Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 2.0 – March 2006

CureSearch

Children's Oncology Group

www.survivorshipguidelines.org

CureSearch
Children's Oncology Group

COG Long-Term Follow-Up Guidelines
Content Outline

CureSearch
Children's Oncology Group

Abstract – Version 2.0
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Release date: March 2006

Status: Updated from Version 1.2 (incorporating modifications based on recommendations from eighteen multidisciplinary task forces within the COG Late Effects Committee)

Overview: These risk-based, exposure-related clinical practice guidelines provide recommendations for screening and management of late effects in survivors of pediatric malignancies. ("Pediatric malignancies" are defined as those malignancies commonly associated with the pediatric population that may arise during childhood, adolescence or young adulthood.) A complementary set of patient education materials, known as "Health Links" accompany the guidelines in order to enhance patient follow-up visits and broaden the application of these guidelines. Additional accompanying materials include detailed instructions, templates for cancer treatment summary forms, and a tool to assist in identifying guideline applicability for individual patients based on therapeutic exposures. The information provided in these guidelines is important for primary healthcare providers in the fields of pediatrics, oncology, internal medicine, family practice, and gynecology, as well as subspecialists in many fields. Implementation of these guidelines is intended to increase awareness of potential late effects and to standardize and enhance follow-up care provided to survivors of pediatric malignancies throughout their lifespan.

Source: Version 2.0 of the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, and related Health Links*, can be downloaded in their entirety from www.survivorshipguidelines.org.

CureSearch
Children's Oncology Group

DISCLAIMER AND NOTICE OF PROPRIETARY RIGHTS

Introduction to Late Effects Guidelines and Health Links: The "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" and accompanying "Health Links" were developed by the Children's Oncology Group as a collaborative effort of the Late Effects Committee and Nursing Discipline.

For Informational Purposes Only: The information and contents of each document or series of documents made available by the Children's Oncology Group relating to late effects of cancer treatment and care or containing the title "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" or the title "Health Link", whether available in print or electronic format (including any digital format, e-mail transmission, or download from the website), shall be known hereinafter as "Informational Content". All Informational Content is for informational purposes only. The Informational Content is not intended to substitute for medical advice, medical care, diagnosis or treatment obtained from a physician or healthcare provider.

> *To cancer patients (if children, their parents or legal guardians):* Please seek the advice of a physician or other qualified healthcare provider with any questions you may have regarding a medical condition and do not rely on the Informational Content. The Children's Oncology Group is a research organization and does not provide individualized medical care or treatment.
>
> *To physicians and other healthcare providers:* The Informational Content is not intended to replace your independent clinical judgment, medical advice, or to exclude other legitimate criteria for screening, health counseling, or intervention for specific complications of childhood cancer treatment. Neither is the Informational Content intended to exclude other reasonable alternative follow-up procedures. The Informational Content is provided as a courtesy, but not intended as a sole source of guidance in the evaluation of childhood cancer survivors. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

No endorsement of any specific tests, products, or procedures is made by Informational Content, the Children's Oncology Group, or affiliated party or member of the Children's Oncology Group.

No Claim to Accuracy or Completeness: While the Children's Oncology Group has made every attempt to assure that the Informational Content is accurate and complete as of the date of publication, no warranty or representation, express or implied, is made as to the accuracy, reliability, completeness, relevance, or timeliness of such Informational Content.

No Liability on Part of Children's Oncology Group and Related Parties/ Agreement to Indemnify and Hold Harmless the Children's Oncology Group and Related Parties: No liability is assumed by the Children's Oncology Group or any affiliated party or member thereof for damage resulting from the use, review, or access of the Informational Content. You agree to the following terms of indemnification: (i) "Indemnified Parties" include authors and contributors to the Informational Content, all officers, directors, representatives, employees, agents, and members of the Children's Oncology Group and affiliated organizations; (ii) by using, reviewing, or accessing the Informational Content, you agree, at your own expense, to indemnify, defend and hold harmless Indemnified Parties from any and all losses, liabilities, or damages (including attorneys' fees and costs) resulting from any and all claims, causes of action, suits, proceedings, or demands related to or arising out of use, review or access of the Informational Content.

Proprietary Rights: The Informational Content is subject to protection under the copyright law and other intellectual property law in the United States and worldwide. The Children's Oncology Group retains excusive copyright and other right, title, and interest to the Informational Content and claims all intellectual property rights available under law. You hereby agree to help the Children's Oncology Group secure all copyright and intellectual property rights for the benefit of the Children's Oncology Group by taking additional action at a later time, action which could include signing consents and legal documents and limiting dissemination or reproduction of Informational Content.

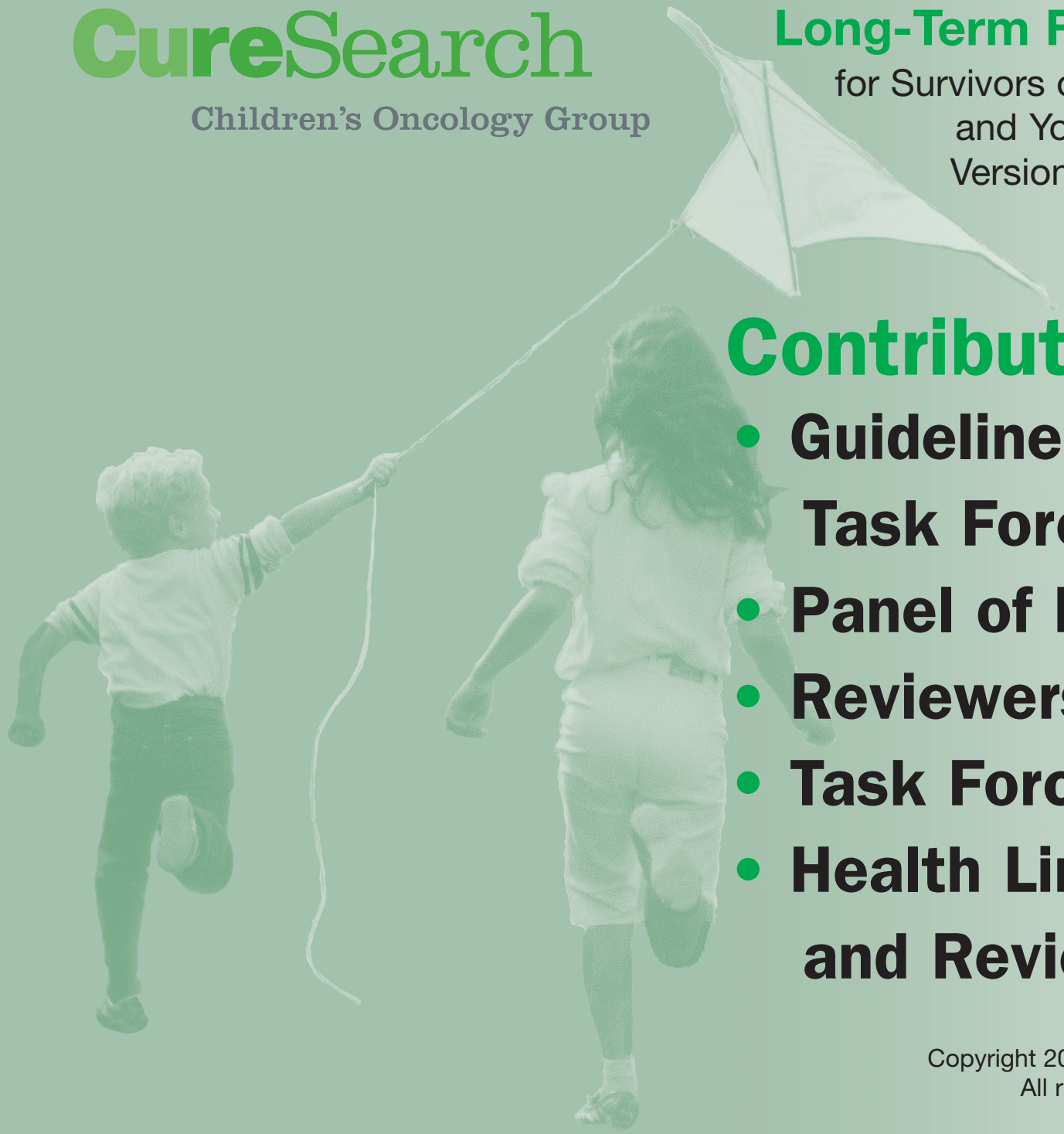
CureSearch

Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 2.0 – March 2006



Contributors

- Guideline Development Task Force
- Panel of Experts
- Reviewers
- Task Force Membership
- Health Link Authors and Reviewers

CureSearch
Children's Oncology Group

Guideline Development Task Force

The Children's Oncology Group Nursing Discipline and Late Effects Committee developed the initial versions (1.0, 1.1, and 1.2) of the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* collaboratively through the efforts of the following individuals:

Melissa M. Hudson, MD
Vice-Chair – COG Late Effects Committee
Member, Department of Hematology-Oncology
Director, After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, Tennessee

Wendy Landier, RN, MSN, CPNP, CPON®
Chair – COG Nursing Clinical Practice Subcommittee
Clinical Director - Survivorship Clinic
City of Hope Comprehensive Cancer Center
Duarte, California

Debra Eshelman, RN, MSN, CPNP
Late Effects Section Leader
– COG Nursing Clinical Practice Subcommittee
Pediatric Nurse Practitioner
After the Cancer Experience (ACE) Program
Children's Medical Center – Dallas
Dallas, Texas

Kathy Forte, RN, MS, CPNP
Co-Chair – COG Nursing Education Subcommittee
Pediatric Nurse Practitioner – Cancer Survivor Program
AFLAC Cancer Center and Blood Disorders Service
Children's Healthcare of Atlanta
Atlanta, Georgia

Joan Darling, PhD
COG Patient Advocate Committee Representative
Lincoln, Nebraska

Allison Hester, RN, MSN, CPNP
Pediatric Nurse Practitioner
After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, Tennessee

Teresa Sweeney, RN, MSN, CPNP
Pediatric Nurse Practitioner
After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, Tennessee

Special Acknowledgment:

With sincere appreciation to
Louis S. "Sandy" Constine, MD
Vice Chair, Department of Radiation Oncology
James P. Wilmont Cancer Center
University of Rochester Medical Center
for his in-depth expert review and extensive contributions to all radiation-related sections in all versions of the COG LTFU Guidelines

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines
Panel of Experts

The following members of the Children's Oncology Group Late Effects Committee participated in comprehensive review and scoring of the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers:*

Smita Bhatia, MD, MPH
Chair – COG Late Effects Committee
Professor and Chair, Division of Population Sciences
City of Hope Comprehensive Cancer Center
Duarte, CA

Melissa M. Hudson, MD
Vice-Chair – COG Late Effects Committee
Member, Department of Hematology-Oncology
Director, After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, TN

F. Daniel Armstrong, PhD
Professor and Associate Chair, Department of Pediatrics
Director, Mailman Center for Child Development
University of Miami School of Medicine
Miami, FL

Julie Blatt, MD
Professor of Pediatrics
Division of Pediatric Hematology-Oncology
University of North Carolina
Chapel Hill, NC

Louis S. Constine, MD
Professor of Radiation Oncology and Pediatrics
Vice Chair, Department of Radiation Oncology
James P. Wilmot Cancer Center
University of Rochester Medical Center
Rochester, NY

Joan Darling, PhD
COG Patient Advocacy Committee Representative
Lincoln, NE

Paul Graham Fisher, MD, MHS
Associate Professor, Neurology and Pediatrics
The Beirne Family Director of Neuro-Oncology
at Packard Hospital
Stanford University Medical Center
Stanford, CA

Carolyn R. Freeman, MB, BS, FRCPC
Professor and Director
Department of Radiation Oncology
McGill University Health Centre
Montreal, Quebec, Canada

Debra L. Friedman MD, MS
Associate Professor of Pediatrics
Fred Hutchinson Cancer Research Center
Seattle, WA

Daniel M. Green, MD
Department of Pediatrics
Roswell Park Cancer Institute
Buffalo, NY
Professor of Pediatrics
School of Medicine and Biomedical Sciences
University at Buffalo, State University of New York
Buffalo, NY

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines
Panel of Experts (cont)

Peter D. Inskip, Sc.D.
Senior Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Bethesda, MD

Nina Kadan-Lottick, MD, MSPH
Associate Research Scientist
Department of Pediatrics
Yale University School of Medicine
New Haven, CT

Wendy Landier, RN, MSN, CPNP, CPON®
Pediatric Nurse Practitioner
Clinical Director, Survivorship Clinic
City of Hope Comprehensive Cancer Center
Duarte, CA

Neyssa Marina, MD
Professor of Pediatrics
Director, Long-Term Survivors Clinic
Department of Pediatrics
Stanford University Medical Center
Stanford, CA

Lillian Meacham, MD
Medical Director, Cancer Survivor Program
Division of Pediatric Endocrinology
Children's Healthcare of Atlanta
Atlanta, GA

Anna T. Meadows, MD
Professor of Pediatrics
University of Pennsylvania School of Medicine
Director, Follow-Up Program
The Children's Hospital of Philadelphia
Philadelphia, PA

Joseph P. Neglia, MD, MPH
Professor of Pediatrics
Division of Hematology, Oncology,
Blood and Marrow Transplantation
University of Minnesota School of Medicine
Minneapolis, MN

Kevin C. Oeffinger, MD
Director, Living Beyond Cancer Program
Memorial Sloan-Kettering Cancer Center
New York, NY

Leslie L. Robison, PhD
Chair, Epidemiology and Cancer Control
St. Jude Children's Research Hospital
Memphis, TN

Charles A. Sklar, MD
Director, Long-Term Follow-Up Program
Memorial Sloan Kettering Cancer Center
New York, NY

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines Reviewers

The following individuals participated in the review process during development of the initial versions (1.0, 1.1, and 1.2) of the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers:*

Arlina Ahluwalia, MD
Department of General Internal Medicine
Stanford University
Palo Alto, CA

F. Daniel Armstrong, PhD
Department of Pediatrics
University of Miami School of Medicine
Miami, FL

Lisa Bashore, RN, MS, CPNP
Pediatric Hematology/Oncology
Cook Children's Medical Center
Fort Worth, TX

Smita Bhatia, MD, MPH
Division of Population Sciences
City of Hope Comprehensive Cancer Center
Duarte, CA

Julie Blatt, MD
Division of Pediatric Hematology-Oncology
University of North Carolina
Chapel Hill, NC

Susan Bock, BSN, RN
Department of Pediatric Specialities
Gundersen Lutheran Clinic
LaCrosse, WI

Cathy Bourne, RN, BHSc(N)
Pediatric Hematology/Oncology
Cancer Care Manitoba
Winnipeg, Manitoba, Canada

Julianne Byrne, PhD
Department of Hematology-Oncology
Children's National Medical Center
Washington, DC

Hope Anne Castoria, BSN, RN, CPON®
Tomorrow Children's Institute
Hackensack University Medical Center
Hackensack, NJ

Laurie Cohen, MD
Division of Endocrinology
Dana Farber Cancer Institute
Boston, MA

Louis S. Constine, MD
Department of Radiation Oncology
University of Rochester Medical Center
Rochester, NY

Lola Cremer, PT
Division of Rehabilitation Services
St. Jude Children's Research Hospital
Memphis, TN

Sarah Donaldson, MD
Radiation Oncology/Radiation Therapy
Stanford University Medical Center
Stanford, CA

Patty Feist
Patient Advocate
Boulder, CO

Paul Fisher, MD
Neurology and Pediatrics
Stanford University Medical Center
Stanford, CA

Carolyn R. Freeman, MB, BS, FRCPC
Department of Radiation Oncology
McGill University Health Centre
Montreal, Quebec, Canada

Debra L. Friedman MD, MS
Pediatric Hematology-Oncology
Fred Hutchinson Cancer Research Center
Seattle, WA

Daniel M. Green, MD
Department of Pediatrics
Roswell Park Cancer Institute
Buffalo, NY

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines
Reviewers (cont)

Mark Greenberg, MB, BCh
Department of Haematology/Oncology
Hospital for Sick Children
Toronto, Ontario, Canada

Wendy Hobbie, MSN, RN, PNP
Division of Oncology
Children's Hospital of Philadelphia
Philadelphia, PA

Nina Kadan-Lottick, MD, MSPH
Department of Pediatrics
Yale University School of Medicine
New Haven, CT
Nancy Keene
Patient Advocate
Annandale, VA

Lisa B. Kenney, MD, MPH
Perini Quality of Life Clinic
Dana-Farber Cancer Institute
Boston, MA

Winnie Kittiko, RN, MS
COG Patient Advocacy Committee
Douglasville, GA

Margaret Kulm, RN, MA
COG Patient Advocacy Committee
Port Ludlow, WA

Missy Layfield
COG Patient Advocacy Committee
Cedar Falls, IA

Marcia Leonard, RN, CPNP
Department of Pediatric Hematology/Oncology
C.S. Mott Children's Hospital
Ann Arbor, MI

Mary Leonard, MD, MSCE
Division of Nephrology
Children's Hospital of Philadelphia
Philadelphia, PA

Louis A. Leone, Esq.
COG Patient Advocacy Committee
Walnut Creek, CA
Neyssa Marina, MD
Pediatric Hematology Oncology
Stanford University Medical Center
Stanford,CA

Leonard Mattano, MD
Pediatric Hematology/Oncology
Kalamazoo Center for Medical Studies
Michigan State University
Kalamazoo, MI

Anne Mauck, RN, MSN, CPNP
Pediatric Hematology/Oncology
Virginia Commonwealth University Health System
Richmond, VA

Charlene Maxen, RN, CNP, CPON®
Hematology/Oncology
Childrens Hospital Medical Center - Akron
Akron, OH

Lillian Meacham, MD
Division of Pediatric Endocrinology
Children's Healthcare of Atlanta
Atlanta, GA

Anna T. Meadows, MD
Division of Oncology
Children's Hospital of Philadelphia
Philadelphia, PA

Grace Powers Monaco, JD
Childhood Cancer Ombudsman Program
Heathsville, VA
Raymond Mulhern, PhD
Division of Behavioral Medicine
St. Jude Children's Research Hospital
Memphis, TN

John R. Mussman
COG Patient Advocacy Committee
Chicago, IL

Michael Neel, MD
Division of Orthopedics
St. Jude Children's Research Hospital
Memphis, TN

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines
Reviewers (cont)

Joseph P. Neglia, MD, MPH
Department of Pediatrics
Division of Hematology, Oncology,
Blood and Marrow Transplantation
University of Minnesota School of Medicine
Minneapolis, MN

Mary Nelson, RN, MS, CPNP, CPON®
Childrens Center for Cancer and Blood Diseases
Childrens Hospital Los Angeles
Los Angeles, CA

Kevin Oeffinger, MD
Department of Pediatrics
Memorial Sloan-Kettering Cancer Center
New York, NY

Roger Packer, MD
Department of Neurology
Children's National Medical Center
Washington, DC

Arnold Paulino, MD
Department of Radiation Oncology
Children's Healthcare of Atlanta – Emory Clinic
Atlanta, GA

Rebecca D. Pentz, PhD
COG Patient Advocacy Committee
Atlanta, GA

Leslie L. Robison, PhD
Department of Epidemiology and Cancer Control
St. Jude Children's Research Hospital
Memphis, TN

David Rosenthal, MD
Department of Pediatrics/Cardiology
Lucile Packard Children's Hospital at Stanford
Palo Alto, CA

Kathy Ruble, RN, MSN, CPNP, AOCN®
Pediatric Oncology
Johns Hopkins Hospital
Baltimore, MD

Kathleen Ruccione, RN, MPH, FAAN, CPON®
Childrens Center for Cancer and Blood Diseases
Childrens Hospital Los Angeles
Los Angeles, CA

Jean Sanders, MD
Pediatric Marrow Transplantation
Children's Hospital Regional Medical Center
Seattle, WA

Cindy Schwartz, MD
Pediatric Hematology/Oncology
Rhode Island Hospital
Providence, RI

Susan Shaw, RN, MS, PNP
Center for Children's Cancer and Blood Disorders
State University of New York at Syracuse
Syracuse, NY

Charles A. Sklar, MD
Department of Pediatrics/Endocrinology
Memorial Sloan-Kettering Cancer Center
New York, NY

Jacquie Toia, RN, ND, CPNP
Hematology/Oncology
Children's Memorial Medical Center
Chicago, IL

Deborah Waber, PhD
Department of Psychiatry
Boston Children's Hospital
Boston, MA

Susan L. Weiner, PhD
The Children's Cause, Inc.
Silver Spring, MD

Fran Wiley, RN, MN
COG Patient Advocacy Committee
Los Angeles, CA

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines
Reviewers (cont)

Suzanne L. Wolden, MD
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
New York, NY

Catherine L. Woodman, MD
COG Patient Advocacy Committee
Iowa City, IA

Lise Yasui
COG Patient Advocacy Committee
Philadelphia, PA

Joseph Zins, PhD
COG Patient Advocacy Committee
Cincinnati, OH

Octavio Zavala
COG Patient Advocacy Committee
Los Angeles, CA

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership

Task Force	Task Force Members	Institution	Expertise
Amputation/ Limb Sparing	Thomas R. Baker, CP Laura Feldman, Patient Advocate Dominic Femino, MD Norman Jaffe, MD Anita Majan, MD Victoria Marchese, PhD, PT* Rajaram Nagarajan, MD, MPH* Teresa Sweeney, RN, MSN, CPNP Mark Yeazel, MD * Co-Chair	CFI Prosthetics and Orthotics Children's Oncology Group Childrens Hospital Los Angeles M.D. Anderson Cancer Center M.D. Anderson Cancer Center St. Jude Children's Research Hospital University of Minnesota Cancer Center St. Jude Children's Research Hospital University of Minnesota	Prosthetics Patient advocacy Orthopedic surgery Pediatric oncology Radiation oncology Physical therapy Pediatric oncology Pediatric oncology nursing Primary care
Auditory/Hearing	Cathy Hodge, Patient Advocate Wendy Landier, RN, MSN, CPNP* Maryrose McInerney, PhD, CCC-A Thomas Merchant, DO, PhD Nicole Robbins, AU Renee F. Reymond, MD Patricia Shearer, MD, MS* * Co-Chair	Children's Oncology Group City of Hope National Medical Center Hackensack University Medical Center St. Jude Children's Research Hospital St. Jude Children's Research Hospital Ochsner Clinic Ochsner Clinic	Patient advocacy Pediatric oncology nursing Audiology Radiation oncology Audiology Primary care Pediatric oncology

