking out lifelong risk-based care is minimal. The transition period is also a frightening time for many survivors and their parents, as they leave the safe and comfortable confines of the pediatric setting for the unpredictability of the adult setting. These fears, which are natural, mirror the emotional and developmental struggles that accompany the development of the adolescent into an independently thinking adult. If the fears are not addressed, however, they can impede the transition process.

Besides the barriers specific to healthcare professionals discussed above, long-term healthcare for survivors is plagued by the scarcity of programs for providing such care. There are fewer than twenty LTFU programs in the United States that provide care for young adult survivors past the age of 25. For various reasons, including limited resources, it is not anticipated that the number of programs will appreciably increase in the near future. As a result, most young adult survivors will be followed by primary care physicians, most of whom are likely to be unfamiliar with the risks of their patients. Compounding the problem is the fact that most adult specialists – including cardiologists, obstetricians and surgeons – are equally unfamiliar with the childhood cancer survivor population. This obviously can affect the quality of care delivered to the survivor presenting with a new and symptomatic late effect. In addition, there is frequently a lack of communication between cancer centers and community physicians. As a result, healthcare provided by professionals who are not cognizant of the exposure-related risks of survivors tends towards two extremes: ordering many unnecessary tests or minimizing the symptoms of the survivor and attributing them to anxiety or depression.

Barriers specific to the medical system are equally daunting. Survivors who live in rural settings or are self-employed usually cannot find affordable insurance, making it difficult to access appropriate healthcare. For survivors with medical insurance, coverage may not include recommended screening tests, such as a screening mammogram for a 27 year-old female Hodgkin's survivor who had mantle radiation. It is not unusual for a survivor to live in an area with a young adult program, only to find that the program is not included in the health maintenance organization's plan.

Many of the barriers identified by Schidlow and Fiel [19] that adolescents with chronic diseases face in making the transition into adult healthcare systems are also applicable to survivors. The patient may exhibit dependent behavior and immaturity. The family may demonstrate an excessive need for control, emotional dependency or a lack of trust in the new healthcare providers. As Schidlow and Fiel emphasize, the pediatric and adult healthcare providers also have obstacles to overcome for a healthy transition. The pediatric provider often has strong emotional bonds with the patient and the family and may feel distress in "letting go." Some pediatric caregivers may believe that they have the necessary skills for

providing care to the survivor as an adult, or they may distrust the adult caregiver. The adult caregiver may also have concerns, specifically about the lack of institutional commitment or perceived heightened care demands.

22.3.4 Methods to Facilitate Transition and Risk-Based Healthcare for Survivors in their Young Adult Years

If an adolescent survivor is followed in a LTFU program, there are several steps that are important to address in order to enhance the transition from the pediatric cancer center to adult services. The primary goal of a successful transition center is, on the one hand, to promote optimal health and well-being, while, on the other hand, facilitating a successful integration into adult life. As Blum reported, the transition goals should be able to provide comprehensive, coordinated, uninterrupted, developmentally appropriate and psychosocially sound healthcare that ultimately leads to adult self-sufficiency [2]. The general principles of transition, as endorsed in position papers of the American Academy of Pediatrics, the American Academy of Family Physicians and the Society for Adolescent Medicine, include: (1) development of a policy for the process (e.g. the concept of transition as the next logical step in the cancer experience continuum); (2) identification of qualified and committed healthcare providers; and (3) survivor family involvement in the process [1, 2]. Additionally, we advocate an assessment of the survivor/family expectations and healthcare beliefs prior to the transition process. Each of these steps in the transition process is described in the following paragraphs.