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Cancer Screening	Louis S. Constine, MD	University of Rochester Medical Center	Radiation oncology
	Lauren Dome, RN, CPNP	St. Jude Children's Research Hospital	Pediatric oncology nursing
	Debra Friedman, MD, MS	Fred Hutchinson Cancer Research Center	Pediatric oncology
	Melissa M. Hudson, MD	St. Jude Children's Research Hospital	Pediatric oncology
	Marilyn Leitch, MD	University of Texas Southwestern Medical Center	Surgery
	Martin Mahoney, MD, PhD, FAAFP	Roswell Park Cancer Institute	Primary care
	Kathy Meeske, PhD, RN	Childrens Hospital Los Angeles	Pediatric oncology nursing
	Ann Mertens, MD	University of Minnesota	Epidemiology
	Monika Metzger, MD	St. Jude Children's Research Hospital	Pediatric oncology
	Kevin C. Oeffinger, MD*	Memorial Sloan-Kettering Cancer Center	Primary care
	Robert Smith, MD	American Cancer Society	Medical oncology
	Octavio Zavala, Patient Advocate	Childrens Hospital Los Angeles	Patient advocacy
	* Chair		
Cardiovascular	Ming Hui Chen, MD, MMSc	Brigham and Women's Hospital	Adult cardiology
	David Hodgson, MD	Princess Margaret Hospital	Radiation oncology
	Karen Kinahan, MS, RN	Northwestern University	Pediatric oncology nursing
	Neyssa Marina, MD*	Stanford University Medical Center	Pediatric oncology
	Kathleen Meeske, PhD, RN	Childrens Hospital Los Angeles	Pediatric oncology nursing
	Angie Pemberton, Patient Advocate	Children's Oncology Group	Patient advocacy
	David Rosenthal,MD*	Stanford University Medical Center	Pediatric cardiology
	Sadhna Shankar, MD*	Vanderbilt Children's Hospital	Pediatric oncology
	Julia Steinberger, MD, MS	University of Minnesota Medical School	Pediatric cardiology
	*Co-Chair		

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Endocrine/Metabolic	Nathalie Alos, MD	Ste-Justine Hospital	Pediatric endocrinology
	Laurie Cohen, MD	Dana-Farber Cancer Institute	Pediatric endocrinology
	Kimberley Dilley, MD, MPH	Children's Memorial Hospital	Primary care
	Eileen Duffey-Lind, RN, MS, PNP	Dana-Farber Cancer Institute	Pediatric oncology nursing
	Wendy Hobbie, MSN, RN, CRNP	The Children's Hospital of Philadelphia	Pediatric oncology nursing
	Patricia Kent, RN, CPNP	Massachusetts General Hospital	Pediatric oncology nursing
	Caroline Laverdiere, MD*	Ste-Justine Hospital	Pediatric oncology
	Lillian R. Meacham, MD	Children's Healthcare of Atlanta	Pediatric endocrinology
	Daniel Mulrooney, MD*	University of Minnesota Cancer Center	Pediatric oncology
	Charles Sklar, MD	Memorial Sloan-Kettering Cancer Center	Pediatric endocrinology
	Stacey Urbach, MD	Hospital for Sick Children	Pediatric endocrinology
	Suzanne Wolden, MD	Memorial Sloan-Kettering Cancer Center	Radiation oncology
	Octavio Zavala, Patient Advocate	Childrens Hospital Los Angeles	Patient advocacy
	*Co-Chair		
Fertility/Reproduction	Sharon Abish, MD	McGill University Health Center	Pediatric oncology
	Jacqueline Casillas, MD	UCLA School of Medicine	Pediatric oncology
	Mishel L. Davis, CRA	Children's Medical Center of Dallas	Pediatric oncology
	James Douglas, MD	Children's Hospital and Regional Medical Center	Radiation oncology
	Fernando A. Ferrer, MD	Connecticut Children's Medical Center	Urology
	Senait Fisseha, MD, JD	University of Michigan	Gynecology
	Daniel Green, MD	Roswell Park Cancer Institute	Pediatric oncology
	Wendy Hobbie, MSN, RN, CRNP	The Children's Hospital of Philadelphia	Pediatric oncology nursing
	Lisa Kenney, MD	Dana-Farber Cancer Institute	Pediatric oncology
	Marcia Leonard, RN, CPNP*	C. S. Mott Children's Hospital	Pediatric oncology nursing
	Wendy Likes, DNSc, ARNP-BC	University of Tennessee	Nursing
	Monika Metzger, MD*	St. Jude Children's Research Hospital	Pediatric oncology
	*Co-Chair		

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Gastrointestinal/Hepatic	Sharon Castellino, MD* Joan Darling, PhD, Patient Advocate Andrew Davidoff, MD Melissa M. Hudson, MD* Kevin McMullen, MD Andrew Muir, MD, MSH Kathy Ruble, RN, CPNP, AOCN Sheila Shope, RN, FNP *Co-Chair	Wake Forest University Baptist Medical Center Children's Oncology Group St. Jude Children's Research Hospital St. Jude Children's Research Hospital Wake Forest University School of Medicine Duke University School of Medicine Johns Hopkins Hospital St. Jude Children's Research Hospital	Pediatric oncology Patient advocacy Pediatric surgery Pediatric oncology Radiation oncology Pediatric GI/hepatology Pediatric oncology nursing Primary care
Hematopoietic Cell Transplant	Scott Baker, MD* Smita Bhatia, MD, MPH* Louis S. Constine, MD Kevin C. Oeffinger, MD Wendy Pelletier, MSW, RSW Susan F. Shaw, RN, MS, PNP Ami Jayant Shah, MD Lise Yasui, Patient Advocate *Co-Chair	University of Minnesota Cancer Center City of Hope National Medical Center University of Rochester Medical Center Memorial Sloan-Kettering Cancer Center Alberta Children's Hospital State University of New York at Syracuse Childrens Hospital Los Angeles Children's Oncology Group	Pediatric oncology Pediatric oncology Radiation oncology Primary care Social work Pediatric oncology nursing Pediatric oncology Patient advocacy
Immune/Spleen	Jill Ginsberg, MD* Karen Mandel, MD, FRCPC, FAAP Anna Meadows, MD* Joanna Perkins, MD, MS *Co-Chair	The Children's Hospital of Philadelphia Children's Hospital of Eastern Ontario The Children's Hospital of Philadelphia Children's Hospitals and Clinics of Minnesota	Pediatric oncology Pediatric oncology Pediatric oncology Pediatric oncology

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Musculoskeletal Dental Dermatologic	La Vette Bowles, RN, FNP Amy Gilliam, MD Sue Kaste, DO Missy Layfield, Patient Advocate Rex Marco, MD Man Wai Ng, DDS, MPH Arnold Paulino, MD* Susan F. Shaw, RN, MS, PNP Sheri Spunt, MD Lynn Tanner, MS, PT *Chair	UCLA School of Medicine University of California San Francisco St. Jude Children's Research Hospital Children's Oncology Group University of Texas Health Sciences at Houston Children's Hospital Boston Methodist Hospital Houston State University of New York at Syracuse St. Jude Children's Research Hospital Children's Hospitals and Clinics of Minnesota	Primary care Pediatric dermatology Diagnostic imaging Patient advocacy Orthopedic oncology Pediatric dentistry Radiation oncology Pediatric oncology nursing Pediatric oncology Physical therapy
Neurocognitive/Behavioral	Danny Armstrong, PhD Pim Brouwers, PhD Kimberley Dilley, MD, MPH Robert Goldsby, MD Jeanne Harvey, RN, MSN, PNP Chad Jacobsen, MD Nina Kadan-Lottick, MD, MSPH Karen McKinley, PsyD, LCSW Ida (Ki) Moore, PhD, RN Paul Nathan, MD, MSc* Fatih Okcu, MD Sunita Patel, PhD* Catherine L. Woodman, MD * Co-Chair	University of Miami School of Medicine National Institute of Mental Health Children's Memorial Hospital Chicago UCSF School of Medicine Washington University Medical Center Rainbow Babies & Children's Hospital Yale University School of Medicine Children's Hospital of the King's Daughters University of Arizona Health Sciences Center The Hospital for Sick Children Texas Children's Cancer Center City of Hope National Medical Center University of Iowa Hospitals and Clinics	Pediatric psychology Pediatric psychology Primary care Pediatric oncology Pediatric oncology nursing Pediatric oncology Pediatric oncology Social Work Pediatric oncology nursing Pediatric oncology Pediatric oncology Pediatric psychology Patient advocacy

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Neurologic (CNS & PNS)	Jean Belasco, MD Jackie Casillas, MD Paul G. Fisher, MD* Michael J. Fisher, MD E. Brannon Morris III, MD Roger Packer, MD* Kathy Ruble, RN, CPNP, AOCN *Co-Chair	The Children's Hospital of Philadelphia UCLA School of Medicine Stanford University Cancer Center The Children's Hospital of Philadelphia St. Jude Children's Research Hospital Children's National Medical Center Johns Hopkins Hospital	Pediatric oncology Pediatric oncology Pediatric neurology Pediatric neuro-oncology Pediatric neurology Pediatric neurology Pediatric oncology nursing
Ocular/Vision	Louis S. Constine, MD Debra Friedman, MD, MS* Sarita Joshi, MD A. Linn Murphree, MD Carol L. Shields, MD Teresa Sweeney, RN, MSN, CPNP Catherine L. Woodman, MD *Chair	University of Rochester Medical Center Fred Hutchinson Cancer Research Center Women and Childrens Hospital Childrens Hospital Los Angeles Wills Eye Hospital St. Jude Children's Research Hospital University of Iowa Hospitals and Clinics	Radiation oncology Pediatric oncology Pediatric oncology Pediatric ophthalmology Pediatric ophthalmology Pediatric oncology nursing Patient advocacy
Psychosocial	Debra Eshelman, RN, MSN, CPNP Mark Greenberg, MD Nina Kadan-Lottick, MD, MSPH* Stuart Kaplan, MD Ann Mertens, PhD Sunita Patel, PhD Sheila Santacroce, PhD, APRN, CPNP Sally Wiard, MSW Octavio Zavalo, Patient Advocate Catherine L. Woodman, MD *Chair	Children's Medical Center of Dallas Hospital for Sick Children Yale University School of Medicine St. Jude Children's Research Hospital University of Minnesota City of Hope National Medical Center Yale University School of Nursing St. Jude Children's Research Hospital Childrens Hospital Los Angeles University of Iowa Hospitals and Clinics	Pediatric oncology nursing Pediatric oncology Pediatric oncology Primary care Epidemiology Pediatric psychology Pediatric oncology nursing Social work Patient advocacy Patient advocacy

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Pulmonary	Julie Blatt, MD*	University of North Carolina at Chapel Hill	Pediatric oncology
	Robert Goldsby, MD*	UCSF School of Medicine	Pediatric oncology
	E. Allen Liles, Jr., MD	University of North Carolina at Chapel Hill	Primary care
	Charlene Maxen, RN, CNP, CPON	Children's Hospital Medical Center of Akron	Pediatric oncology nursing
	David E. Morris, MD	University of North Carolina at Chapel Hill	Radiation oncology
	Angie Pemberton, Patient Advocate	Children's Oncology Group	Patient advocacy
	David L. Robinowitz, MD, MHS, MS	UCSF Pediatric Pulmonary Medicine	Pulmonary
	Aimee Sznewajs, RN, MS, PNP	UCSF Children's Hospital	Pediatric oncology nursing
	Richard Wardrop, III, MD	University of North Carolina at Chapel Hill	Primary care
	* Co-Chair		
Skeletal: Osteonecrosis Osteopenia Osteoporosis	Arlina Ahluwalia, MD	Stanford University Medical Center	Primary care
	Natia Esiashvili, MD	Emory University	Radiation oncology
	Sue Kaste, DO	St. Jude Children's Research Hospital	Diagnostic imaging
	Missy Layfield, Patient Advocate	Children's Oncology Group	Patient advocacy
	Victoria Marchese, PhD, PT	St. Jude Children's Research Hospital	Physical therapy
	Leonard A. Mattano, Jr., MD*	Kalamazoo Center for Medical Sciences	Pediatric oncology
	Lillian R. Meacham, MD*	Children's Healthcare of Atlanta	Pediatric endocrinology
	Susan Shannon, RN, MSN, CPNP, CPON	Miller Children's Hospital/Harbor-UCLA	Pediatric oncology nursing
	Karen Wasilewski, MD	Children's Healthcare of Atlanta	Pediatric oncology
	*Co-Chair		

CureSearch
Children's Oncology Group

COG Long Term Follow-Up Guidelines
Task Force Membership (cont)

Task Force	Task Force Members	Institution	Expertise
Subsequent Malignant Neoplasms	Smita Bhatia, MD, MPH* Louis S. Constine, MD Debra Friedman, MD, MS Wendy Landier, RN, MSN, CPNP Joseph Neglia, MD, MPH* Sadhna Shankar, MD Lise Yasui, Patient Advocate Mark Yeazel, MD *Co-Chair	City of Hope National Medical Center University of Rochester Medical Center Fred Hutchinson Cancer Research Center City of Hope National Medical Center University of Minnesota Cancer Center Vanderbilt Children's Hospital Children's Oncology Group University of Minnesota	Pediatric oncology Radiation oncology Pediatric oncology Pediatric oncology nursing Pediatric oncology Pediatric oncology Patient advocacy Primary care
Urinary Tract	Joan Darling, PhD, Patient Advocate Fernando Ferrer, MD Daniel Green, MD Deborah Jones, MD Anne Mauck, RN, MSN, CPNP Arnold Paulino, MD Michael Ritchey, MD Patricia Shearer, MD, MS Sheri L. Spunt, MD* *Chair	Children's Oncology Group Connecticut Children's Medical Center Roswell Park Cancer Institute LeBonheur Children's Medical Center Virginia Commonwealth University Methodist Hospital Houston Pediatric Urology Associates Phoenix Ochsner Clinic St. Jude Children's Research Hospital	Patient advocacy Pediatric urology Radiation oncology Pediatric nephrology Pediatric oncology nursing Radiation oncology Urology Pediatric oncology Pediatric oncology

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines Health Link Authors

The following individuals participated in writing the patient education materials *(Health Links) for the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers:*

Thomas R. Baker, CP
CFI Prosthetics and Orthotics
Memphis, TN

Julie Blatt, MD
Division of Pediatric Hematology-Oncology
University of North Carolina
Chapel Hill, NC

Sharon M. Castellino, MD
Department of Pediatrics, Hematology/Oncology
Wake Forest University Health Sciences,
Winston-Salem, NC

Debra Eshelman, RN, MSN, CPNP
After the Cancer Experience (ACE) Program
Children's Medical Center – Dallas
Dallas, TX

Fernando A. Ferrer, MD
Department of Surgery
Connecticut Children's Medical Center
Hartford, CT

Sarah Friebert, MD
Division of Hematology/Oncology
Childrens Hospital Medical Center of Akron
Akron, OH

Debra L. Friedman, MD, MS
Pediatric Hematology-Oncology
Fred Hutchinson Cancer Research Center
Seattle, WA

Sharon Frierdich, RN, MS, CPNP
Pediatric Hematology/Oncology
University of Wisconsin Children's Hospital
Madison, WI

Allison Hester, RN, MSN, CPNP
After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, TN

Melissa M. Hudson, MD
After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, TN

Asako Komiya, RN, MSN, PNP
Department of Epidemiology and Outcomes Research
City of Hope Comprehensive Cancer Center
Duarte, CA

Deborah Lafond, MS, RNCS, PNP, CPON®
Hematology/Oncology
Children's National Medical Center
Washington, DC

Wendy Landier, RN, MSN, CPNP, CPON®
Department of Pediatric Hematology/Oncology
City of Hope Comprehensive Cancer Center
Duarte, CA

Marcia Leonard, RN, CPNP
Pediatric Hematology/Oncology and
Long-Term Follow-Up Clinic
C.S. Mott Children's Hospital
Ann Arbor, MI

Victoria Marchese, PhD, PT
Department of Epidemiology and Cancer Control
St. Jude Children's Research Hospital
Memphis, TN

Anne Mauck, RN, MSN, CPNP
Pediatric Hematology/Oncology
Virginia Commonwealth University Health System
Richmond, VA

Charlene Maxen, RN, CNP, CPON®
Division of Hematology/Oncology
Childrens Hospital Medical Center of Akron
Akron, OH

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines
Health Link Authors (cont)

Katherine Myint-Hpu, MSN, MPH, PNP
Leukemia/Lymphoma Clinic
Georgetown University Hospital
Washington, DC

Rajaram Nagarajan, MD, MPH
University of Minnesota Cancer Center
Pediatric Hematology/Oncology/BMT
Minneapolis, MN

Kevin Oeffinger MD
Division of Pediatrics
Memorial Sloan-Kettering Cancer Cente
New York, NY

Arnold Paulino, MD
Division of Radiation Oncology
Methodist Hospital
Houston, TX
Sunita Patel, PhD
Department of Pediatric Hematology/Oncology
City of Hope Comprehensive Cancer Center
Duarte, CA

Michael Ritchey, MD
Pediatric Urology Associates
Phoenix, AZ

Kathy Ruble, RN, CPNP, AOCN®
Long Term Follow-Up Program
Johns Hopkins University
Baltimore, MD

Sheila Judge Santacroce, PhD, APRN, CPNP
School of Nursing
Yale University
New Haven, CT

Margery Schaffer, RN, MSN, CPNP
Department of Hematology/Oncology
Children's Medical Center
Dayton, OH

Susan Shannon, RN, MSN, CPNP, CPON®
"STAR" Late Effects Program
Miller Children's Hospital
Long Beach, CA

Patricia Shearer, MD, MS
Pediatric Hematology/Oncology
Ochsner Clinic
New Orleans, LA

Sheila Shope, RN, FNP
After Completion of Therapy Clinic
St. Jude Children's Hospital
Memphis, TN

Sheri L. Spunt, MD
Hematology/Oncology
St. Jude Children's Research Hospital
Memphis, TN

Teresa Sweeney, RN, MSN, CPNP
After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, TN

Sally Wiard, MSW, LCSW
After Completion of Therapy Clinic
St. Jude Children's Research Hospital
Memphis, TN

Health Link Graphic Artist:
Devika Bhatia
Westridge School
Pasadena, CA

CureSearch
Children's Oncology Group

Long-Term Follow-Up Guidelines Health Link Reviewers

The following individuals participated in reviewing the patient education materials *(Health Links) for the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers:*

Daniel Armstrong, PhD
Lisa Bashore, MS, RN, CPNP, CPON®
Smita Bhatia, MD, MPH
Julie Blatt, MD
Sarah Bottomley, MN, RN, CPNP, CPON®
Emmett J. Broxson, Jr., MD
Billie Buchert, RN, BSN
Jacqueline Casillas, MD
Joe Don Cavender, MSN, RN, CPNP
Vimal Chadha, MD
Louis S. Constine, MD
Joan Darling, PhD
Nancy L. Dunn, MD
J. Dominic Femino, MD
Debra L. Friedman, MD
Daniel Green, MD
Elizabeth Hall, CPNP
Scott Hawkins, LMSW
Melissa M. Hudson, MD
Winnie Kittiko, RN, MS
Peggy Kulm, RN, MA
Wendy Landier, RN, MSN, CPNP, CPON®
Missy Layfield
Thanh Le, MD
Marcia Leonard, RN, CPNP
Neyssa Marina, MD
Gita Massey, MD
Lillian R. Meacham, MD
Jill Meredith, RN, BSN, OCN®
Revonda Mosher, RN, MSN, CPNP, CPON®
John R. Mussman
Man Wai Ng, DDS
Kevin Oeffinger, MD
Josee Pacifico, RN, BSc (N)
Rebecca D. Pentz, PhD
Priscilla Rieves, MS, RN, CPNP
Michael L. Ritchey, MD
Leslie L. Robison, PhD
Kathleen Ruccione, RN, MPH, FAAN, CPON®
E. Clifton Russell, MD
Susan Shaw, RN, MS, PNP
Charles A. Sklar, MD
Johanne Soucy, RN, B.SC.N
Karen Stormer, RN, CNS, CPON®
Joetta Deswarte-Wallace, RN, MSN
Edward Walz, MD
Fran Wiley, RN, MN
Roberta G. Williams, MD
Catherine L. Woodman, MD
Lise Yasui
Octavio Zavala