In late adolescence, during the latter part of the high school years, the LTFU team should discuss the concept of transitioning from the pediatric healthcare environment to one suited for young adults. Educational efforts of the LTFU team should clearly state that the healthcare needs of the survivor, as he or she enters the young adult years, will extend beyond the expertise of the pediatric oncology center and staff. Communicating transition as the next natural step along the cancer experience continuum and facilitating strategies to enable this process will contribute to survivor independence and positive functional outcomes. The LTFU team, which primarily uses nurse practitioners and nurses as key educators, should: (1) emphasize the inclusion of the survivor's current medical team in the transition process; (2) discuss the transfer of medical records and the oncology medical summary; (3) stress the ongoing communication between the former team and new providers; (4) highlight the importance of the survivor/family as a key providers of healthcare information; (5) focus on the survivor as self-advocate; and (6) emphasize the goals of healthcare maintenance. Obviously, the movement into adult care is dependent upon unique institutional and individual circumstances and assumes that a plan is in place. Transitional plans should always include an assessment of survivor readiness, ability to understand the importance of risk-based care, expectations of the process and an emphasis on individualized care that is focused on physical, psychological, emotional, cultural, spiritual and vocational needs. It is important to emphasize to young adults who feel strongly connected to their pediatric oncology team that transitioning to adult services as a means to maintain their health is a not a loss but a reason for celebration [16]. While acknowledging the very real feelings of loss, focusing on the future and the transition as an important step can facilitate the process.

The LTFU program should work with the survivor and her family to identify an adult setting with equivalency in quality and intensity of services and an adult healthcare professional experienced and knowledgeable about risk-based care [12, 17]. As noted above, few young adult programs exist. When a young adult program is not an option, the LTFU should identify a cadre of primary care physicians in the community who "welcome" survivors into their practice and develop a relationship that facilitates communication. Although this can be a difficult task, the LTFU enhances its overall transition efforts by systematically developing and educating a group of primary care physicians in the community. It is not enough to simply find a physician to "care" for the survivor. To be effective in this process requires ongoing work by the LTFU team in the community, with face-to-face meetings with primary care physicians

(either individually or as a group) to foster these relationships. This will provide the LTFU program and the survivor/family several options for choosing a primary care physician. A critical component of the process is effective two-way communication between the LTFU program and the primary care physician about the health risks and needs of the individual survivor. As new information is disseminated in the cancer literature, the LTFU program needs to update the primary care physician. Connecting the primary care physician to the Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (www.survivorshipguidelines.org) and assisting with questions is an important part of facilitating risk-based care. Having an ongoing relationship with the primary care physician will also enhance the likelihood of collecting information about the health outcomes of the survivor as part of the LTFU database. Needless to say, this process is difficult and demands time and resources. However, without it, most survivors transitioning from the LTFU will have few, if any, options for risk-based care.

Transition cannot be accomplished without the "buy in" of the survivor and her parents. There may be fear and ambivalence, especially on the part of the parent, about leaving the pediatric treating center. With effective educational sessions through adolescence, the concept of transition and the need for ongoing follow-up and health maintenance throughout the lifespan of the survivor should be emphasized. With each decision, the survivor and family must be actively involved and their fears and concerns discussed. Having a rotating board or panel of survivors and parents to provide feedback and evaluate the LTFU transition process can be a positive and beneficial experience for all groups.

The challenge of transition is not unique to childhood cancer survivors. Adolescents with chronic diseases, such as cystic fibrosis, juvenile diabetes and sickle cell anemia, face similar obstacles. In recent years, the concept of medical homes, strongly endorsed and supported by the American Academy of Pediatrics, has been developed [16]. This effort seeks to create comprehensive, multidisciplinary healthcare for children with chronic diseases. It is hoped that, in the near future, these efforts will lead to interventions that can be generalized to facilitate healthcare during the transition into young adulthood. There are, however, some unique differences between most childhood cancer survivors and children with chronic diseases. Notably, the chronic disease causing special needs generally persists into adulthood, whereas the cancer is cured. Further, the long-term healthcare problems of the adolescent or young adult with a chronic childhood illness is a result of the illness. In contrast, the healthcare problems of cancer survivors are usually a consequence of their treatment. Perhaps most importantly, though, the majority of survivors who experience health problems in adulthood will be relatively asymptomatic during their adolescent and early young adult years. Thus, the symptomatic "cues to care" experienced by the individual with chronic disease will often not be shared by the asymptomatic survivor.