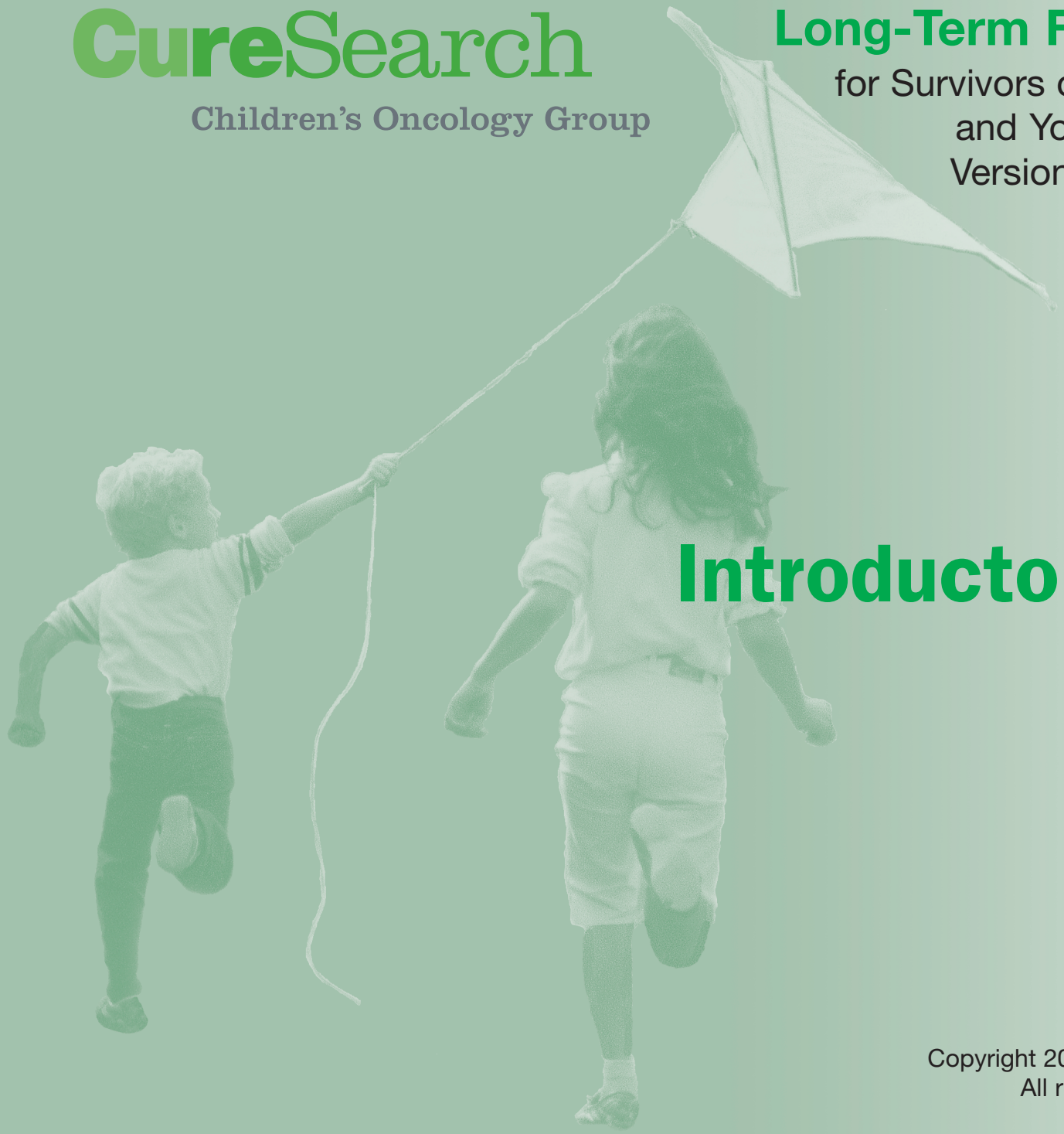
CureSearch

Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 2.0 – March 2006



Introductory Material

CureSearch
Children's Oncology Group

Introduction – Version 2.0
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Overview:

The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG-LTFU Guidelines) are risk-based, exposure-related clinical practice guidelines for screening and management of late effects resulting from therapeutic exposures used during treatment for pediatric malignancies. These guidelines represent a statement of consensus from a panel of experts in the late effects of pediatric cancer treatment. The guidelines are both evidence-based (utilizing established associations between therapeutic exposures and late effects to identify high-risk categories) and grounded in the collective clinical experience of experts (matching the magnitude of the risk with the intensity of the screening recommendations). Since therapeutic interventions for a specific pediatric malignancy may vary considerably based on the patient's age, presenting features, and treatment era, a therapy-based design was chosen to permit modular formatting of the guidelines by therapeutic exposure. Importantly, the recommended periodic screening underscores the use of a thorough history and physical examination (H&P) as the primary assessment for cancer-related treatment effects. In this regard, 101 (74%) of the screening recommendations outlined for the 136 therapeutic exposures in the COG-LTFU Guidelines comprise assessments derived primarily from the H&P, with 68 (50%) relying solely on the H&P and 33 (24%) relying on the H&P plus a baseline diagnostic study (e.g., lab, imaging), whereas 31 (23%) include periodic laboratory, diagnostic imaging, or other testing, and 4 (3%) recommend no screening (agents with no known late effects). Interventions exceeding minimal screening are provided for consideration in individuals with positive screening tests. Medical citations supporting the association of each late effect with a specific therapeutic exposure are included. Patient education materials complementing the guidelines have been organized into Health Links that feature health protective counseling on 42 topics, enhancing patient follow-up visits and broadening application of the guidelines. Additional accompanying materials include detailed instructions, templates for cancer treatment summary forms, and a tool to assist in identifying guideline applicability for individual patients based on therapeutic exposures.

Goal:

Implementation of these guidelines is intended to increase quality of life and decrease complication-related healthcare costs for pediatric cancer survivors by providing standardized and enhanced follow-up care throughout the lifespan that (a) promotes healthy lifestyles, (b) provides for ongoing monitoring of health status, (c) facilitates early identification of late effects, and (d) provides timely intervention for late effects.

Introduction – Version 2.0 (cont)

Target Population:

The recommendations for periodic screening evaluations provided in the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* are appropriate for asymptomatic survivors of childhood, adolescent, or young adult cancers who present for routine exposure-related medical follow-up. More extensive evaluations are presumed, as clinically indicated, for survivors presenting with signs and symptoms suggesting illness or organ dysfunction.

Focus:

These guidelines are intended for use beginning two or more years following the completion of cancer therapy, and provide a framework for ongoing late effects monitoring in childhood cancer survivors; however, these guidelines are not intended to provide guidance for follow-up of the pediatric cancer survivor's primary disease.

Intended Users:

The COG-LTFU Guidelines were developed as a resource for clinicians who provide ongoing healthcare to survivors of pediatric malignancies. The information within these guidelines is important for clinicians (e.g., physicians, nurse practitioners, physician assistants, nurses) in the fields of pediatrics, oncology, internal medicine, family practice, and gynecology, as well as subspecialists in many fields (e.g., endocrinology, cardiology, pulmonology). A basic knowledge of ongoing issues related to the long-term follow-up needs of this patient population is assumed. Healthcare professionals who do not regularly care for survivors of pediatric malignancies are encouraged to consult with a pediatric oncology long-term follow-up center if any questions or concerns arise when reviewing or using these guidelines.

Although the information within the guidelines will certainly prove valuable to the survivors themselves, at this time the only version available is targeted to healthcare professionals. Therefore, survivors who choose to review these guidelines are strongly encouraged to do so with the assistance of a healthcare professional knowledgeable about long-term follow-up care for survivors of childhood, adolescent, and young adult cancers. This is important in order to put the recommendations in perspective, avoid over-testing, address potential anxieties, and provide a comprehensive evaluation of the survivor's health status. The Children's Oncology Group itself does not provide individualized treatment advice to patients or their families, and strongly recommends discussing this information with a qualified medical professional.

Introduction – Version 2.0 (cont)

Developer:

The COG-LTFU Guidelines were developed as a collaborative effort of the Children's Oncology Group Nursing Discipline and Late Effects Committee. All Children's Oncology Group members have complied with the COG conflict of interest policy, which requires disclosure of any potential financial or other conflicting interests.

Funding Source:

This work was supported by the Children's Oncology Group grant U10 CA098543 from the National Cancer Institute.

Evidence Collection:

Pertinent information from the published medical literature over the past 20 years (updated as of October 2005) was retrieved and reviewed during the development and updating of these guidelines. For each therapeutic exposure, a complete search was performed via MEDLINE (National Library of Medicine, Bethesda, MD). Keywords included "childhood cancer therapy," "complications," and "late effects," combined with keywords for each therapeutic exposure. References from the bibliographies of selected articles were used to broaden the search.

Methods:

In 2002, the leadership of the Children's Oncology Group Late Effects Committee and Nursing Discipline appointed a 7-member task force, with representation from the Late Effects Committee, Nursing Discipline, and Patient Advocacy Committee. The task force was convened to review and summarize the medical literature and develop a draft of clinical practice guidelines to direct long-term follow-up care for pediatric cancer survivors. The task force followed a modified version of the guideline development process established by the National Comprehensive Cancer Network (NCCN), integrating available literature with expert opinion using reiterative feedback loops.

The original draft went through several iterations within the task force prior to initial review. Multidisciplinary experts in the field, including nurses, physicians (pediatric oncologists and other subspecialists), patient advocates, behavioral specialists, and other healthcare professionals, were then recruited by the task force to provide an extensive, targeted review of the draft, including focused review of selected guideline sections. Revisions were made based on these recommendations. The revised draft was then sent out to additional multidisciplinary experts for further review. A total of 62 individuals participated in the review process. The guidelines subsequently underwent comprehensive review and scoring by a panel of experts in the late effects of pediatric malignancies, comprised of multidisciplinary representatives from the COG Late Effects Committee.

Introduction – Version 2.0 (cont)

Methods (cont):

In a parallel effort led by the Nursing Clinical Practice Subcommittee, complementary patient education materials (*Health Links*) were developed. Each *Health Link* underwent two levels of review; first by the Nursing Clinical Practice Subcommittee to verify accuracy of content and recommendations, and then by members of the Late Effects Committee (to provide expert medical review) and Patient Advocacy Committee (to provide feedback regarding presentation of content to the lay public).

Grading Criteria:

The guidelines were scored by the multidisciplinary panel of experts using a modified version of the National Comprehensive Cancer Network "Categories of Consensus" system. Each score reflects the expert panel's assessment of the strength of data from the literature linking a specific late effect with a therapeutic exposure, coupled with an assessment of the appropriateness of the screening recommendation based on the expert panel's collective clinical experience. "High-level evidence" (category 1) was defined as evidence derived from high quality case control or cohort studies. "Lower-level evidence" (category 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series and clinical experience. Rather than submitting recommendations representing major disagreements, items scored as "Category 3" were either deleted or revised by the panel of experts to provide at least a "Category 2B" score for all recommendations included in the guidelines.

Pre-Release Review:

The initial version of the guidelines (*Version 1.0 – Children's Oncology Group Late Effects Screening Guidelines*) was released to the Children's Oncology Group membership in March 2003 for a six-month trial period. This allowed for initial feedback from the COG membership, resulting in additional review and revision of the guidelines by the Late Effects Committee prior to public release.

Revisions:

The guidelines were initially released to the public (*Version 1.1 – Childhood Cancer Survivor Long-Term Follow-Up Guidelines*) on the Children's Oncology Group Website in September 2003. Following this release, clarification regarding the applicability of the guidelines to the adolescent and young adult populations of cancer survivors was requested. In response, additional minor modifications were made and the title of the guidelines was changed. A revised version (*Version 1.2 – Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*) was released to the public on the Children's Oncology Group Website in March 2004.

Introduction – Version 2.0 (cont)

Revisions: (cont)

In order to keep the guidelines current and clinically meaningful, the COG Late Effects Committee organized 18 multi disciplinary task forces in March 2004. These task forces were charged with the responsibility for monitoring the medical literature in regard to specific system-related clinical topics relevant to the guidelines (e.g., cardiovascular, neurocognitive, fertility/reproductive), providing periodic reports to the Late Effects Committee, and recommending revisions to the guidelines and their associated health education materials and references (including the addition of therapeutic exposures) as new information became available. Task force members were assigned according to their respective areas of expertise and clinical interest. A list of these task forces and their membership is included in the "Contributors" section of this document. The revisions incorporated into the current release of these guidelines (Version 2.0 – March 2006) reflect the contributions and recommendations of these task forces.

All revisions proposed by the task forces were evaluated by a panel of experts, and if accepted, assigned a score (see "Scoring Explanation" section of this document). Proposed revisions that were rejected by the expert panel were returned with explanation to the relevant task force chair. If desired, task force chairs were given an opportunity to respond by providing additional justification and resubmitting the rejected task force recommendation(s) for further consideration by the expert panel. A total of 34 sections and 9 Health Links were added to Version 2.0 of these guidelines.

Plan for Updates:

The 18 task forces described above will continue to monitor the literature and report to the Late Effects committee on a bi-annual basis. Periodic revisions to these guidelines are planned as new information becomes available. Clinicians are advised to check the Children's Oncology Group website periodically for the latest updates and revisions to the guidelines, which will be posted at www.survivorshipguidelines.org.

Definitions:

"Late effects" are defined as therapy-related complications or adverse effects that persist or arise after completion of treatment for a pediatric malignancy. "Pediatric malignancies" are defined as those malignancies commonly associated with the pediatric population that may arise during childhood, adolescence or young adulthood. "Consensus" is defined as general agreement among the panel of experts.

Introduction – Version 2.0 (cont)

Recommendations and Rationale:

Screening and follow-up recommendations are organized by therapeutic exposure and included throughout the guidelines. Pediatric cancer survivors represent a relatively small but growing population at high risk for various therapy-related complications. Although several well-conducted studies on large populations of childhood cancer survivors have demonstrated associations between specific exposures and late effects, the size of the survivor population and the rate of occurrence of late effects does not allow for clinical studies that would assess the impact of screening recommendations on the morbidity and mortality associated with the late effect. Therefore, scoring of each exposure reflects the expert panel's assessment of the level of literature support linking the therapeutic exposure with the late effect coupled with an assessment of the appropriateness of the recommended screening modality in identifying the potential late effect based on the panel's collective clinical experience.

Potential Benefits and Harms:

Potential benefits of implementing these guidelines into clinical practice include earlier identification of and intervention for late onset therapy-related complications in this at-risk population, potentially reducing or ameliorating the impact of late complications on the health status of survivors. In addition, ongoing healthcare that promotes healthy lifestyle choices and provides ongoing monitoring of health status is important for all cancer survivors.

Potential harms of guideline implementation include increased patient anxiety related to enhanced awareness of possible complications, as well as the potential for false-positive screening evaluations, leading to unnecessary further workup. In addition, costs of long-term follow-up care may be prohibitive for some patients, particularly those lacking health insurance, or those with insurance that does not cover the recommended screening evaluations.

Patient Preferences:

Ultimately, as with all clinical guidelines, decisions regarding screening and clinical management for any specific patient should be individually tailored, taking into consideration the patient's treatment history, risk factors, co-morbidities, and lifestyle. These guidelines are therefore not intended to replace clinical judgment or to exclude other reasonable alternative follow-up procedures. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

Introduction – Version 2.0 (cont)

Implementation Considerations:

Implementation of these guidelines is intended to standardize and enhance follow-up care provided to survivors of pediatric malignancies throughout the lifespan. Considerations in this regard include the practicality and efficiency of applying these broad guidelines in individual clinical situations. Studies to address guideline implementation and refinement are a top priority of the COG Late Effects Committee, and proposals to study feasibility of guideline use in limited institutions are currently underway. Issues to be addressed include description of anticipated barriers to application of the recommendations in the guidelines and development of review criteria for measuring changes in care when the guidelines are implemented. Additional concerns surround the lack of current evidence establishing the efficacy of screening for late complications in pediatric cancer survivors. While most clinicians believe that ongoing surveillance for these late complications is important in order to allow for early detection and intervention for complications that may arise, development of studies addressing the efficacy of this approach is imperative in order to determine which screening modalities are optimal for asymptomatic survivors.

In addition, the clinical utility of this lengthy document has also been a top concern of the COG Late Effects Committee. While recognizing that the length and depth of these guidelines is important in order to provide clinically-relevant, evidence-based recommendations and supporting health education materials, clinician time limitations and the effort required to identify the specific recommendations relevant to individual patients have been identified as barriers to their clinical application. Therefore, the COG Late Effects Committee is currently partnering with the Baylor School of Medicine in order to develop a web-based interface, known as "Passport for Care," that will generate individualized exposure-based recommendations from these guidelines in a clinician-focused format for ease of patient-specific application of the guidelines in the clinical setting. As additional information regarding implementation of the Passport for Care web-based interface becomes available, updates will be posted at www.survivorshipguidelines.org.

CureSearch
Children's Oncology Group

Explanation of Scoring for the Long-Term Follow-Up Guidelines

These guidelines represent a statement of consensus from a multidisciplinary panel of experts in the late effects of pediatric cancer treatment. The guidelines outline minimum recommendations for specific health screening evaluations in order to detect potential late effects arising as a result of therapeutic exposures received during treatment of childhood, adolescent, and young adult cancers.

Each score relates to the **strength of the association of the identified late effect with the specific therapeutic exposure based on current literature, and is coupled with a recommendation for periodic health screening based on the collective clinical experience of the panel of experts.** This is due to the fact that there are no randomized clinical trials (and none forthcoming in the foreseeable future) on which to base recommendations for periodic screening evaluations in this population; therefore, the guidelines should not be misconstrued as representing conventional "evidence-based clinical practice guidelines" or "standards of care".

Each item was scored based on the level of evidence currently available to support it. Scores were assigned according to a modified version of the National Comprehensive Cancer Network "Categories of Consensus," as follows:

Category	Statement of Consensus
1	There is uniform consensus of the panel that: (1) there is high-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.
2A	There is uniform consensus of the panel that: (1) there is lower-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.
2B	There is non-uniform consensus of the panel that: (1) there is lower-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members.
3	There is major disagreement that the recommendation is appropriate

CureSearch
Children's Oncology Group

Explanation of Scoring for the Long-Term Follow-Up Guidelines (cont)

Uniform consensus: Near-unanimous agreement of the panel with some possible neutral positions.
Non-uniform consensus: The majority of panel members agree with the recommendation; however, there is recognition among panel members that, given the quality of evidence, clinicians may choose to adopt different approaches.
High-level evidence: Evidence derived from high quality case control or cohort studies.
Lower-level evidence: Evidence derived from non-analytic studies, case reports, case series, and clinical experience.

All "Category 1" recommendations reflect uniform consensus among the reviewers. "Category 2" recommendations are designated as "2A" (there is uniformity of consensus among the reviewers regarding strength of evidence and appropriateness of the screening recommendation) or "2B" (there is non-uniform consensus among the reviewers regarding strength of evidence and appropriateness of the screening recommendation).

Rather than submitting recommendations representing major disagreements, items scored as "Category 3" were either deleted or revised by the panel of experts to provide at least a "Category 2B" score for all recommendations included in the guidelines.

CureSearch
Children's Oncology Group

Instructions for Use – Version 2.0
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

GUIDELINE ORGANIZATION:

The *Children's Oncology Group Long-Term Follow-Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* are organized according to therapeutic exposures, arranged by column as follows:

Section Number	Unique identifier for each guideline section corresponding with listing in Index.
Therapeutic Agent	Therapeutic intervention for malignancy, including chemotherapy, radiation, surgery, blood/serum products, hematopoietic cell transplant, and other therapeutic modalities.
Risk Factors	Host factors (e.g., age, sex, race, genetic predisposition), treatment factors (e.g., cumulative dose of therapeutic agent, mode of administration, combinations of agents), medical conditions (e.g., pre-morbid or co-morbid conditions), and health behaviors (e.g., diet, smoking, alcohol use) that may increase risk of developing the complication.
Highest Risk Factors	Conditions (host factors, treatment factors, medical conditions and/or health behaviors) associated with the highest risk for developing the complication.
Periodic Evaluations	Recommended screening evaluations, including health history, physical examination, laboratory evaluation, imaging, and psychosocial assessment. Recommendation for minimum frequency of periodic evaluations is based on risk factors and magnitude of risk, as supported by the medical literature and/or the combined clinical experience of the reviewers and panel of experts.

CureSearch
Children's Oncology Group

Instructions for Use – Version 2.0 (cont)

Health Counseling/ Further Considerations

Health Links: Health education materials developed specifically to accompany these guidelines. Title(s) of Health Link(s) relevant to each guideline section are referenced in this column. Health Link documents are included in Appendix II, and are also available on the COG website at www.survivorshipguidelines.org.
Counseling: Suggested patient counseling regarding measures to prevent/reduce risk or promote early detection of the potential treatment complication.
Resources: Books and websites that may provide the clinician with additional relevant information.
Considerations for Further Testing and Intervention: Recommendations for further diagnostic evaluations beyond minimum screening for individuals with positive screening tests, recommendations for consultation and/or referral, and recommendations for management of exacerbating or predisposing conditions.

System

Body system (e.g., auditory, musculoskeletal) most relevant to each guideline section.

Score

Score assigned by expert panel representing the strength of data from the literature linking a specific late effect with a therapeutic exposure coupled with an assessment of the appropriateness of the screening recommendation based on collective clinical experience.

Cancer Screening Recommendations

Sections 137 – 145 contain preventive screening recommendations for common adult-onset cancers, organized by column as follows:

Organ: The organ at risk for developing malignancy.

At Risk Population: Populations generally considered at increased risk for the specified malignancy based on risk factors such as age, gender, genetic susceptibility, personal or family history, health-related behaviors or co-morbidities.

Highest Risk: Populations considered by the panel of experts or other evaluating bodies (such as the American Cancer Society) as being at significantly increased risk for the specified malignancy. Risk factors may include therapeutic exposures resulting from cancer treatment, as well as other factors listed above (e.g., genetic susceptibility).

Instructions for Use – Version 2.0 (cont)

Cancer Screening Recommendations (cont)

Periodic Evaluations:
Standard Risk: Guidelines provided under the "Standard Risk" category are per the American Cancer Society recommendations for standard-risk populations and are included here for reference. In addition, clinicians are encouraged to consult recommendations from other organizations, such as the U. S. Preventive Services Task Force (http://www.ahrq.gov/clinic/serfiles.htm).
Highest Risk: Recommendations for high-risk populations, when applicable, are specified and may differ from recommendations for the standard risk groups due to the significantly increased risk of the specified malignancy within the high-risk group.

References

References are listed immediately following each guideline section. Included are medical citations that provide evidence for the association of the therapeutic intervention with the specific treatment complication and/or evaluation of predisposing risk factors. In addition, some general review articles have been included in the Reference section for clinician convenience.

The following documents are also included to further assist with application of these guidelines:

Explanation of Scoring

Elucidation of the process used by the panel of experts to assign scores to each guideline section.

Index

Due to significant overlap of toxicities between therapeutic agents, and in order to avoid an enormously lengthy document, duplicate entries have been avoided as much as possible. Therefore, ***use of the Index or Patient-Specific Guideline Identification Tool*** (see Appendix I) ***is imperative*** in order to determine each potential late effect associated with each therapeutic agent within this document.

USING THE COG LTFU GUIDELINES TO DEVELOP INDIVIDUALIZED SCREENING RECOMMENDATIONS:

In order to accurately derive individualized screening recommendations for a specific childhood cancer survivor using the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*, the following procedure should be followed. (Note: For ease of use, a Patient-Specific Guideline Identification Tool has been developed to streamline the following process and is included in Appendix I).

Instructions for Use – Version 2.0 (cont)

1. **Obtain the survivor's Summary of Cancer Treatment** (see templates and instructions for comprehensive and abbreviated treatment summaries in Appendix I). Note: In order to generate accurate exposure-based follow-up recommendations from these guidelines, the following information regarding the survivor's diagnosis and treatment is required, at minimum:
   - Date of diagnosis
   - Survivor's sex
   - Survivor's date of birth
   - Names of all chemotherapy agents received. For list of chemotherapeutic agents addressed by these guidelines, see "Chemotherapy" portion of Index - Sections 6-37. For list of generic and brand names of chemotherapy agents, see *Chemotherapy Agents* in Appendix I.
   - Cumulative dose of all anthracycline chemotherapy received (i.e., doxorubicin, daunorubicin, idarubicin, mitoxantrone and epirubicin), and age at first anthracycline dose (if unknown, age at first exposure is presumed to be age at diagnosis).
   - For carboplatin: Whether patient received myeloablative dose (i.e., for HCT conditioning).
   - For cytarabine and methotrexate:
     - Route of administration (i.e., IV, IM, SQ, PO, IT, IO)
     - If IV: Designation of "high dose" (any single dose ≥1000 mg/m^2) versus "standard dose" (all single doses <1000 mg/m^2)
   - All radiation field(s) and total radiation dose (in Gy) to each field (for chest, thoracic spine, and upper abdominal radiation, include age at first dose). For list of radiation fields addressed by these guidelines, see "Radiation" portion of Index - Sections 38-91. For clarification of anatomical areas included in common radiation fields, see *Radiation Fields Defined* in Appendix I.
   - Whether or not the survivor underwent a hematopoietic cell transplant (HCT), and if so, whether or not the survivor ever developed chronic graft-versus-host disease (cGVHD).
   - Names of all relevant surgical procedures. For list of surgical procedures addressed by these guidelines, see "Surgery" portion of Index - Sections 107-132.
   - Names of all other therapeutic modalities. For list of other therapeutic modalities addressed by these guidelines, see "Other Therapeutic Modalities" portion of Index - Sections 133-36.
2. **Develop a list of guideline sections relevant to the survivor:**
   - Sections 1 and 2 ("Any Cancer Experience") and 146 ("General Health Screening") are relevant to all survivors.
   - For survivors diagnosed prior to 1993, include relevant sections based on date of diagnosis:
     - If survivor was diagnosed prior to 1972, include Section 3
     - If survivor was diagnosed prior to 1993, include Section 4
     - If survivor was diagnosed between 1977 and 1985, include Section 5

Instructions for Use – Version 2.0 (cont)

- For survivors who received chemotherapy, include relevant sections:
  - If survivor received any chemotherapy, include Section 6.
  - Review "Chemotherapy" portion of the Index and include Sections 7-37 as applicable based on survivor's chemotherapy exposures (Note: Some alkylating agent sections are gender-specific)
- For survivors who received radiation therapy, include relevant sections:
  - If survivor received any radiation therapy, include Sections 38 – 39
  - Review "Radiation" portion of the Index and include Sections 40-91 as applicable based on survivor's radiation exposures (Note: Some sections are gender-specific and some are relevant only for patients who received the minimum specified dose of radiation to the indicated field).
  - Exception: If the survivor's only radiation exposure was TBI, do NOT include sections 40 or 41. For convenience, all sections applicable to TBI are located between pages 102 - 118 of the guidelines.
- For survivors who underwent hematopoietic cell transplant (HCT), include Sections 92-97. If the survivor developed chronic GVHD, also include sections 98-106
- For survivors who underwent surgery, review "Surgery" portion of Index and include Sections 107-132 as applicable based on survivor's surgical history. (Note: Some sections are gender-specific).
- For survivors who received other therapeutic modalities, review "Other Therapeutic Modalities" portion of Index and include Sections 133-136 as applicable.
- Include cancer screening guidelines (sections 137-145) as applicable based on survivor's sex and current age.

3. **Review all guideline sections generated in the list above, and develop a plan for screening the individual survivor**, taking into consideration the survivor's relevant risk factors, current health, co-morbidities, health-related behaviors and preferences.

Instructions for Use – Version 2.0 (cont)

Note: The above procedure is applicable to generation of follow-up guidelines from the current version of this document; however, the COG Late Effects Committee recognizes that as new evidence becomes available and these guidelines are updated, additional details regarding the childhood cancer survivor's therapeutic exposures may be required in order to generate comprehensive recommendations. Therefore, we strongly advise that a comprehensive treatment summary be prepared for each childhood cancer survivor, including a record of all therapeutic exposures with applicable dates, details of administration, and cumulative doses of all agents, including those not currently addressed by these guidelines.

The COG Late Effects Committee and Nursing Discipline recognize that the time required to identify patient-specific recommendations from these guidelines is significant, and has been identified as a barrier to clinical use. Therefore, the COG Late Effects Committee is currently partnering with the Baylor School of Medicine in order to develop a web-based interface, known as "Passport for Care," that will generate individualized exposure-based recommendations from these guidelines in a clinician-focused format for ease of patient-specific application in the clinical setting. As additional information regarding implementation of the "Passport for Care" web-based interface becomes available, updates will be posted at www.survivorshipguidelines.org. In the meantime, use of the Patient-Specific Guideline Identification Tool and Index to Health Links by Guideline Section Number (see Appendix I) should serve to reduce the time required for patient-specific application of these guidelines.

We are hopeful that this revised version of the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* will enhance the follow-up care provided to this unique group of cancer survivors. If you have questions, suggestions, or concerns regarding use of these guidelines, please contact:

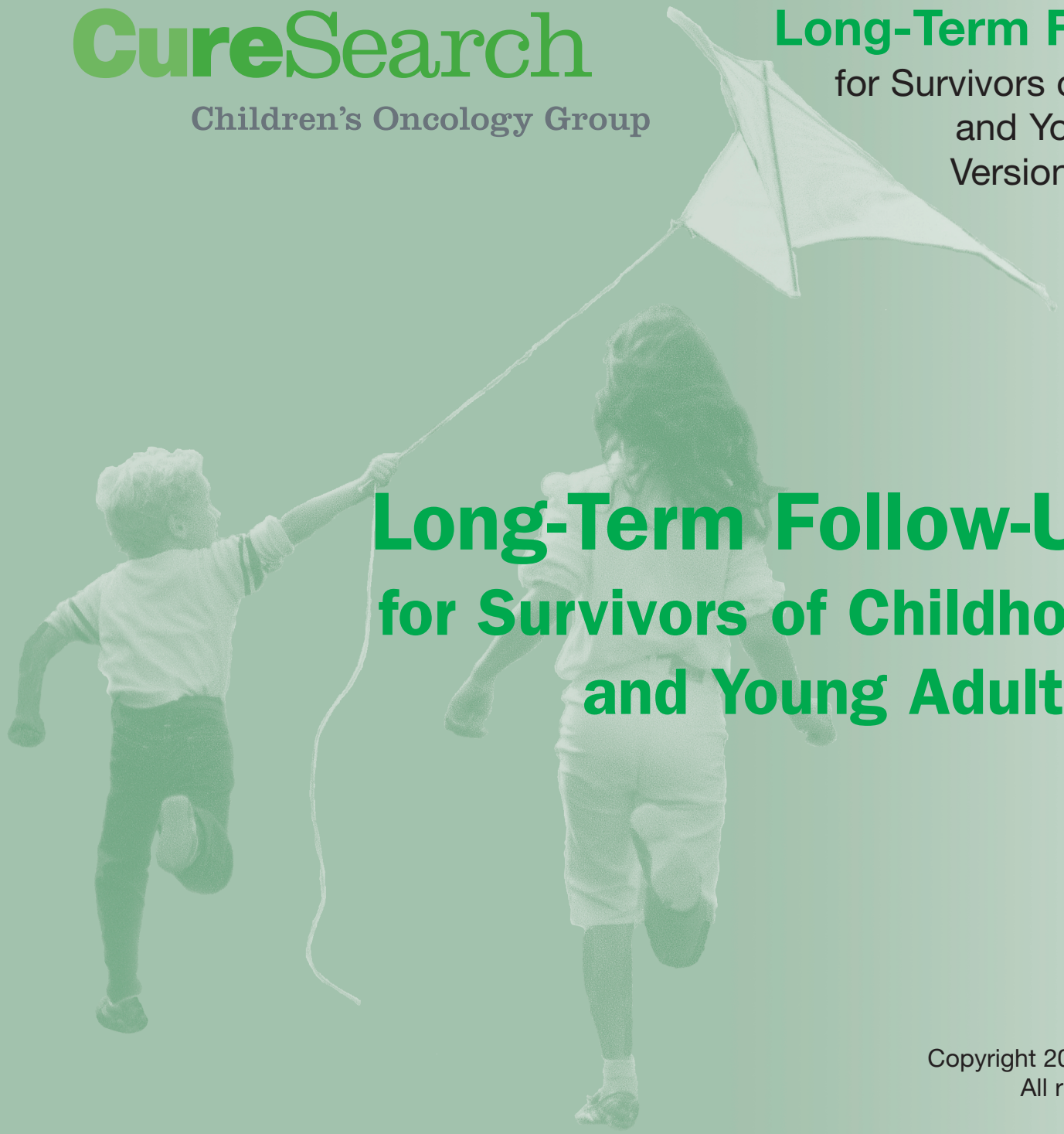
Melissa M. Hudson, MD
Vice-Chair – COG Late Effects Committee
St. Jude Children's Research Hospital
Memphis, Tennessee
(901) 495-4781
Melissa.Hudson@stjude.org

Wendy Landier, RN, MSN, CPNP
Chair – COG Nursing Clinical Practice/
Survivorship Subcommittee
City of Hope Comprehensive Cancer Center
Duarte, California
(626) 301-8426
wlandier@coh.org

Smita Bhatia, MD, MPH
Chair – COG Late Effects Committee
City of Hope Comprehensive Cancer Center
Duarte, California
(626) 301-8426
sbhatia@coh.org

CureSearch

Children's Oncology Group



Long-Term Follow-Up Guidelines
for Survivors of Childhood, Adolescent, and Young Adult Cancers

ANY CANCER EXPERIENCE

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
1	**Any Cancer Experience** **Info Link:** The Children's Oncology Group Long-Term Follow-Up Guidelines apply to patients who have been off therapy for a minimum of 2 years.	**Psychosocial Disorders** Social withdrawal Educational problems	**Host Factors** Female sex Family history of depression, anxiety, or mental illness **Social Factors** Lower household income Lower educational achievement **Treatment Factors** HCT	**Host Factors** CNS tumor CNS-directed therapy Premorbid learning or emotional difficulties **Social Factors** Failure to graduate from high school	**HISTORY** **Psychosocial assessment, with attention to:** - Educational and/or vocational progress - Depression - Anxiety - Post-traumatic stress - Social withdrawal (Yearly)	**Health Links** **Introduction to Long-Term Follow-Up** **Emotional Issues** **Educational Issues** **Chronic Pain after Childhood Cancer** **Resources** 'Childhood Cancer Survivors' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Sebastopol, CA: O'Reilly & Associates, 2000 'Educating the Child with Cancer' edited by Nancy Keene, Candlelighters Childhood Cancer Foundation, Bethesda, MD, 2003. See also: www.cancer.gov ('Facing Forward' series for survivors) www.cancer.org (smoking cessation) www.nccn.org (chronic pain) **Considerations for Further Testing and Intervention** Consider psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Consider appropriate psychotropic medications. Consider evaluation of parent for post-traumatic stress syndrome. Consider social work consultation. Refer as indicated to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. Screen for physical sources of fatigue, such as anemia, sleep disturbances, nutritional deficiencies, cardiomyopathy, pulmonary fibrosis, hypothyroidism, or other endocrinopathy. **SYSTEM = Psychosocial** **SCORE = 2A**
		Mental health disorders Depression Anxiety Post-traumatic stress	**Host Factors** Female sex Family history of depression, anxiety, or mental illness **Social Factors** Lower household income Lower educational achievement **Treatment Factors** HCT	**Host Factors** CNS tumor CNS-directed therapy Premorbid learning or emotional difficulties **Social Factors** Failure to graduate from high school		
		Risky behaviors Behaviors known to increase the likelihood of subsequent illness or injury	**Social Factors** Lower household income	**Host Factors** Older age at diagnosis **Social Factors** Lower educational achievement		
		Psychosocial disability due to pain	**Treatment Factors** Amputation Radiation to bone/joint Limb-sparing surgery Vincristine exposure **Medical Conditions** Osteonecrosis	**Host Factors** CNS tumor Hodgkin lymphoma		
		Fatigue	**Host Factors** Female sex Depression Obesity **Social Factors** Unemployment	**Treatment Factors** Pulmonary radiation		

SECTION 1 REFERENCES

Psychosocial - General

Arvidson J, Larsson B, Lonnerholm G. A long-term follow-up study of psychosocial functioning after autologous bone marrow transplantation in childhood. *Psychooncology*. Mar-Apr 1999;8(2):123-134.

Boman K, Bodegard G. Long-term coping in childhood cancer survivors: influence of illness, treatment and demographic background factors. *Acta Paediatr*. Jan 2000;89(1):105-111.

Felder-Puig R, Peters C, Matthes-Martin S, et al. Psychosocial adjustment of pediatric patients after allogeneic stem cell transplantation. *Bone Marrow Transplant*. Jul 1999;24(1):75-80.

Zebrack BJ, Zeltzer LK, Whitton J, et al. 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*. Jul 2002;110(1 Pt 1):42-52.

Zeltzer LK, Chen E, Weiss R, et al. Comparison of psychologic outcome in adult survivors of childhood acute lymphoblastic leukemia versus sibling controls: a cooperative Children's Cancer Group and National Institutes of Health study. *J Clin Oncol*. Feb 1997;15(2):547-556.

Social withdrawal/educational problems

Brown RT, Madan-Swain A. Cognitive, neuropsychological, and academic sequelae in children with leukemia. *J Learn Disabil*. Feb 1993;26(2):74-90.

Brown RT, Madan-Swain A, Walco GA, et al. Cognitive and academic late effects among children previously treated for acute lymphocytic leukemia receiving chemotherapy as CNS prophylaxis. *J Pediatr Psychol*. Oct 1998;23(5):333-340.

Deasy-Spinetta P. School issues and the child with cancer. *Cancer*. May 15 1993;71(10 Suppl):3261-3264.

Lim JW, Zebrack B. Social networks and quality of life for long-term survivors of leukemia and lymphoma. *Support Care Cancer*. Jul 9 2005.

Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. Feb 15 2003;97(4):1115-1126.

Mulhern RK, Wasserman AL, Friedman AG, Fairclough D. Social competence and behavioral adjustment of children who are long-term survivors of cancer. *Pediatrics*. Jan 1989;83(1):18-25.

Pastore G, Mosso ML, Magnani C, Luzzatto L, Bianchi M, Terracini B. Physical impairment and social life goals among adult long-term survivors of childhood cancer: a population-based study from the childhood cancer registry of Piedmont, Italy. *Tumori*. Nov-Dec 2001;87(6):372-378.

Rauck AM, Green DM, Yasui Y, Mertens A, Robison LL. Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study. *Med Pediatr Oncol*. Jul 1999;33(1):60-63.

Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer. *Support Care Cancer*. Oct 2001;9(7):489-513.

Mental health disorders

Hobbie WL, Stuber M, Meeske K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *J Clin Oncol*. Dec 15 2000;18(24):4060-4066.

Ross L, Johansen C, Dalton SO, et al. Psychiatric hospitalizations among survivors of cancer in childhood or adolescence. *N Engl J Med*. Aug 14 2003;349(7):650-657.

Rourke MT, Stuber ML, Hobbie WL, Kazak AE. Posttraumatic stress disorder: understanding the psychosocial impact of surviving childhood cancer into young adulthood. *J Pediatr Oncol Nurs*. Jul 1999;16(3):126-135.

Santacroce SJ. Parental uncertainty and posttraumatic stress in serious childhood illness. J Nurs Scholarsh. 2003;35(1):45-51.

Stuber ML, Christakis DA, Houskamp B, Kazak AE. Posttrauma symptoms in childhood leukemia survivors and their parents. *Psychosomatics*. May-Jun 1996;37(3):254-261.

Stuber ML, Kazak AE, Meeske K, Barakat L. Is posttraumatic stress a viable model for understanding responses to childhood cancer? *Child Adolesc Psychiatr Clin N Am*. Jan 1998;7(1):169-182.

Stuber ML, Kazak AE, Meeske K, et al. Predictors of posttraumatic stress symptoms in childhood cancer survivors. *Pediatrics*. Dec 1997;100(6):958-964.

von Essen L, Enskar K, Kreuger A, Larsson B, Sjoden PO. Self-esteem, depression and anxiety among Swedish children and adolescents on and off cancer treatment. *Acta Paediatr*. Feb 2000;89(2):229-236.

SECTION 1 REFERENCES - continued

Risky behaviors

Emmons K, Li FP, Whitton J, et al. Predictors of smoking initiation and cessation among childhood cancer survivors: a report from the childhood cancer survivor study. *J Clin Oncol*. Mar 15 2002;20(6):1608-1616.

Hollen PJ, Hobbie WL, Finley SM, Hiebert SM. The relationship of resiliency to decision making and risk behaviors of cancer-surviving adolescents. *J Pediatr Oncol Nurs*. Sep-Oct 2001;18(5):188-204.

Mulhern RK, Tyc VL, Phipps S, et al. Health-related behaviors of survivors of childhood cancer. Med Pediatr Oncol. Sep 1995;25(3):159-165.

Tyc VL, Hadley W, Allen D, et al. Predictors of smoking intentions and smoking status among nonsmoking and smoking adolescents. *Addict Behav*. Aug 2004;29(6):1143-1147.

Tyc VL, Hadley W, Crockett G. Prediction of health behaviors in pediatric cancer survivors. Med Pediatr Oncol. Jul 2001;37(1):42-46.

Tyc VL, Lensing S, Klosky J, Rai SN, Robinson L. A comparison of tobacco-related risk factors between adolescents with and without cancer. *J Pediatr Psychol*. Jun 2005;30(4):359-370.

Psychosocial disability due to pain

Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia. *JAMA*. Jul 24-31 1996;276(4):313-318.

Banks S, Kerns R. Explaining high rates of depression in chronic pain: a diathesis-stress framework. *Psychol Bull*. 1996;119:95-110.

Chapman CR, Gavrin J. Suffering: the contributions of persistent pain. *Lancet*. Jun 26 1999;353(9171):2233-2237.

Coghill RC, McHaffie JG, Yen YF. Neural correlates of interindividual differences in the subjective experience of pain. *Proc Natl Acad Sci U S A*. Jul 8 2003;100(14):8538-8542.

Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol*. Oct 1999;82(4):1934-1943.

Fernandez E, Turk DC. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. *Pain*. Aug 1989;38(2):123-135.

Holzberg AD, Robinson ME, Geisser ME, Gremillion HA. The effects of depression and chronic pain on psychosocial and physical functioning. *Clin J Pain*. Jun 1996;12(2):118-125.

Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. *J Pain*. May 2004;5(4):195-211.

Thomas EM, Weiss SM. Nonpharmacological interventions with chronic cancer pain in adults. *Cancer Control*. Mar-Apr 2000;7(2):157-164.

Zaza C, Reyno L, Moulin DE. The multidimensional pain inventory profiles in patients with chronic cancer-related pain: an examination of generalizability. *Pain*. Jul 2000;87(1):75-82.

Fatigue

Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol*. Jul 15 2001;19(14):3385-3391.

Hinds PS, Hockenberry-Eaton M, Gilger E, et al. Comparing patient, parent, and staff descriptions of fatigue in pediatric oncology patients. *Cancer Nurs*. Aug 1999;22(4):277-288; quiz 288-279.

Jacobsen PB. Assessment of fatigue in cancer patients. *J Natl Cancer Inst Monogr*. 2004(32):93-97.

Knobel H, Havard Loge J, Brit Lund M, Forfang K, Nome O, Kaasa S. Late medical complications and fatigue in Hodgkin's disease survivors. *J Clin Oncol*. Jul 1 2001;19(13):3226-3233.

Langeveld N, Ubbink M, Smets E. 'I don't have any energy': The experience of fatigue in young adult survivors of childhood cancer. *Eur J Oncol Nurs*. Mar 2000;4(1):20-28.

Langeveld NE, Grootenhuis MA, Voute PA, de Haan RJ, van den Bos C. No excess fatigue in young adult survivors of childhood cancer. *Eur J Cancer*. Jan 2003;39(2):204-214.

Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr*. 2004(32):40-50.

ANY CANCER EXPERIENCE (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
2	**Any Cancer Experience**	**Limitations in healthcare and insurance access**	**Social Factors** Lower household income Lower educational achievement		**HISTORY** **Psychosocial assessment, with attention to healthcare insurance and access** (Yearly)	**Health Links** **Finding Healthcare** **Considerations for Further Testing and Intervention** Social work consultation **SYSTEM = Psychosocial** **SCORE = 2A**

SECTION 2 REFERENCES

Dolgin MJ, Somer E, Buchvald E, Zaizov R. Quality of life in adult survivors of childhood cancer. *Soc Work Health Care*. 1999;28(4):31-43.

Hays DM. Adult survivors of childhood cancer. Employment and insurance issues in different age groups. *Cancer*. May 15 1993;71(10 Suppl):3306-3309.

Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer. *Support Care Cancer*. Nov 2002;10(8):579-600.

Monaco GP, Fiduccia D, Smith G. Legal and societal issues facing survivors of childhood cancer. *Pediatr Clin North Am*. Aug 1997;44(4):1043-1058.

Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Fam Med*. Jan-Feb 2004;2(1):61-70.

BLOOD/SERUM PRODUCTS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
3	**Diagnosed prior to 1972**: Potential exposure to blood/serum products prior to initiation of Hepatitis B screening of blood supply (1972 in the United States – dates may differ in other countries) **Info Link:** Since the vast majority of patients received some type of blood product during childhood cancer treatment, screening based on date of diagnosis/treatment is recommended unless there is absolute certainty that the patient did not receive any blood or blood products. Relevant exposures include packed red cells, whole blood, granulocytes, platelets, fresh frozen plasma, cryoprecipitate, IVIG, VZIG, factor concentrates, and allogeneic marrow, cord blood, or stem cells.	**Chronic Hepatitis B**	**Host Factors** Living in hyperendemic area **Treatment Factors** Blood products before 1972 **Health Behaviors** IV drug use Unprotected sex Multiple partners High-risk sexual behavior Sexually transmitted diseases Tattoos Body piercing	**Host Factors** Chronic immunosuppression	**SCREENING** **Hepatitis B surface antigen (HBsAg)** **Hepatitis B core antibody (anti HBc or HBcAb)** (Once in patients who received treatment for cancer prior to 1972. *Note: Date may vary for international patients.*)	**Health Links** **Hepatitis** **Considerations for Further Testing and Intervention** Gastroenterology or hepatology consultation for patients with chronic hepatitis. Hepatitis A immunization in patients lacking immunity. **SYSTEM = Immune** **SCORE = 1**

SECTION 3 REFERENCES

Cheah PL, Looi LM, Lin HP, Yap SF. A case of childhood hepatitis B virus infection related primary hepatocellular carcinoma with short malignant transformation time. *Pathology*. Jan 1991;23(1):66-68.

Dodd RY. The risk of transfusion-transmitted infection. *N Engl J Med*. Aug 6 1992;327(6):419-421.

Locasciulli A, Alberti A, Rossetti F, et al. Acute and chronic hepatitis in childhood leukemia: a multicentric study from the Italian Pediatric Cooperative Group for Therapy of Acute Leukemia (AIL-AIEOP). *Med Pediatr Oncol*. 1985;13(4):203-206.

Willers E, Webber L, Delport R, Kruger M. Hepatitis B--a major threat to childhood survivors of leukaemia/lymphoma. *J Trop Pediatr*. Aug 2001;47(4):220-225.

BLOOD/SERUM PRODUCTS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
4	**Diagnosed prior to 1993:** Potential exposure to blood/serum products prior to initiation of Hepatitis C screening of blood supply (1993 in the United States – dates may differ in other countries) **Info Link:** Since the vast majority of patients received some type of blood product during childhood cancer treatment, screening based on date of diagnosis/treatment is recommended unless there is absolute certainty that the patient did not receive any blood or blood products. Relevant exposures include packed red cells, whole blood, granulocytes, platelets, fresh frozen plasma, cryoprecipitate, IVIG, VZIG, factor concentrates, and allogeneic marrow, cord blood, or stem cells.	**Chronic Hepatitis C**	**Host Factors** Living in hyperendemic area **Treatment Factors** Blood products before 1993 **Health Behaviors** IV drug use Unprotected sex Multiple partners High-risk sexual behavior Sexually transmitted diseases Tattoos Body piercing	**Host Factors** Chronic immunosuppression **Treatment Factors** Blood products prior to 1986 (when surrogate screening of blood donors with ALT was initiated and donors with self-reported high-risk behaviors were deferred)	**SCREENING** **Hepatitis C antibody** (Once in patients who received treatment for cancer prior to 1993. Note: Date may vary for international patients.) **Hepatitis C PCR (to establish chronic infection)** (Once in patients with positive Hepatitis C antibody)	**Health Links** **Hepatitis** **Considerations for Further Testing and Intervention** Screen for viral hepatitis in patients with persistently abnormal liver function regardless of transfusion history. Consider HCV PCR screening in transfused at-risk HCV-antibody negative patients with abnormal liver function and/ or persistent immunosuppression (e.g., HCT recipients with chronic GVHD). Gastroenterology or hepatology consultation for management of patients with chronic hepatitis. Hepatitis A and B immunization in patients lacking immunity. **SYSTEM = Immune** **SCORE = 1**

SECTION 4 REFERENCES

Arico M, Maggiore G, Silini E, et al. Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. *Blood*. Nov 1 1994;84(9):2919-2922.

Castellino S, Lensing S, Riely C, et al. 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*. Apr 1 2004;103(7):2460-2466.

Recommendations for prevention and control of hepatitis C virus (HCV) and HCV-related disease. Atlanta, GA: Centers for Disease Control and Prevention; October 16, 1998 1998. 47 (RR-19).

Cesaro S, Petris MG, Rossetti F, et al. Chronic hepatitis C virus infection after treatment for pediatric malignancy. *Blood*. Aug 1 1997;90(3):1315-1320.

Fink FM, Hocker-Schulz S, Mor W, et al. Association of hepatitis C virus infection with chronic liver disease in paediatric cancer patients. *Eur J Pediatr*. Jun 1993;152(6):490-492.

Locasciulli A, Testa M, Pontisso P, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. *Blood*. Dec 1 1997;90(11):4628-4633.

Ohata K, Hamasaki K, Toriyama K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer*. Jun 15 2003;97(12):3036-3043.

Paul IM, Sanders J, Ruggiero F, Andrews T, Ungar D, Eyster ME. Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. *Blood*. Jun 1 1999;93(11):3672-3677.

Peffault de Latour R, Levy V, Asselah T, et al. Long-term outcome of hepatitis C infection after bone marrow transplantation. *Blood*. Mar 1 2004;103(5):1618-1624.

Strasser SI, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood*. May 15 1999;93(10):3259-3266.

BLOOD/SERUM PRODUCTS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
5	**Diagnosed between 1977 and 1985:** Potential exposure to blood/serum products prior to initiation of HIV screening of blood supply (between 1977 and 1985 in the United States – dates may differ in other countries) **Info Link:** Since the vast majority of patients received some type of blood product during childhood cancer treatment, screening based on date of diagnosis/treatment is recommended unless there is absolute certainty that the patient did not receive any blood or blood products. Relevant exposures include packed red cells, whole blood, granulocytes, platelets, fresh frozen plasma, cryoprecipitate, IVIG, VZIG, factor concentrates, and allogeneic marrow, cord blood, or stem cells.	**HIV infection**	**Treatment Factors** Blood products between 1977 and 1985 **Medical Conditions** HPV infection **Health Behaviors** IV drug use Unprotected sex Multiple partners High-risk sexual behavior Sexually transmitted diseases Tattoos Body piercing		**SCREENING** **HIV 1 & 2 antibodies** (Once in patients who received treatment for cancer between 1977 and 1985. Note: Dates may vary for international patients.)	**Counseling** Standard counseling regarding safe sex, universal precautions, and high-risk behaviors that exacerbate risk **Considerations for Further Testing and Intervention** Infectious disease consultation for patients with chronic infection. **SYSTEM = Immune** **SCORE = 1**

SECTION 5 REFERENCES

Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA*. Feb 26 2003;289(8):959-962.

Lackritz EM, Satten GA, Aberle-Grasse J, et al. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. *N Engl J Med*. Dec 28 1995;333(26):1721-1725.

Samson S, Busch M, Ward J, et al. Identification of HIV-infected transfusion recipients: the utility of crossreferencing previous donor records with AIDS case reports. *Transfusion*. Mar-Apr 1990;30(3):214-218.

CHEMOTHERAPY

ANY CHEMOTHERAPY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
6	**Any Chemotherapy**	**Dental abnormalities** Tooth/root agenesis Root thinning/shortening Enamel dysplasia	**Host Factors** Any patient who had not developed permanent dentition at time of cancer therapy **Treatment Factors** Any radiation treatment involving the oral cavity or salivary glands	**Host Factors** Younger age at treatment, especially < 5 years old	**PHYSICAL** **Oral exam** (Yearly) **SCREENING** **Dental exam and cleaning** (Every six months)	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Regular dental care including fluoride applications. Baseline panorex prior to dental procedures to evaluate root development. **SYSTEM = Dental** **SCORE = 1**

SECTION 6 REFERENCES

Duggal MS, Curzon ME, Bailey CC, Lewis IJ, Prendergast M. Dental parameters in the long-term survivors of childhood cancer compared with siblings. *Oral Oncol*. Sep 1997;33(5):348-353.

Goho C. Chemoradiation therapy: effect on dental development. *Pediatr Dent*. Jan-Feb 1993;15(1):6-12.

Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. *Med Pediatr Oncol*. Aug 1995;25(2):96-101.

Kaste SC, Hopkins KP, Bowman LC, Santana VM. Dental abnormalities in children treated for neuroblastoma. *Med Pediatr Oncol*. Jan 1998;30(1):22-27.

Kaste SC, Hopkins KP, Jones D, Crom D, Greenwald CA, Santana VM. Dental abnormalities in children treated for acute lymphoblastic leukemia. *Leukemia*. Jun 1997;11(6):792-796.

Maguire A, Welbury RR. Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development. *Dent Update*. Jun 1996;23(5):188-194.

Nasman M, Forsberg CM, Dahllof G. Long-term dental development in children after treatment for malignant disease. *Eur J Orthod*. Apr 1997;19(2):151-159.

Raney RB, Asmar L, Vassilopoulou-Sellin R, et al. 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. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. Med *Pediatr Oncol*. Oct 1999;33(4):362-371.

Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. *Cancer*. Dec 15 1990;66(12):2645-2652.

CHEMOTHERAPY

ALKYLATING AGENTS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
7 (Male)	**ALKYLATING AGENTS** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **HEAVY METALS** Carboplatin Cisplatin **NON-CLASSICAL ALKYLATORS** Dacarbazine (DTIC) Temozolomide	**Gonadal dysfunction (testicular)** Delayed/arrested puberty Hypogonadism Oligospermia Azoospermia Infertility	**Treatment Factors** Higher cumulative doses of alkylators or combinations of alkylators Combined with radiation to: - Abdomen/pelvis - Testes - Brain, cranium (neuroendocrine axis) **Health Behaviors** Smoking **Info Link** Doses that cause gonadal dysfunction show individual variation. Germ cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function. Prepubertal status does not protect from gonadal injury in males.	**Host Factors** Male gender **Treatment Factors** MOPP ≥ 3 cycles Busulfan ≥ 600 mg/m^2 Cyclophosphamide cumulative dose ≥ 7.5 gm/m^2 or as conditioning for HCT Any alkylators combined with: - Testicular radiation - Pelvic radiation - TBI	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** **Testicular volume by Prader orchidometry** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Testosterone** (Baseline at age 14 **and** as clinically indicated in patients with delayed puberty and/or clinical signs and symptoms of testosterone deficiency) **Semen analysis** (As requested by patient and for evaluation of infertility. Periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years post therapy)	**Health Links** **Male Health Issues** **Resources** Extensive information regarding infertility for patients and healthcare professionals is available on the following websites: American Society for Reproductive Medicine (www.asrm.org) Fertile Hope (www.fertilehope.org) **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to alkylating agents. Recovery of fertility may occur years after therapy. **Considerations for Further Testing and Intervention** Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology/urology referral for infertility evaluation and consultation regarding assisted reproductive technologies. **SYSTEM = Male reproductive** **SCORE =** **Alkylating Agents: 1** **Heavy Metals: 2A** **Non-Classical Alkylators: 2A**

SECTION 7 REFERENCES

da Cunha MF, Meistrich ML, Fuller LM, et al. Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. *J Clin Oncol*. Jun 1984;2(6):571-577.

Gerl A, Muhlbayer D, Hansmann G, Mraz W, Hiddemann W. The impact of chemotherapy on Leydig cell function in long term survivors of germ cell tumors. *Cancer*. Apr 1 2001;91(7):1297-1303.

Kenney LB, Laufer MR, Grant FD, Grier H, Diller L. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. *Cancer*. Feb 1 2001;91(3):613-621.

Muller J. Disturbance of pubertal development after cancer treatment. *Best Pract Res Clin Endocrinol Metab*. Mar 2002;16(1):91-103.

Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol*. Jul 1999;33(1):2-8.

Somali M, Mpatakoias V, Avramides A, et al. Function of the hypothalamic-pituitary-gonadal axis in long-term survivors of hematopoietic stem cell transplantation for hematological diseases. *Gynecol Endocrinol*. Jul 2005;21(1):18-26.

CHEMOTHERAPY

ALKYLATING AGENTS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
7 (Female)	**ALKYLATING AGENTS** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **HEAVY METALS** Carboplatin Cisplatin **NON-CLASSICAL ALKYLATORS** Dacarbazine (DTIC) Temozolomide	**Gonadal dysfunction (ovarian)** Delayed/arrested puberty Premature menopause Infertility	**Treatment Factors** Higher cumulative doses of alkylators or combinations of alkylators Combined with radiation to: - Abdomen/pelvis - Lumbar or sacral spine (from ovarian scatter) - Brain, cranium (neuroendocrine axis) **Health Behaviors** Smoking **Info Link** Doses that cause gonadal dysfunction show individual variation. Females can typically maintain gonadal function at higher cumulative doses than males.	**Treatment Factors** MOPP > 3 cycles Busulfan > 600 mg/m^2 Cyclophosphamide cumulative dose > 7.5 gm/m^2 or as conditioning for HCT Any alkylators combined with: - Pelvic radiation - TBI	**HISTORY** **Pubertal (onset, tempo)** **Menstrual/pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Estradiol** (Baseline at age 13 **and** as clinically indicated in patients with delayed puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency)	**Health Links** **Female Health Issues** **Resources** Extensive information regarding infertility for patients and healthcare professionals is available on the following websites: American Society for Reproductive Medicine (www.asrm.org) Fertile Hope (www.fertilehope.org) **Counseling** Counsel currently menstruating women at increased risk of early menopause to be cautious about delaying childbearing. Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to alkylating agents. Recovery of fertility may occur years after therapy. **Considerations for Further Testing and Intervention** Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Consider 2 months off hormonal replacement in women with ovarian failure to assess ovarian recovery. **SYSTEM = Female reproductive** **SCORE =** **Alkylating Agents: 1** **Heavy Metals: 2A** **Non-Classical Alkylators: 2A**

SECTION 7 REFERENCES

Afify Z, Shaw PJ, Clavano-Harding A, Cowell CT. Growth and endocrine function in children with acute myeloid leukaemia after bone marrow transplantation using busulfan/cyclophosphamide. *Bone Marrow Transplant.* May 2000;25(10):1087-1092.

Bath LE, Wallace WH, Critchley HO. Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. *BJOG.* Feb 2002;109(2):107-114.

Byrne J, Fears TR, Gail MH, et al. Early menopause in long-term survivors of cancer during adolescence. *Am J Obstet Gynecol.* Mar 1992;166(3):788-793.

KMuller J. Disturbance of pubertal development after cancer treatment. *Best Pract Res Clin Endocrinol Metab.* Mar 2002;16(1):91-103.

Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol.* Jul 1999;33(1):2-8.

Teinturier C, Hartmann O, Valteau-Couanet D, Benhamou E, Bougneres PF. Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. *Bone Marrow Transplant.* Nov 1998;22(10):989-994.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
8	**ALKYLATING AGENTS** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **HEAVY METALS** Carboplatin Cisplatin **NON-CLASSICAL ALKYLATORS** Dacarbazine (DTIC) Temozolomide	**Acute myeloid leukemia** **Myelodysplasia**	**Treatment Factors** Less than 10 years since exposure to agent Higher cumulative alkylator dose or combination of alkylators *Note*: Melphalan and mechlorethamine are more potent leukemogens than cyclophosphamide **Medical Conditions** Splenectomy (conflicting evidence)		**HISTORY** **Fatigue** **Bleeding** **Easy bruising** (Yearly, up to 10 years after exposure to agent) **PHYSICAL** **Dermatologic exam (pallor, petechiae, purpura)** (Yearly, up to 10 years after exposure to agent) **SCREENING** **CBC/differential** (Yearly, up to 10 years after exposure to agent)	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Counsel to promptly report fatigue, pallor, petechiae, or bone pain. **Considerations for Further Testing and Intervention** Bone marrow exam as clinically indicated **SYSTEM = SMN** **SCORE =** **Alkylating Agents: 1** **Heavy Metals: 2A** **Non-Classical Alkylators: 2A**

SECTION 8 REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med*. Mar 21 1996;334(12):745-751.

Cheruku R, Hussain M, Tyrkus M, Edelstein M. Myelodysplastic syndrome after cisplatin therapy. *Cancer*. Jul 1 1993;72(1):213-218.

Forrest DL, Nevill TJ, Naiman SC, et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. *Bone Marrow Transplant*. Nov 2003;32(9):915-923.

Greene MH, Harris EL, Gershenson DM, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann Intern Med*. Sep 1986;105(3):360-367.

Hosing C, Munsell M, Yazji S, et al. Risk of therapy-related myelodysplastic syndrome/acute leukemia following high-dose therapy and autologous bone marrow transplantation for non-Hodgkin's lymphoma. *Ann Oncol*. Mar 2002;13(3):450-459.

Howe R, Micallef IN, Inwards DJ, et al. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. *Bone Marrow Transplant*. Aug 2003;32(3):317-324.

Meadows AT, Obringer AC, Marrero O, et al. Second malignant neoplasms following childhood Hodgkin's disease: treatment and splenectomy as risk factors. *Med Pediatr Oncol*. 1989;17(6):477-484.

Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. *Blood*. Jun 15 1994;83(12):3780-3786.

Schellong G, Riepenhausen M, Creutzig U, et al. Low risk of secondary leukemias after chemotherapy without mechlorethamine in childhood Hodgkin's disease. German-Austrian Pediatric Hodgkin's Disease Group. *J Clin Oncol*. Jun 1997;15(6):2247-2253.

Schneider DT, Hilgenfeld E, Schwabe D, et al. Acute myelogenous leukemia after treatment for malignant germ cell tumors in children. *J Clin Oncol*. Oct 1999;17(10):3226-3233.

CHEMOTHERAPY

ALKYLATING AGENTS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
9	**ALKYLATING AGENTS** Busulfan Carmustine (BCNU) Lomustine (CCNU)	**Pulmonary fibrosis**	**Treatment Factors** Higher cumulative doses Combined with bleomycin **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** BCNU ≥ 600 mg/m^2 Busulfan ≥ 500 mg (transplant doses) Combined with: - Chest radiation - TBI	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **PHYSICAL** **Pulmonary exam** (Yearly) **SCREENING** **Chest x-ray** **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: www.smokefree.gov **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Due to the potential pulmonary toxicity of this therapy, patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for symptomatic pulmonary dysfunction. Influenza and pneumococcal vaccines. **SYSTEM = Pulmonary** **SCORE = 1**

SECTION 9 REFERENCES

Ginsberg SJ, Comis RL. The pulmonary toxicity of antineoplastic agents. *Semin Oncol*. Mar 1982;9(1):34-51.

Kreisman H, Wolkove N. Pulmonary toxicity of antineoplastic therapy. *Semin Oncol*. Oct 1992;19(5):508-520.

O'Driscoll BR, Hasleton PS, Taylor PM, Poulter LW, Gattameneni HR, Woodcock AA. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med*. Aug 9 1990;323(6):378-382.

Stolp B, Assistant Medical Director Divers Alert Network, Director Anesthesiology Emergency Airway Services, Durham, N.C. Risks associated with SCUBA diving in childhood cancer survivors. Personal communication to Landier W, Bhatia S Aug 23, 2002.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
10	**ALKYLATING AGENTS** Busulfan	**Cataracts**	**Treatment Factors** Combined with corticosteroids	**Treatment Factors** Combined with cranial, orbital, or eye radiation TBI Longer interval since treatment	**HISTORY** **Visual difficulties** (Yearly) **PHYSICAL** **Eye exam (visual acuity, funduscopic exam for lens opacity)** (Yearly)	**Health Links** **Cataracts** **Considerations for Further Testing and Intervention** Ophthalmology consultation if problem identified. Refer patients with visual deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Ocular** **SCORE = 2B**

SECTION 10 REFERENCES

Dahlgren S, Holm G, Svanborg N, Watz R. Clinical and morphological side-effects of busulfan (Myleran) treatment. *Acta Med Scand*. Jul-Aug 1972;192(1-2):129-135.

Holmstrom G, Borgstrom B, Calissendorff B. Cataract in children after bone marrow transplantation: relation to conditioning regimen. *Acta Ophthalmol Scand*. Apr 2002;80(2):211-215.