The preceding comments are intended for the survivor who is involved in an LTFU program. In reality, however, well over half of survivors are not followed in an LTFU setting. What can the LTFU programs do for these survivors? First, to promote change, the community of LTFU providers must adopt the role of the activist. Risk-based care of childhood cancer survivors, while strongly supported by the evidence, is the exception rather than the rule. As stated by Schwartz, it is essential that LTFU providers advocate for survivorship, increase awareness with respect to the issues and, finally, work to improve the currently inadequate delivery of care to this population [21]. This includes working with and educating insurance companies and managed care organizations and communicating with state and federal legislators. Efforts to develop informational systems on the Internet that are easy to access and navigate will also help disseminate needed information to survivors and healthcare professionals.

References

1. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine (2002) A consensus statement on the health care transitions for young adults with special health care needs. Pediatrics 110:1304–1306
2. Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP, Slap GB (1993) Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. J Adolesc Health 14:570–576
3. Green DM (2003) Late effects of treatment for cancer during childhood and adolescence. Curr Probl Cancer 27:127–142
4. Hewitt M, Weiner SL, Simone JV (eds) (2003) Childhood Cancer Survivorship: Improving Care and Quality of Life. National Academies Press, Washington DC
5. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, Yeazel M, Recklitis CJ, Marina N, Robison LL, Oeffinger KC (2003) Health Status of adult survivors who are long-term childhood cancer survivors: a report for the Childhood Cancer Survivor Study. JAMA 290:1583–1592
6. Kadan-Lottick NS, Robison LL, Gurney JG, Neglia JP, Yasui Y, Hayashi R et al. (2002) Childhood cancer survivors' knowledge about their past diagnosis and treatment – childhood cancer survivor study. JAMA 287:1832–1839
7. MacLean WE, Foley GV, Ruccione K, Sklar C (1996) Transitions in the care of adolescent and young adult survivors of childhood cancer. Cancer 78:1340–1344
8. Mertens AC, Cotter KL, Foster BM, Zebrack BJ, Hudson MM, Eshelman D, Loftis L, Sozio M, Oeffinger KC (2004) Improving health care for adult survivors of childhood cancer: recommendations from a Delphi panel of health policy experts. Health Policy (in press)
9. Neglia JP, Nesbit ME Jr (1993) Care and treatment of long-term survivors of childhood cancer. Cancer 71 [Suppl 10]: 3386–3391
10. Oeffinger KC (2000) Childhood cancer survivors and primary care physicians. J Fam Pract 49:689–690
11. Oeffinger KC (2001) Longitudinal cancer-related health care for adult survivors of childhood cancer. National Cancer Policy Board Commissioned Paper, Institute of Medicine
12. Oeffinger KC (2003) Longitudinal risk-based health care for adult survivors of childhood cancer. Curr Probl Cancer 27:143–67
13. Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR (1998) Programs for adult survivors of childhood cancer. J Clin Oncol 16:2864–2867
14. Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM (2000) Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. Cancer 88:1687–1695
15. Oeffinger KC, Mertens AC, Hudson MM, Gurney JG, Casillas J, Chen H, Yeazel M, Whitton J, Robison LL (2004) Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Fam Med (in press)
16. Reiss J, Gibson R (2002) Health care transition: destinations unknown. Pediatrics 110:1307–1314
17. Rosen DS (1993) Transition to adult health care for adolescents and young adults with cancer. Cancer 71:3411–3414
18. Scal P, Evans T, Blozis S, Okinow N, Blum R (1999) Trends in transition from pediatric to adult health care services for young adults with chronic conditions. J Adolesc Health 24:259–264
19. Schidlow DV, Fiel SB (1990) Life beyond pediatrics: transition of chronically ill adolescents from pediatric to adult health care systems. Med Clin North Am 74:1113–1120
20. Schwartz CL (1995) Late effects of treatment in long-term survivors of cancer. Cancer Treat Rev 21:355–366
21. Schwartz CL (2003) Health status of childhood cancer survivors: cure is more than eradication of cancer. JAMA 290:1641–1643
22. Zebrack BJ, Eshelman D, Hudson MM, Mertens AC, Cotter KL, Foster BM, Loftis L, Sozio M, Oeffinger KC (2004) Health care for childhood cancer survivors: barriers to optimal care and suggestions for long-term follow-up. Cancer (in press)

Subject Index

U

V

W

X