Socie G, Clift RA, Blaise D, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood*. Dec 15 2001;98(13):3569-3574.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
11	**ALKYLATING AGENTS** Cyclophosphamide Ifosfamide	**Urinary tract toxicity** Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis	**Treatment Factors** Higher cumulative doses (decreased incidence with Mesna) Combined with pelvic radiation **Health Behaviors** Alcohol use Smoking	**Treatment Factors** Cyclophosphamide dose ≥ 3 gm/m^2 Pelvic radiation dose ≥ 30 Gy	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly) **SCREENING** **Urinalysis** (Yearly)	**Health Links** **Bladder Health** **Counseling** Counsel to promptly report dysuria or gross hematuria **Considerations for Further Testing and Intervention** Urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as ≥ 5 RBC/HFP on at least 2 occasions). Nephrology or urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/creatinine ratio. Urology referral for patients with culture negative macroscopic hematuria. **SYSTEM = Urinary** **SCORE = 1**

SECTION 11 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.
Heyn R, Raney RB, Jr., Hays DM, et al. Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. *J Clin Oncol*. Apr 1992;10(4):614-623.
Jerkins GR, Noe HN, Hill D. Treatment of complications of cyclophosphamide cystitis. *J Urol*. May 1988;139(5):923-925.
Stillwell TJ, Benson RC, Jr. Cyclophosphamide-induced hemorrhagic cystitis. A review of 100 patients. *Cancer*. Feb 1 1988;61(3):451-457.
Stillwell TJ, Benson RC, Jr., Burgert EO, Jr. Cyclophosphamide-induced hemorrhagic cystitis in Ewing's sarcoma. *J Clin Oncol*. Jan 1988;6(1):76-82.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
12	**ALKYLATING AGENTS** Cyclophosphamide	**Bladder malignancy**	**Treatment Factors** Combined with pelvic radiation **Health Behaviors** Alcohol use Smoking		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly) **SCREENING** **Urinalysis** (Yearly)	**Health Links** **Bladder Health** **Counseling** Counsel to promptly report dysuria or gross hematuria. **Considerations for Further Testing and Intervention** Urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as > 5 RBC/HFP on at least 2 occasions). Nephrology or urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/creatinine ratio. Urology referral for patients with culture negative macroscopic hematuria. **SYSTEM = SMN** **SCORE = 2A**

SECTION 12 REFERENCES

Kersun LS, Wimmer RS, Hoot AC, Meadows AT. Secondary malignant neoplasms of the bladder after cyclophosphamide treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer.* Mar 2004;42(3):289-291.

Pedersen-Bjergaard J, Ersboll J, Hansen VL, et al. Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med.* Apr 21 1988;318(16):1028-1032.

Travis LB, Curtis RE, Glimelius B, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst.* Apr 5 1995;87(7):524-530.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
13	**ALKYLATING AGENTS** Ifosfamide	**Renal toxicity** Glomerular toxicity Tubular toxicity (renal tubular acidosis, Fanconi's syndrome, hypophosphatemic rickets)	**Host Factors** Younger age at treatment Mononephric **Treatment Factors** Higher cumulative dose Combined with other nephrotoxic agents, such as: - Cisplatin - Carboplatin - Aminoglycosides - Amphotericin - Immunosuppressants - Methotrexate - Radiation impacting the kidney **Medical Conditions** Tumor infiltration of kidney(s) Pre-existing renal impairment Nephrectomy	**Host Factors** Age < 5 years at time of treatment **Treatment Factors** Ifosfamide dose ≥60 grams/m^2 Renal radiation dose ≥ 15 Gy	**PHYSICAL** **Blood pressure** (Yearly) **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** (Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated.) **Urinalysis** (Yearly)	**Health Links** **Kidney Health** See also: **Single Kidney Health** **Considerations for Further Testing and Intervention** Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 1**

SECTION 13 REFERENCES

Arndt C, Morgenstern B, Hawkins D, Wilson D, Liedtke R, Miser J. Renal function following combination chemotherapy with ifosfamide and cisplatin in patients with osteogenic sarcoma. *Med Pediatr Oncol*. Feb 1999;32(2):93-96.

Burk CD, Restaino I, Kaplan BS, Meadows AT. Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. *J Pediatr*. Aug 1990;117(2 Pt 1):331-335.

Fels LM, Bokemeyer C, van Rhee J, Schmoll HJ, Stolte H. Evaluation of late nephrotoxicity in long-term survivors of Hodgkin's disease. *Oncology*. Jan-Feb 1996;53(1):73-78.

Ho PT, Zimmerman K, Wexler LH, et al. A prospective evaluation of ifosfamide-related nephrotoxicity in children and young adults. *Cancer*. Dec 15 1995;76(12):2557-2564.

Langer T, Stohr W, Bielack S, Paulussen M, Treuner J, Beck JD. Late effects surveillance system for sarcoma patients. Pediatr Blood *Cancer*. Apr 2004;42(4):373-379.

Loebstein R, Atanackovic G, Bishai R, et al. Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. *J Clin Pharmacol*. May 1999;39(5):454-461.

Raney B, Ensign LG, Foreman J, et al. Renal toxicity of ifosfamide in pilot regimens of the intergroup rhabdomyosarcoma study for patients with gross residual tumor. *Am J Pediatr Hematol Oncol*. Nov 1994;16(4):286-295.

Skinner R, Sharkey IM, Pearson AD, Craft AW. Ifosfamide, mesna, and nephrotoxicity in children. *J Clin Oncol*. Jan 1993;11(1):173-190.

Skinner R, Cotterill SJ, Stevens MC. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. *Br J Cancer*. May 2000;82(10):1636-1645.

Skinner R. Chronic ifosfamide nephrotoxicity in children. *Med Pediatr Oncol*. Sep 2003;41(3):190-197.

CHEMOTHERAPY

HEAVY METALS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
14	**HEAVY METALS** Carboplatin (in myeloablative doses only) Cisplatin **Info Link:** Patients who received carboplatin in non-myeloablative doses do not appear to be at risk for clinically significant ototoxicity based on results of currently available studies.	**Ototoxicity** Sensorineural hearing loss Tinnitus Vertigo	**Host Factors** Age < 4 years at treatment **Treatment Factors** Combined with: - Cranial/ear radiation - Ototoxic drugs (e.g., aminoglycosides, loop diuretics) **Medical Conditions** Chronic otitis Cerumen impaction Renal dysfunction	**Host Factors** CNS neoplasm **Treatment Factors** Cumulative cisplatin dose ≥ 360 mg/m^2 High dose cisplatin (i.e., 40 mg/m^2 per day x 5 days per course) Cisplatin administered after cranial/ear radiation Carboplatin conditioning for HCT Radiation involving ear ≥ 30 Gy	**HISTORY** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** (Yearly) **PHYSICAL** **Otoscopic exam** (Yearly) **SCREENING** **Complete pure tone audiogram or brainstem auditory evoked response [BAER, ABR]** (Baseline at entry into long-term follow-up. If hearing loss is detected, test at least yearly, or as recommended by audiologist. For patients who also received cranial/ear radiation, test yearly after completion of therapy for 5 years [for patients <10 years old, continue yearly until age 10], then every 5 years. If clinical suspicion of hearing loss at any time, test as clinically indicated. If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions [OAEs].) **Info Link:** Complete pure tone audiogram should include testing of both ears: (1) Air conduction from 250 to 8000 Hz (2) Bone conduction if air conduction thresholds exceed bone by 15dB at any frequency (3) Speech discrimination evaluation. OAEs measure outer hair cell function only. Because carboplatin selectively damages inner hair cells, patients treated with carboplatin should not be evaluated with OAEs.	**Health Links** **Hearing Loss** **Educational Issues** **Considerations for Further Testing and Intervention** Audiology consultation for amplification in patients with progressive hearing loss. Speech and language therapy for children with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources. Consider specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**

SECTION 14 REFERENCES

Bertolini P, Lassalle M, Mercier G, et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. *J Pediatr Hematol Oncol*. Oct 2004;26(10):649-655.

Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: a practical grading system. *Med Pediatr Oncol*. 1991;19(4):295-300.

Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and Children's Cancer Group 8882. *J Clin Oncol*. Jul 1 2004;22(13):2691-2700.

Kortmann RD, Kuhl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. *Int J Radiat Oncol Biol Phys*. Jan 15 2000;46(2):269-279.

Landier W, Merchant T. Adverse effects of cancer treatment on hearing. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood and Adolescent Cancer. A Multidisciplinary Approach*, Second Edition. Heidelberg, Germany: Springer-Verlag; 2005:109-123.

Macdonald MR, Harrison RV, Wake M, Bliss B, Macdonald RE. Ototoxicity of carboplatin: comparing animal and clinical models at the Hospital for Sick Children. *J Otolaryngol*. Jun 1994;23(3):151-159.

Parsons SK, Neault MW, Lehmann LE, et al. Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. *Bone Marrow Transplant*. Oct 1998;22(7):669-674.

Punnett A, Bliss B, Dupuis LL, Abdolell M, Doyle J, Sung L. Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study. *Pediatr Blood Cancer*. Jun 2004;42(7):598-603.

Schell MJ, McHaney VA, Green AA, et al. Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. *J Clin Oncol*. Jun 1989;7(6):754-760.

Shearer PD. Hearing impairment In: Wallace H, Green D, eds. *Late Effects of Childhood Cancer*. London: Arnold; 2004: 49-54.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
15	**HEAVY METALS** Carboplatin Cisplatin	**Peripheral sensory neuropathy** **Info Link:** Neuropathy presents as persistent effect after therapy and is typically not late in onset	**Treatment Factors** Combined with: - Vincristine - Taxanes - Gemcitabine	**Treatment Factors** Cumulative cisplatin dose ≥ 300 mg/m^2	**HISTORY** **Peripheral neuropathy** (Yearly until 2 to 3 years after therapy. Monitor yearly if symptoms persist.) **PHYSICAL** **Neurologic exam** (Yearly until 2 to 3 years after therapy. Monitor yearly if symptoms persist.)	**Health Links** **Peripheral Neuropathy** **Considerations for Further Testing and Intervention** Physical therapy referral for patients with symptomatic neuropathy. Physical and occupational therapy assessment of hand function. Consider treatment with agent effective for neuropathic pain (e.g., gabapentin or amitriptyline). **SYSTEM = PNS** **SCORE = 2A**

SECTION 15 REFERENCES

Bosnjak S, Jelic S, Susnjar S, Luki V. Gabapentin for relief of neuropathic pain related to anticancer treatment: a preliminary study. *J Chemother*. Apr 2002;14(2):214-219.

Cvitkovic E. Cumulative toxicities from cisplatin therapy and current cytoprotective measures. *Cancer Treat Rev*. Aug 1998;24(4):265-281.

Hilkens PH, ven den Bent MJ. Chemotherapy-induced peripheral neuropathy. *J Peripher Nerv Syst*. 1997;2:350-361.

Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. *Cancer Treat Rev*. Apr 1994;20(2):191-214.

Verstappen CC, Postma TJ, Hoekman K, Heimans JJ. Peripheral neuropathy due to therapy with paclitaxel, gemcitabine, and cisplatin in patients with advanced ovarian cancer. *J Neurooncol*. Jun 2003;63(2):201-205.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
16	**HEAVY METALS** Carboplatin Cisplatin	**Renal toxicity** Glomerular injury Tubular injury Renal insufficiency	**Host Factors** Mononephric **Treatment Factors** Combined with other nephrotoxic agents such as: - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants - Methotrexate - Radiation impacting the kidney **Medical Conditions** Diabetes mellitus Hypertension Nephrectomy	**Treatment Factors** Cisplatin dose ≥ 200 mg/m^2 Renal radiation dose ≥ 15 Gy	**PHYSICAL** **Blood pressure** (Yearly) **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** (Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated.) **Urinalysis** (Yearly)	**Health Links** **Kidney Health** See also: **Single Kidney Health** **Counseling** In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis **Considerations for Further Testing and Intervention** Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

SECTION 16 REFERENCES

Arndt C, Morgenstern B, Hawkins D, Wilson D, Liedtke R, Miser J. Renal function following combination chemotherapy with ifosfamide and cisplatin in patients with osteogenic sarcoma. *Med Pediatr Oncol.* Feb 1999;32(2):93-96.

Bianchetti MG, Kanaka C, Ridolfi-Luthy A, Hirt A, Wagner HP, Oetliker OH. Persisting renotubular sequelae after cisplatin in children and adolescents. *Am J Nephrol.* 1991;11(2):127-130.

Ceremuzynski L, Gebalska J, Wolk R, Makowska E. Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. *J Intern Med.* Jan 2000;247(1):78-86.

Dentino M, Luft FC, Yum MN, Williams SD, Einhorn LH. Long term effect of cis-diamminedichloride platinum (CDDP) on renal function and structure in man. *Cancer.* Apr 1978;41(4):1274-1281.

Hutchison FN, Perez EA, Gandara DR, Lawrence HJ, Kaysen GA. Renal salt wasting in patients treated with cisplatin. *Ann Intern Med.* Jan 1988;108(1):21-25.

Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J.* Sep 1998;136(3):480-490.

Marina NM, Poquette CA, Cain AM, Jones D, Pratt CB, Meyer WH. Comparative renal tubular toxicity of chemotherapy regimens including ifosfamide in patients with newly diagnosed sarcomas. *J Pediatr Hematol Oncol.* Mar-Apr 2000;22(2):112-118.

von der Weid NX, Erni BM, Mamie C, Wagner HP, Bianchetti MG. Cisplatin therapy in childhood: renal follow up 3 years or more after treatment. Swiss Pediatric Oncology Group. *Nephrol Dial Transplant.* Jun 1999;14(6):1441-1444.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
17	**HEAVY METALS** Carboplatin Cisplatin	**Dyslipidemia**	**Host Factors** Family history of dyslipidemia **Medical Conditions** Overweight/Obesity		**SCREENING** **Fasting lipid profile** (Baseline at entry into long-term follow-up, then as per United States Preventive Task Force Recommendations: www.ahrq.gov/clinic/prevenix.htm)	**Health Links** **Diet and Physical Activity** **Considerations for Further Testing and Intervention** Counsel regarding lipid lowering strategies including diet, exercise, and weight loss in patients with dyslipidemia. Consider pharmacologic therapy (e.g., statins) in patients with dyslipidemia. **SYSTEM = Cardiovascular** **SCORE = 2B**

SECTION 17 REFERENCES

Ellis PA, Fitzharris BM, George PM, Robinson BA, Atkinson CH, Colls BM. Fasting plasma lipid measurements following cisplatin chemotherapy in patients with germ cell tumors. *J Clin Oncol*. Oct 1992;10(10):1609-1614.

Gietema JA, Meinardi MT, Messerschmidt J, et al. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. *Lancet*. Mar 25 2000;355(9209):1075-1076.

Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol*. Apr 2000;18(8):1725-1732.

Raghavan D, Cox K, Childs A, Grygiel J, Sullivan D. Hypercholesterolemia after chemotherapy for testis cancer. *J Clin Oncol*. Sep 1992;10(9):1386-1389

CHEMOTHERAPY

ANTIMETABOLITES

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
18	**ANTIMETABOLITES** Cytarabine (high dose IV) **Info Link**: High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change **Info Link**: Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New deficits may emerge over time.	**Host Factors** Younger age at treatment CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy **Treatment Factors** In combination with: - Dexamethasone - TBI - Cranial radiation - Methotrexate (IT, IO, high-dose IV) - Longer elapsed time since therapy **Info Link** Acute toxicity predominates if administered systemically as a single agent. May contribute to late neurotoxicity if combined with high dose or intrathecal methotrexate and/or cranial radiation.	**Host Factors** Age < 3 years old at time of treatment Female sex Premorbid or family history of learning or attention problems **Treatment Factors** Radiation dose ≥ 24 Gy Single fraction TBI (10 Gy)	**HISTORY** **Educational and/or vocational progress** (Yearly) **SCREENING** **Referral for formal neuropsychological evaluation** (Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress)	**Health Links** **Educational Issues** **Considerations for Further Testing and Intervention** Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Refer patients with neurocognitive deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Consider use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution - lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 2A**

SECTION 18 REFERENCES

Baker WJ, Royer GL, Jr., Weiss RB. Cytarabine and neurologic toxicity. *J Clin Oncol*. Apr 1991;9(4):679-693.

Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. *J Pediatr Psychol*. Jan-Feb 2005;30(1):65-78.

Hwang TL, Yung WK, Estey EH, Fields WS. Central nervous system toxicity with high-dose Ara-C. *Neurology*. Oct 1985;35(10):1475-1479.

Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol*. Oct 2000;15(7):603-630.

Nand S, Messmore HL, Jr., Patel R, Fisher SG, Fisher RI. Neurotoxicity associated with systemic high-dose cytosine arabinoside. *J Clin Oncol*. Apr 1986;4(4):571-575.

Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. *Cancer Treat Rev*. Apr 1994;20(2):191-214.

Vaughn DJ, Jarvik JG, Hackney D, Peters S, Stadtmauer EA. High-dose cytarabine neurotoxicity: MR findings during the acute phase. *AJNR Am J Neuroradiol*. Jul-Aug 1993;14(4):1014-1016.

Vera P, Rohrlich P, Stievenart JL, et al. Contribution of single-photon emission computed tomography in the diagnosis and follow-up of CNS toxicity of a cytarabine-containing regimen in pediatric leukemia. *J Clin Oncol*. Sep 1999;17(9):2804-2810.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
19	**ANTIMETABOLITES** Cytarabine (high dose IV) **Info Link**: High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Clinical leukoencephalopathy** Spasticity Ataxia Dysarthria Dysphagia Hemiparesis Seizures **Info Link**: Clinical leukoencephalopathy may present with or without imaging abnormalities (e.g., leukoencephalopathy, cerebral lacunes, cerebral atrophy, dystrophic calcifications, mineralizing microangiopathy). Transient white matter anomalies may follow radiotherapy and high-dose chemotherapy for medulloblastoma/PNET, may mimic tumor recurrence, and signify risk of persistent neurologic sequelae. Neuroimaging changes do not always correlate with degree of cognitive dysfunction. Prospective studies are needed to define the dose/effect relationship of neurotoxic agents. *Note: new deficits may emerge over time.*	**Host Factors** Younger age at treatment CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy **Treatment Factors** Combined with: - Methotrexate (IT, IO, high-dose IV) - Dexamethasone - Cranial radiation	**Treatment Factors** Radiation dose ≥ 24 Gy	**HISTORY** **Cognitive, motor, and/or sensory deficits** **Seizures** **Other neurologic symptoms** (Yearly) **PHYSICAL** **Spasticity** **Ataxia** **Dysarthria** **Hemiparesis** (Yearly)	**Considerations for Further Testing and Intervention** Brain MRI, Brain CT with MR angiography as clinically indicated; preferred study based on intracranial lesion to be evaluated: - MRI: White matter - Gadolinium-enhanced MRI: Microvascular injury - CT: Calcifications Neurology consultation and follow-up as clinically indicated. **SYSTEM = CNS** **SCORE = 2A**

SECTION 19 REFERENCES

Baker WJ, Royer GL, Jr., Weiss RB. Cytarabine and neurologic toxicity. *J Clin Oncol*. Apr 1991;9(4):679-693.
Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. *J Pediatr Psychol*. Jan-Feb 2005;30(1):65-78.
Hwang TL, Yung WK, Estey EH, Fields WS. Central nervous system toxicity with high-dose Ara-C. *Neurology*. Oct 1985;35(10):1475-1479.
Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol*. Oct 2000;15(7):603-630.
Nand S, Messmore HL, Jr., Patel R, Fisher SG, Fisher RI. Neurotoxicity associated with systemic high-dose cytosine arabinoside. *J Clin Oncol*. Apr 1986;4(4):571-575.
Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. *Cancer Treat Rev*. Apr 1994;20(2):191-214.
Vaughn DJ, Jarvik JG, Hackney D, Peters S, Stadtmauer EA. High-dose cytarabine neurotoxicity: MR findings during the acute phase. *AJNR Am J Neuroradiol*. Jul-Aug 1993;14(4):1014-1016.
Vera P, Rohrlich P, Stievenart JL, et al. Contribution of single-photon emission computed tomography in the diagnosis and follow-up of CNS toxicity of a cytarabine-containing regimen in pediatric leukemia. J *Clin Oncol*. Sep 1999;17(9):2804-2810.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
20	**ANTIMETABOLITES** Cytarabine (low dose IV) Cytarabine IO Cytarabine IT Cytarabine SQ **Info Link**: Low-dose IV is defined as any single dose < 1000 mg/m^2	**No known late effects** **Info Link**: Acute toxicities predominate, from which the majority of patients recover without sequelae.				**SYSTEM = N/A** **SCORE = 1**

SECTION 20 REFERENCES

No known late effects

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
21	**ANTIMETABOLITES** Mercaptopurine (6MP) Thioguanine (6TG) **Info Link**: Acute hepatotoxicity reported with thioguanine used in CCG 1952 (regimens B1 and B2) for ALL maintenance therapy requires longer follow-up to determine long-term sequelae. See COG Website (CCG 1952 protocol page) for updated advisories.	**Hepatic dysfunction** **Veno-occlusive disease (VOD)** **Info Link**: Acute toxicities predominate from which the majority of patients recover without sequelae. Delayed hepatic dysfunction may occur after a history of acute VOD, presenting as portal hypertension with liver biopsy indicating nodular regenerative hyperplasia, fibrosis, or siderosis.	**Medical Conditions** Viral hepatitis Previous VOD Siderosis	**Medical Conditions** Chronic viral hepatitis	**PHYSICAL** **Scleral icterus** **Jaundice** **Ascites** **Hepatomegaly** **Splenomegaly** (Yearly) **SCREENING** **ALT** **AST** **Bilirubin** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.)	**Health Links** **Liver Health** **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunization in patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 2A**

SECTION 21 REFERENCES

Broxson EH, Dole M, Wong R, Laya BF, Stork L. Portal hypertension develops in a subset of children with standard risk acute lymphoblastic leukemia treated with oral 6-thioguanine during maintenance therapy. *Pediatr Blood Cancer*. Mar 2005;44(3):226-231.

Castellino S, Lensing S, Riely C, et al. 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*. Apr 1 2004;103(7):2460-2466.

Einhorn M, Davidsohn I. Hepatotoxicity of Mercaptopurine. *JAMA*. Jun 1 1964;188:802-806.

Lichtman SM, Attivissimo L, Goldman IS, Schuster MW, Buchbinder A. Secondary hemochromatosis as a long-term complication of the treatment of hematologic malignancies. *Am J Hematol*. Aug 1999;61(4):262-264.

Ohata K, Hamasaki K, Toriyama K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer*. Jun 15 2003;97(12):3036-3043.

Piel B, Vaidya S, Lancaster D, Taj M, Pritchard-Jones K. Chronic hepatotoxicity following 6-thioguanine therapy for childhood acute lymphoblastic leukaemia. *Br J Haematol*. May 2004;125(3):410-411; author reply 412.

CHEMOTHERAPY

ANTIMETABOLITES (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
22	**ANTIMETABOLITES** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO **Info Link:** High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Osteopenia** **Osteoporosis** Osteopenia is defined as bone mineral density ≥ 1 and < 2.5 SD below mean Osteoporosis is defined as bone mineral density ≥ 2.5 SD below mean **Info Link**: The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density (BMD) of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the mean. A T-score of ≥ 2.5 standard deviations BELOW the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. There are no defined standards for referral or treatment of low BMD in children.	**Host Factors** Both genders are at risk **Treatment Factors** Corticosteroids Cranial radiation HCT/TBI **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use	**Host Factors** Older age at time of treatment **Treatment Factors** Methotrexate cumulative dose ≥ 40 gm/m^2 Prolonged corticosteroid therapy (e.g., for chronic GVHD)	**SCREENING** **Bone density evaluation (DEXA or quantitative CT)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.) **Info Link:** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	**Health Links** **Bone Health** **Resources** National Osteoporosis Foundation Website: www.nof.org **Considerations for Further Testing and Intervention** Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency, correction of chronic metabolic acidosis that could accelerate bone loss). Endocrine consultation for patients with osteoporosis or history of multiple fractures for pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators). **SYSTEM = Musculoskeletal** **SCORE = 2B**

SECTION 22 REFERENCES

Holzer G, Krepler P, Koschat MA, Grampp S, Dominkus M, Kotz R. Bone mineral density in long-term survivors of highly malignant osteosarcoma. *J Bone Joint Surg Br*. Mar 2003;85(2):231-237.

Kaste SC. Bone-mineral density deficits from childhood cancer and its therapy. A review of at-risk patient cohorts and available imaging methods. *Pediatr Radiol*. May 2004;34(5):373-378; quiz 443-374.

Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia*. May 2001;15(5):728-734.

Madsen KL, Adams WC, Van Loan MD. Effects of physical activity, body weight and composition, and muscular strength on bone density in young women. *Med Sci Sports Exerc*. Jan 1998;30(1):114-120.

Mandel K, Atkinson S, Barr RD, Pencharz P. Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. Apr 1 2004;22(7):1215-1221.

Muller HL, Schneider P, Bueb K, et al. Volumetric bone mineral density in patients with childhood craniopharyngioma. *Exp Clin Endocrinol Diabetes*. May 2003;111(3):168-173.

Nysom K, Holm K, Michaelsen KF, Hertz H, Muller J, Molgaard C. Bone mass after treatment for acute lymphoblastic leukemia in childhood. *J Clin Oncol*. Dec 1998;16(12):3752-3760.

Schwartz AM, Leonidas JC. Methotrexate osteopathy. *Skeletal Radiol*. 1984;11(1):13-16.

van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. *Med Pediatr Oncol*. Oct 2000;35(4):415-420.

van Leeuwen BL, Kamps WA, Jansen HW, Hoekstra HJ. The effect of chemotherapy on the growing skeleton. *Cancer Treat Rev*. Oct 2000;26(5):363-376.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
23	**ANTIMETABOLITES** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO **Info Link:** High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Renal toxicity** **Info Link:** Acute toxicities predominate, from which the majority of patients recover without sequelae	**Host Factors** Mononephric **Treatment Factors** Combined with other nephrotoxic agents such as: - Cisplatin/carboplatin - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants - Radiation impacting the kidney **Medical Conditions** Diabetes mellitus Hypertension Nephrectomy	**Treatment Factors** Treatment before 1970	**PHYSICAL** **Blood pressure** (Yearly) **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** (Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated.) **Urinalysis** (Yearly)	**Health Links** **Kidney Health** See also: **Single Kidney Health** **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 2A**

SECTION 23 REFERENCES

Abelson HT, Fosburg MT, Beardsley GP, et al. Methotrexate-induced renal impairment: clinical studies and rescue from systemic toxicity with high-dose leucovorin and thymidine. *J Clin Oncol.* Mar 1983;1(3):208-216.

Christensen ML, Rivera GK, Crom WR, Hancock ML, Evans WE. Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. *J Clin Oncol.* May 1988;6(5):797-801.

Kreusser W, Herrmann R, Tschope W, Ritz E. Nephrological complications of cancer therapy. *Contrib Nephrol.* 1982;33:223-238.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
24	**ANTIMETABOLITES** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO **Info Link:** High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Hepatic dysfunction** **Info Link:** Acute toxicities predominate from which the majority of patients recover without sequelae	**Treatment Factors** Abdominal radiation **Medical Conditions** Viral hepatitis	**Treatment Factors** Treatment before 1970 **Medical Conditions** Chronic viral hepatitis	**PHYSICAL** **Scleral icterus** **Jaundice** **Ascites** **Hepatomegaly** **Splenomegaly** (Yearly) **SCREENING** **ALT** **AST** **Bilirubin** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.)	**Health Links** **Liver Health** **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunization in patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 2A**

SECTION 24 REFERENCES

Locasciulli A, Mura R, Fraschini D, et al. High-dose methotrexate administration and acute liver damage in children treated for acute lymphoblastic leukemia. A prospective study. *Haematologica*. Jan-Feb 1992;77(1):49-53.

McIntosh S, Davidson DL, O'Brien RT, Pearson HA. Methotrexate hepatotoxicity in children with leukemia. *J Pediatr*. Jun 1977;90(6):1019-1021.

Weber BL, Tanyer G, Poplack DG, et al. Transient acute hepatotoxicity of high-dose methotrexate therapy during childhood. *NCI Monogr*. 1987(5):207-212.

CHEMOTHERAPY

ANTIMETABOLITES (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
25	**ANTIMETABOLITES** Methotrexate (high dose IV) Methotrexate IO Methotrexate IT **Info Link:** High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change **Info Link:** Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New deficits may emerge over time.	**Host Factors** Younger age at treatment CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy **Treatment Factors** In combination with: - Dexamethasone - TBI - Cranial radiation - Cytarabine (high-dose IV) - Longer elapsed time since therapy	**Host Factors** Age < 3 years old at time of treatment Female sex Premorbid or family history of learning or attention problems **Treatment Factors** Radiation dose ≥ 24 Gy Single fraction TBI (10 Gy)	**HISTORY** **Educational and/or vocational progress** (Yearly) **SCREENING** **Referral for formal neuropsychological evaluation** (Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress)	**Health Links** **Educational Issues** **Considerations for Further Testing and Intervention** Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Refer patients with neurocognitive deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training; Consider use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution - lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

SECTION 25 REFERENCES

Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. *J Pediatr Psychol*. Jan-Feb 2005;30(1):65-78.

Espy KA, Moore IM, Kaufmann PM, Kramer JH, Matthay K, Hutter JJ. Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: a prospective study. *J Pediatr Psychol*. Jan-Feb 2001;26(1):1-9.

Iuvone L, Mariotti P, Colosimo C, Guzzetta F, Ruggiero A, Riccardi R. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. *Cancer*. Dec 15 2002;95(12):2562-2570.

Kingma A, Van Dommelen RI, Mooyaart EL, Wilmink JT, Deelman BG, Kamps WA. No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. *J Pediatr Hematol Oncol*. Feb 2002;24(2):106-114.

Langer T, Martus P, Ottensmeier H, Hertzberg H, Beck JD, Meier W. CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. *Med Pediatr Oncol*. May 2002;38(5):320-328.

Mennes M, Stiers P, Vandenbussche E, et al. Attention and information processing in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *Pediatr Blood Cancer*. May 2005;44(5):478-486.

Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol*. Oct 2000;15(7):603-630.

Mulhern RK, Palmer SL. Neurocognitive late effects in pediatric cancer. *Curr Probl Cancer*. Jul-Aug 2003;27(4):177-197.

Riva D, Giorgi C, Nichelli F, et al. Intrathecal methotrexate affects cognitive function in children with medulloblastoma. *Neurology*. Jul 9 2002;59(1):48-53.

Waber DP, Carpentieri SC, Klar N, et al. Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone. *J Pediatr Hematol Oncol*. May-Jun 2000;22(3):206-213.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
26	**ANTIMETABOLITES** Methotrexate (high dose IV) Methotrexate IO Methotrexate IT Info Link: High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Clinical leukoencephalopathy** Spasticity Ataxia Dysarthria Dysphagia Hemiparesis Seizures **Info Link:** Clinical leukoencephalopathy may present with or without imaging abnormalities (e.g., leukoencephalopathy, cerebral lacunes, cerebral atrophy, dystrophic calcifications, mineralizing microangiopathy). Transient white matter anomalies may follow radiotherapy and high-dose chemotherapy for medulloblastoma/PNET, may mimic tumor recurrence, and signify risk of persistent neurologic sequelae. Neuroimaging changes do not always correlate with degree of cognitive dysfunction. Prospective studies are needed to define the dose/effect relationship of neurotoxic agents. *Note: new deficits may emerge over time.*	**Host Factors** Younger age at treatment CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy **Treatment Factors** Combined with: - Cytarabine (high-dose IV) - Dexamethasone - Cranial radiation	**Treatment Factors** Radiation dose ≥ 24 Gy	**HISTORY** **Cognitive, motor, and/or sensory deficits** **Seizures** **Other neurologic symptoms** (Yearly) **PHYSICAL** **Spasticity** **Ataxia** **Dysarthria** **Hemiparesis** (Yearly)	**Considerations for Further Testing and Intervention** Brain MRI, Brain CT with MR angiography as clinically indicated; preferred study based on intracranial lesion to be evaluated: - MRI: White matter - Gadolinium-enhanced MRI: Microvascular injury - CT: Calcifications Neurology consultation and follow-up as clinically indicated **SYSTEM = CNS** **SCORE = 1**

SECTION 26 REFERENCES

Hertzberg H, Huk WJ, Ueberall MA, et al. CNS late effects after ALL therapy in childhood. Part I: Neuroradiological findings in long-term survivors of childhood ALL--an evaluation of the interferences between morphology and neuropsychological performance. The German Late Effects Working Group. *Med Pediatr Oncol*. Jun 1997;28(6):387-400.

Lovblad K, Kelkar P, Ozdoba C, Ramelli G, Remonda L, Schroth G. Pure methotrexate encephalopathy presenting with seizures: CT and MRI features. *Pediatr Radiol*. Feb 1998;28(2):86-91.

Matsumoto K, Takahashi S, Sato A, et al. Leukoencephalopathy in childhood hematopoietic neoplasm caused by moderate-dose methotrexate and prophylactic cranial radiotherapy--an MR analysis. *Int J Radiat Oncol Biol Phys*. Jul 15 1995;32(4):913-918.

Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol*. Oct 2000;15(7):603-630.

Porto L, Kieslich M, Schwabe D, Zanella FE, Lanfermann H. Central nervous system imaging in childhood leukaemia. *Eur J Cancer*. Sep 2004;40(14):2082-2090.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
27	**ANTHRACYCLINE ANTIBIOTICS** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone* *Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family.	**Acute myeloid leukemia**	**Treatment Factors** Less than 5 years since exposure to agent		**HISTORY** **Fatigue** **Bleeding** **Easy bruising** (Yearly up to 10 years after exposure to agent) **PHYSICAL** **Dermatologic exam (pallor, petechiae, purpura)** (Yearly up to 10 years after exposure to agent) **SCREENING** **CBC/differential** (Yearly up to 10 years after exposure to agent)	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Counsel to promptly report fatigue, pallor, petechiae, or bone pain **Considerations for Further Testing and Intervention** Bone marrow exam as clinically indicated **SYSTEM = SMN** **SCORE = 1**

SECTION 27 REFERENCES

Felix CA. Leukemias related to treatment with DNA topoisomerase II inhibitors. *Med Pediatr Oncol*. May 2001;36(5):525-535.

Le Deley MC, Leblanc T, Shamsaldin A, et al. 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*. Mar 15 2003;21(6):1074-1081.

CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
28	**ANTHRACYCLINE ANTIBIOTICS** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone* *Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included here because of its cardiotoxic potential. **Info Link:** Use the following formulas to convert to doxorubicin/daunorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 3.5 *Note: There is a paucity of literature to support isotoxic dose conversion; however, the above conversion factors may be used for convenience in order to gauge screening frequency. Clinical judgment should ultimately be used to determine indicated screening for individual patients.*	**Cardiac toxicity** Cardiomyopathy Arrhythmias Subclinical left ventricular dysfunction (systolic dysfunction as assessed by ECHO or MUGA) **Info Link:** Dose levels correlating with cardiotoxicity are derived from adult studies. Childhood cancer patients exhibit clinical and subclinical toxicity at lower levels. Certain conditions (such as isometric exercise, pregnancy, and viral infections) have been anecdotally reported to precipitate cardiac decompensation. Prospective studies are needed to define risk factors. *Note: Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of daunomycin and doxorubicin, assuming an equivalent relative cardiotoxicity per mg dose. Idarubicin and mitoxantrone are more cardiotoxic than doxorubicin or daunorubicin on a mg per mg dose basis. In limited studies, epirubicin has similar dose equivalency to daunomycin and doxorubicin.*	**Treatment Factors** Combined with radiation involving the heart Combined with other cardiotoxic chemotherapy: - Cyclophosphamide conditioning for HCT - Amsacrine **Medical Conditions** Obesity Congenital heart disease Febrile illness Pregnancy **Health Behaviors** Isometric exercise Smoking Drug use (e.g., cocaine, diet pills, ephedra, mahuang)	**Host Factors** Female sex Black/of African descent Younger than age 5 years at time of treatment **Treatment Factors** Higher cumulative anthracycline doses: - Patients 18 years or older at time of treatment: ≥ 550 mg/m² - Patients younger than 18 years at time of treatment: ≥ 300 mg/m² - Any dose in infant Chest radiation ≥ 30 Gy Longer time elapsed since treatment	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 years:** **Abdominal symptoms (nausea, vomiting)** (Yearly) **Info Link:** Exertional intolerance is uncommon in young patients (< 25 years). Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in young patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** (Yearly) **SCREENING** **ECHO or MUGA for evaluation of systolic function** (Baseline at entry to long-term follow-up, then periodically, based on age at treatment, history of chest radiation and cumulative anthracycline dose - *see table on next page*.) **EKG (include evaluation of QTc interval)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.)	**Health Links** **Heart Health** **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure, and heart-healthy diet. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. Limited high repetition weight lifting (i.e., lifting a lighter weight with ease no more than 15 to 20 times in a row) is much less stressful to the heart and is more likely to be safe. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Consider excess risk of isometric exercise program in any high risk patient (defined as needing screening every 1 or 2 years). Females only: Additional cardiology evaluation in patients who received ≥ 300 mg/m² or < 300 mg/m² plus chest radiation who are pregnant or planning pregnancy. Evaluation to include an echocardiogram before and periodically during pregnancy (especially during third trimester) and monitoring during labor and delivery due to risk of cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

28

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM OR MUGA SCAN

Age at Treatment*	Chest Radiation	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	<200 mg/m^2	Every 2 years
		≥200 mg/m^2	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
		≥100 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
≥5 years old	Yes	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
		≥200 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
Any age with decrease in serial function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)
†Based on equivalent mg of doxorubicin/daunorubicin

SECTION 28 REFERENCES

Ali MK, Ewer MS, Gibbs HR, Swafford J, Graff KL. Late doxorubicin-associated cardiotoxicity in children. The possible role of intercurrent viral infection. *Cancer*. Jul 1 1994;74(1):182-188.
Green DM, Hyland A, Chung CS, Zevon MA, Hall BC. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. *J Clin Oncol*. Oct 1999;17(10):3207-3215.
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*. Apr 1 2001;19(7):1926-1934.
Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol*. Jul 1993;11(7):1208-1215.
Jakacki RI, Goldwein JW, Larsen RL, Barber G, Silber JH. Cardiac dysfunction following spinal irradiation during childhood. *J Clin Oncol*. Jun 1993;11(6):1033-1038.
Kremer LC, van Dalen EC, Offringa M, Ottenkamp J, Voute PA. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *J Clin Oncol*. Jan 1 2001;19(1):191-196.
Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. *J Clin Oncol*. Apr 1997;15(4):1544-1552.
Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med*. Jun 29 1995;332(26):1738-1743.
Nysom K, Holm K, Lipsitz SR, et al. Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. Feb 1998;16(2):545-550.
Sorensen K, Levitt G, Bull C, Chessells J, Sullivan I. Anthracycline dose in childhood acute lymphoblastic leukemia: issues of early survival versus late cardiotoxicity. *J Clin Oncol*. Jan 1997;15(1):61-68.

CHEMOTHERAPY

ANTI-TUMOR ANTIBIOTICS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
29	**ANTI-TUMOR ANTIBIOTICS** Bleomycin	**Pulmonary toxicity** Interstitial pneumonitis Pulmonary fibrosis Acute respiratory distress syndrome (very rare)	**Host Factors** Younger age at treatment **Treatment Factors** Higher cumulative dose Combined with: - Busulfan - Carmustine (BCNU) - Lomustine (CCNU) **Medical Conditions** Renal dysfunction High dose oxygen support such as during general anesthesia **Health Behaviors** Smoking	**Treatment Factors** Bleomycin dose ≥ 400 U/m^2 (injury observed in doses 60-100 U/m^2 in children) Combined with: - Chest radiation - TBI	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **PHYSICAL** **Pulmonary exam** (Yearly) **SCREENING** **Chest x-ray** **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	**Health Links** **Pulmonary Health** **Bleomycin Alert** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: www.smokefree.gov **Counseling** SCUBA diving should be avoided (potential exacerbation of pulmonary fibrosis as a result of increased oxygen concentrations associated with underwater pressures). Notify healthcare providers of history of bleomycin therapy and risk of worsening fibrosis with high oxygen exposure such as during general anesthesia. Administration of high concentrations of oxygen may result in chronic progressive pulmonary fibrosis. Counsel regarding tobacco avoidance/smoking cessation. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia. Pulmonary consultation in patients with symptomatic or progressive pulmonary dysfunction. Influenza and pneumococcal vaccines. **SYSTEM = Pulmonary** **SCORE =** **Interstitial pneumonitis: 1** **Pulmonary fibrosis: 1** **ARDS: 2B**

SECTION 29 REFERENCES

Goldiner PL, Carlon GC, Cvitkovic E, Schweizer O, Howland WS. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. *Br Med J*. Jun 24 1978;1(6128):1664-1667.

Kreisman H, Wolkove N. Pulmonary toxicity of antineoplastic therapy. *Semin Oncol*. Oct 1992;19(5):508-520.

Marina NM, Greenwald CA, Fairclough DL, et al. Serial pulmonary function studies in children treated for newly diagnosed Hodgkin's disease with mantle radiotherapy plus cycles of cyclophosphamide, vincristine, and procarbazine alternating with cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine. *Cancer*. Apr 1 1995;75(7):1706-1711.

Mefferd JM, Donaldson SS, Link MP. Pediatric Hodgkin's disease: pulmonary, cardiac, and thyroid function following combined modality therapy. *Int J Radiat Oncol Biol Phys*. Mar 1989;16(3):679-685.

Stolp B, Assistant Medical Director Divers Alert Network, Director Anesthesiology Emergency Airway Services, Durham, N.C. Risks associated with SCUBA diving in childhood cancer survivors. Personal communication to Landier W, Bhatia S Aug 23, 2002.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
30	**ANTI-TUMOR ANTIBIOTICS** Dactinomycin	**No known late effects** **Info Link:** Dactinomycin has been associated with acute veno-occlusive disease, from which the majority of patients recover without sequelae				**SYSTEM = N/A** **SCORE = 1**

SECTION 30 REFERENCES

Green DM, Norkool P, Breslow NE, Finklestein JZ, D'Angio GJ. 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*. Sep 1990;8(9):1525-1530.

CHEMOTHERAPY

CORTICOSTEROIDS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
31	**CORTICOSTEROIDS** Dexamethasone Prednisone	**Osteopenia** **Osteoporosis** Osteopenia is defined as bone mineral density ≥ 1 and < 2.5 SD below mean Osteoporosis is defined as bone mineral density ≥ 2.5 SD below mean **Info Link:** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density (BMD) of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the mean. A T-score of ≥ 2.5 standard deviations BELOW the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. There are no defined standards for referral or treatment of low BMD in children.	**Host Factors** Both genders are at risk **Treatment Factors** Methotrexate Cranial radiation HCT/TBI **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use	**Host Factors** Older age at time of treatment **Treatment Factors** Glucocorticoid cumulative dose ≥ 9 gm/m^2 prednisone equivalent Dexamethasone effect is more potent than prednisone	**SCREENING** **Bone density evaluation (DEXA or quantitative CT)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.) **Info Link:** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	**Health Links** **Bone Health** **Resources** National Osteoporosis Foundation Website: www.nof.org **Considerations for Further Testing and Intervention** Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency, correction of chronic metabolic acidosis that could accelerate bone loss). Endocrine consultation for patients with osteoporosis or history of multiple fractures for pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators). **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 31 REFERENCES

Aisenberg J, Hsieh K, Kalaitzoglou G, et al. Bone mineral density in young adult survivors of childhood cancer. *J Pediatr Hematol Oncol*. May-Jun 1998;20(3):241-245.

Atkinson SA, Halton JM, Bradley C, Wu B, Barr RD. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: influence of disease, drugs and nutrition. *Int J Cancer Suppl*. 1998;11:35-39.

Kaste SC, Chesney RW, Hudson MM, Lustig RH, Rose SR, Carbone LD. Bone mineral status during and after therapy of childhood cancer: an increasing population with multiple risk factors for impaired bone health. *J Bone Miner Res*. Dec 1999;14(12):2010-2014.

Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia*. May 2001;15(5):728-734.

Leonard MB. Assessment of bone health in children and adolescents with cancer: promises and pitfalls of current techniques. *Med Pediatr Oncol*. Sep 2003;41(3):198-207.

Mandel K, Atkinson S, Barr RD, Pencharz P. Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. Apr 1 2004;22(7):1215-1221.

Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. Sep 15 2000;18(18):3262-3272.

Nysom K, Holm K, Michaelsen KF, Hertz H, Muller J, Molgaard C. Bone mass after treatment for acute lymphoblastic leukemia in childhood. *J Clin Oncol*. Dec 1998;16(12):3752-3760.

van Leeuwen BL, Kamps WA, Jansen HW, Hoekstra HJ. The effect of chemotherapy on the growing skeleton. *Cancer Treat Rev*. Oct 2000;26(5):363-376.

CHEMOTHERAPY

CORTICOSTEROIDS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
32	**CORTICOSTEROIDS** Dexamethasone Prednisone	**Osteonecrosis** (Avascular Necrosis) **Info Link:** Osteonecrosis typically occurs during the acute treatment phase, may progress over time or resolve. Multifocal osteonecrosis is significantly more common (3:1) than unifocal.	**Host Factors** Both genders are at risk Host polymorphisms may confer increased risk **Treatment Factors** Combined with high-dose radiation to any bone Dexamethasone effect is more potent than prednisone **Medical Conditions** Sickle cell disease	**Host Factors** Age ≥ 10 years at time of treatment **Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**HISTORY** **Joint pain** **Swelling** **Immobility** **Limited range of motion** (Yearly) **PHYSICAL** **Musculoskeletal exam** (Yearly)	**Health Links** **Osteonecrosis** **Considerations for Further Testing and Intervention** MRI as clinically indicated in patients with history suggestive of osteonecrosis (should be done soon after symptom onset). Orthopedic consultation in patients with positive imaging and/or symptoms of osteonecrosis. Physical therapy evaluation (for non-pharmacologic pain management, range of motion, strengthening, stretching, functional mobility). **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 32 REFERENCES

Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: An emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. *Haematologica*. Jul 2003;88(7):747-753.

Beltran J, Herman LJ, Burk JM, et al. Femoral head avascular necrosis: MR imaging with clinical-pathologic and radionuclide correlation. *Radiology*. Jan 1988;166(1 Pt 1):215-220.

Burger B, Beier R, Zimmermann M, Beck JD, Reiter A, Schrappe M. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)--experiences from trial ALL-BFM 95. *Pediatr Blood Cancer*. Mar 2005;44(3):220-225.

Koo KH, Ahn IO, Kim R, et al. Bone marrow edema and associated pain in early stage osteonecrosis of the femoral head: prospective study with serial MR images. *Radiology*. Dec 1999;213(3):715-722.

Korholz D, Bruder M, Engelbrecht V, Ruther W, Gobel U. Aseptic osteonecrosis in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. Jul-Aug 1998;15(4):307-315.

Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. Sep 15 2000;18(18):3262-3272.

Ojala AE, Paakko E, Lanning FP, Lanning M. Osteonecrosis during the treatment of childhood acute lymphoblastic leukemia: a prospective MRI study. *Med Pediatr Oncol*. Jan 1999;32(1):11-17.

Relling MV, Yang W, Das S, et al. Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia. *J Clin Oncol*. Oct 1 2004;22(19):3930-3936.

Ribeiro RC, Fletcher BD, Kennedy W, et al. Magnetic resonance imaging detection of avascular necrosis of the bone in children receiving intensive prednisone therapy for acute lymphoblastic leukemia or non-Hodgkin lymphoma. *Leukemia*. Jun 2001;15(6):891-897.

Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol*. Jun 15 2001;19(12):3066-3072.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
33	**CORTICOSTEROIDS** Dexamethasone Prednisone	**Cataracts**	**Treatment Factors** Combined with: - TBI - Busulfan	**Treatment Factors** TBI Cranial, orbital, or eye radiation Longer interval since treatment	**HISTORY** **Visual difficulties** (Yearly) **PHYSICAL** **Eye exam (visual acuity, funduscopic exam for lens opacity)** (Yearly)	**Health Links** **Cataracts** **Considerations for Further Testing and Intervention** Ophthalmology consultation if problem identified. Refer patients with visual deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Ocular** **SCORE = 1**

SECTION 33 REFERENCES

Benyunes MC, Sullivan KM, Deeg HJ, et al. Cataracts after bone marrow transplantation: long-term follow-up of adults treated with fractionated total body irradiation. *Int J Radiat Oncol Biol Phys*. Jun 15 1995;32(3):661-670.

Hoover DL, Smith LE, Turner SJ, Gelber RD, Sallan SE. Ophthalmic evaluation of survivors of acute lymphoblastic leukemia. *Ophthalmology*. Feb 1988;95(2):151-155.

Kaye LD, Kalenak JW, Price RL, Cunningham R. Ocular implications of long-term prednisone therapy in children. *J Pediatr Ophthalmol Strabismus*. May-Jun 1993;30(3):142-144.

Pakisch B, Langmann G, Langmann A, et al. Ocular sequelae of multimodal therapy of hematologic malignancies in children. *Med Pediatr Oncol*. 1994;23(4):344-349.2001;19(12):3066-3072.

CHEMOTHERAPY

ENZYMES

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
34	**ENZYMES** Asparaginase	**No known late effects** **Info Link:** Acute toxicities predominate, from which the majority of patients recover without sequelae				**SYSTEM = N/A** **SCORE = 1**

SECTION 34 REFERENCES

Duval M, Suciu S, Ferster A, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. *Blood.* Apr 15 2002;99(8):2734-2739.

Parsons SK, Skapek SX, Neufeld EJ, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. *Blood.* Mar 15 1997;89(6):1886-1895.

CHEMOTHERAPY

PLANT ALKALOIDS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
35	**PLANT ALKALOIDS** Vinblastine Vincristine	**Peripheral sensory or motor neuropathy** Areflexia Weakness Foot drop Paresthesias **Info Link:** Acute toxicities most commonly occur and usually resolve prior to patients entering long-term follow-up. Neuropathy can persist after treatment and is typically not late in onset.	**Treatment Factors** Combined with platinum chemotherapy, gemcitabine or taxanes **Medical Conditions** Anorexia Severe weight loss	**Medical Conditions** Charcot-Marie-Tooth disease	**HISTORY** **Peripheral neuropathy** (Yearly, until 2 to 3 years after therapy. Monitor yearly if symptoms persist.) **PHYSICAL** **Neurologic exam** (Yearly, until 2 to 3 years after therapy; continue to monitor yearly if symptoms persist)	**Health Links** **Peripheral Neuropathy** **Considerations for Further Testing and Intervention** Physical therapy referral for patients with symptomatic neuropathy. Physical therapy and occupational therapy assessment of hand function. Consider treatment with an anticonvulsant effective for neuropathic pain (e.g., gabapentin and amitriptyline). **SYSTEM = PNS** **SCORE = 2A**

SECTION 35 REFERENCES

Chauvenet AR, Shashi V, Selsky C, Morgan E, Kurtzberg J, Bell B. Vincristine-induced neuropathy as the initial presentation of Charcot-Marie-Tooth disease in acute lymphoblastic leukemia: a Pediatric Oncology Group study. *J Pediatr Hematol Oncol*. Apr 2003;25(4):316-320.

Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. *Cancer*. Apr 1 1996;77(7):1356-1362.

Lehtinen SS, Huuskonen UE, Harila-Saari AH, Tolonen U, Vainionpaa LK, Lanning BM. Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukemia. *Cancer*. May 1 2002;94(9):2466-2473.

Trobaugh-Lotrario AD, Smith AA, Odom LF. Vincristine neurotoxicity in the presence of hereditary neuropathy. *Med Pediatr Oncol*. Jan 2003;40(1):39-43.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
36	**PLANT ALKALOIDS** Vinblastine Vincristine	**Vasospastic attacks** (Raynaud's phenomenon)	**Health Behaviors** Smoking Illicit drug use		**HISTORY** **Vasospasms of hands, feet, nose, lips, cheeks, or earlobes related to stress or cold temperatures** (Yearly) **PHYSICAL** **Physical exam of affected area** (As Indicated)	**Health Links** **Raynaud's Phenomenon** **Counseling** Counsel to wear appropriate protective clothing in cold environments and not to use tobacco or illicit drugs **Considerations for Further Testing and Intervention** Consider vasodilating medications (calcium- channel blockers, alpha blockers) for patients with frequent, severe vasospastic attacks unresponsive to behavioral management. **SYSTEM = Cardiovascular** **SCORE = 2A**

SECTION 36 REFERENCES

Bokemeyer C, Berger CC, Kuczyk MA, Schmoll HJ. Evaluation of long-term toxicity after chemotherapy for testicular cancer. *J Clin Oncol*. Nov 1996;14(11):2923-2932.

Doll DC, Ringenberg QS, Yarbro JW. Vascular toxicity associated with antineoplastic agents. *J Clin Oncol*. Sep 1986;4(9):1405-1417.

Vogelzang NJ, Bosl GJ, Johnson K, Kennedy BJ. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med*. Sep 1981;95(3):288-292.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
37	**EPIPODOPHYLLOTOXINS** Etoposide (VP16) Teniposide (VM26) **Info Link:** Administration schedules since approximately 1990 have been modified to reduce the risk of this complication.	**Acute myeloid leukemia**	**Medical Conditions** Splenectomy (conflicting evidence)	**Treatment Factors** Weekly or twice weekly administration Less than 5 years since exposure to agent	**HISTORY** **Fatigue** **Bleeding** **Easy bruising** (Yearly, up to 10 years after exposure to agent) **PHYSICAL** **Dermatologic exam (pallor, petechiae, purpura)** (Yearly, up to 10 years after exposure to agent) **SCREENING** **CBC/differential** (Yearly, up to 10 years after exposure to agent)	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Counsel to promptly report fatigue, pallor, petechiae, or bone pain **Considerations for Further Testing and Intervention** Bone marrow exam as clinically indicated **SYSTEM = SMN** **SCORE = 1**

SECTION 37 REFERENCES

Pui CH. Epipodophyllotoxin-related acute myeloid leukaemia. *Lancet*. Dec 7 1991;338(8780):1468.

Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med*. Dec 12 1991;325(24):1682-1687.

Smith MA, Rubinstein L, Anderson JR, et al. Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J Clin Oncol*. Feb 1999;17(2):569-577.

RADIATION

ALL FIELDS (INCLUDING TBI)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
38	**All Radiation Fields** (Including TBI) **Info Link:** General factors influencing radiation toxicity include daily fraction size, cumulative dose, age of patient at irradiation and type of radiation used. Toxicity may not be manifest until growth is completed or patient ages.	**Secondary benign or malignant neoplasm** Occurring in or near radiation field **Info Link:** Patients with bilateral or familial retinoblastoma (implying a germline mutation) are at increased risk for developing second malignant neoplasms	**Host Factors** Cancer predisposing mutation (e.g., p53, RB1, NF1) Younger age at treatment **Treatment Factors** High cumulative radiation dose Large radiation treatment volumes Alkylating agent exposure	**Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Inspection and palpation of skin and soft tissues in irradiated field(s)** (Yearly) **SCREENING** **Other evaluations based on treatment volumes** (See recommendations for specific fields)	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** There is currently a deficiency in the literature regarding whether or not TBI is a risk factor for the development of breast cancer. Monitoring for breast cancer in females who received TBI should be determined on an individual basis. Surgical and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 38 REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Fletcher O, Easton D, Anderson K, Gilham C, Jay M, Peto J. Lifetime risks of common cancers among retinoblastoma survivors. *J Natl Cancer Inst*. Mar 3 2004;96(5):357-363.

Forrest DL, Nevill TJ, Naiman SC, et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. *Bone Marrow Transplant*. Nov 2003;32(9):915-923.

Howe R, Micallef IN, Inwards DJ, et al. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. *Bone Marrow Transplant*. Aug 2003;32(3):317-324.

Kolb HJ, Socie G, Duell T, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Ann Intern Med*. Nov 16 1999;131(10):738-744.

Menu-Branthomme A, Rubino C, Shamsaldin A, et al. Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. *Int J Cancer*. May 20 2004;110(1):87-93.

Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst*. Apr 18 2001;93(8):618-629.

Rowlings PA, Curtis RE, Passweg JR, et al. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *J Clin Oncol*. Oct 1999;17(10):3122-3127.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
39	**All Radiation Fields** (Including TBI)	**Dysplastic nevi** **Skin cancer** Basal cell carcinoma Squamous cell carcinoma Melanoma	**Host Factors** Gorlin's syndrome (nevoid basal cell carcinoma syndrome)	**Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**HISTORY** **Skin lesions** **Changing moles (asymmetry, bleeding, increasing size, indistinct borders)** (Yearly) **PHYSICAL** **Dermatologic exam of irradiated fields** (Yearly)	**Health Links** **Skin Health** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Dermatology consultation for evaluation and monitoring of atypical nevi. Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 39 REFERENCES

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.

Cancer Prevention and Early Detection Facts and Figures: American Cancer Society; 2005.

Curtis RE, Metayer C, Rizzo JD, et al. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. *Blood*. May 15 2005;105(10):3802-3811.

Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. *J Natl Cancer Inst*. Dec 18 1996;88(24):1848-1853.

Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Jun 1 2005;23(16):3733-3741.

Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol*. May 2001;36(5):549-554.

RADIATION

ALL FIELDS (EXCEPT TBI)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
40	**All Radiation Fields** (Except TBI)	**Dermatologic changes** Fibrosis Telangiectasias Permanent hair loss Altered skin pigmentation	**Host Factors** Younger age at treatment **Treatment Factors** Total radiation dose ≥ 40 Gy Large dose fractions (e.g ≥ 2 Gy per fraction)	**Treatment Factors** Radiation dose ≥ 50 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Dermatologic exam of irradiated fields** (Yearly)	**Health Links** **Skin Health** **SYSTEM = Dermatologic** **SCORE = 1**

SECTION 40 REFERENCES

Lawenda BD, Gagne HM, Gierga DP, et al. Permanent alopecia after cranial irradiation: dose-response relationship. *Int J Radiat Oncol Biol Phys.* Nov 1 2004;60(3):879-887.

Marcus RB, DiCaprio MR, Lindskog DM, McGrath BE, Gamble K, Scarborough M. Musculoskeletal, Integument, Breast. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach, Second Edition.* Heidelberg, Germany: Springer-Verlag; 2005:262-269.

RADIATION

ALL FIELDS (EXCEPT TBI) (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
41	**All Radiation Fields** (Except TBI)	**Bone malignancies**	**Host Factors** Adolescent at treatment Cancer-predisposing mutation (e.g., p53, RB1, NF1) **Treatment Factors** Higher radiation dose Combined with alkylating agents	**Treatment Factors** Radiation dose ≥ 30 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**HISTORY** **Bone pain (especially in irradiated field)** (Yearly) **PHYSICAL** **Palpation of bones in irradiated field** (Yearly)	**Counseling** Counsel patient to report symptoms promptly (e.g., bone pain, bone mass, persistent fevers) **Considerations for Further Testing and Intervention** X-ray or other diagnostic imaging in patients with clinical symptoms. Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 41 REFERENCES

Hawkins MM, Wilson LM, Burton HS, et al. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst*. Mar 6 1996;88(5):270-278.

Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. *J Natl Cancer Inst*. Jul 15 1998;90(14):1039-1071.

Newton WA, Jr., Meadows AT, Shimada H, Bunin GR, Vawter GF. Bone sarcomas as second malignant neoplasms following childhood cancer. *Cancer*. Jan 1 1991;67(1):193-201.

Tucker MA, D'Angio GJ, Boice JD, Jr., et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med*. Sep 3 1987;317(10):588-593.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
42	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal** **TBI**	**Brain tumor** (benign or malignant)	**Host Factors** Younger age at treatment Neurofibromatosis **Treatment Factors** Higher radiation dose	**Host Factors** Age < 6 years at time of treatment Ataxia telangiectasia	**HISTORY** **Headaches** **Vomiting** **Cognitive, motor or sensory deficits** **Seizures and other neurologic symptoms** (Yearly) **PHYSICAL** **Neurologic exam** (Yearly)	**Considerations for Further Testing and Intervention** Brain MRI as clinically indicated for symptomatic patients. Consider brain MRI every other year for patients with neurofibromatosis beginning 2 years after radiation therapy. Neurosurgical consultation for tissue diagnosis and/or resection. Neuro-oncology consultation for medical management. **SYSTEM = SMN** **SCORE = 1**

SECTION 42 REFERENCES

Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. *J Natl Cancer Inst*. Jul 15 1998;90(14):1039-1071.

Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst*. Apr 18 2001;93(8):618-629.

Walter AW, Hancock ML, Pui CH, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. *J Clin Oncol*. Dec 1998;16(12):3761-3767.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
43	**Cranial** **Ear/Infratemporal** **TBI**	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change **Info Link:** Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. *Note: New deficits may emerge over time.*	**Host Factors** Younger age at treatment Primary CNS tumor CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy Head/neck tumors with brain in radiation field **Treatment Factors** Radiation in combination with: - Dexamethasone - TBI - Methotrexate (IT, IO, high-dose IV) - Cytarabine (high-dose IV) Higher radiation dose Larger radiation field Greater cortical volumes Cranial radiation in combination with TBI Longer elapsed time since therapy	**Host Factors** Age < 3 years at time of treatment Female sex Supratentorial tumor Premorbid or family history of learning or attention problems	**HISTORY** **Educational and/or vocational progress** (Yearly) **SCREENING** **Referral for formal neuropsychological evaluation** (Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress)	**Health Links** **Educational Issues** **Considerations for Further Testing and Intervention** Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Refer patients with neurocognitive deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Consider use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution - lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

SECTION 43 REFERENCES

Butler RW, Hill JM, Steinherz PG, Meyers PA, Finlay JL. Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. *J Clin Oncol*. Dec 1994;12(12):2621-2629.

Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. *J Pediatr Psychol*. Jan-Feb 2005;30(1):65-78.

Keene N, Hobbie W, Ruccione K, eds. *Childhood Cancer Survivors: A Practical Guide to Your Future*. Sebastopol, CA: O'Reilly; 2002.

Mulhern RK, Palmer SL, Reddick WE, et al. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. *J Clin Oncol*. Jan 15 2001;19(2):472-479.

Palmer SL, Gajjar A, Reddick WE, et al. Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology*. Oct 2003;17(4):548-555.

Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Med Pediatr Oncol*. Jan 2003;40(1):26-34.

Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *J Clin Oncol*. Aug 1 2001;19(15):3470-3476.

Waber DP, Tarbell NJ, Fairclough D, et al. Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. *J Clin Oncol*. Oct 1995;13(10):2490-2496.

Walter AW, Mulhern RK, Gajjar A, et al. Survival and neurodevelopmental outcome of young children with medulloblastoma at St Jude Children's Research Hospital. *J Clin Oncol*. Dec 1999;17(12):3720-3728.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
44	**Cranial**	**Clinical leukoencephalopathy** Spasticity Ataxia Dysarthria Dysphagia Hemiparesis Seizures **Info Link:** Clinical leukoencephalopathy may present with or without imaging abnormalities (e.g., leukoencephalopathy, cerebral lacunes, cerebral atrophy, dystrophic calcifications, mineralizing microangiopathy). Transient white matter anomalies may follow radiotherapy and high-dose chemotherapy for medulloblastoma/PNET, may mimic tumor recurrence, and signify risk of persistent neurologic sequelae. Neuroimaging changes do not always correlate with degree of cognitive dysfunction. Prospective studies are needed to define the dose/effect relationship of neurotoxic agents. *Note: New deficits may emerge over time.*	**Host Factors** Younger age at treatment CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy **Treatment Factors** In combination with: - Dexamethasone - Methotrexate (IT, IO, high-dose IV) - Cytarabine (high-dose IV) - Higher radiation dose Larger radiation field Greater cortical volumes Longer elapsed time since therapy	**Host Factors** Radiation dose ≥ 24 Gy **Treatment Factors** Fraction dose ≥ 3 Gy	**HISTORY** **Cognitive, motor, and/or sensory deficits** **Seizures** **Other neurologic symptoms** (Yearly) **PHYSICAL** **Spasticity** **Ataxia** **Dysarthria** **Hemiparesis** (Yearly)	**Considerations for Further Testing and Intervention** Brain MRI, Brain CT with MR angiography as clinically indicated; preferred study based on intracranial lesion to be evaluated: - MRI: White matter - Gadolinium-enhanced MRI: Microvascular injury - CT: Calcifications Neurology consultation and follow-up as clinically indicated **SYSTEM = CNS** **SCORE = 1**

SECTION 44 REFERENCES

Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. *Neurologist*. Nov 2004;10(6):293-310.

Faraci M, Lanino E, Dini G, et al. Severe neurologic complications after hematopoietic stem cell transplantation in children. *Neurology*. Dec 24 2002;59(12):1895-1904.

Fouladi M, Chintagumpala M, Laningham FH, et al. White matter lesions detected by magnetic resonance imaging after radiotherapy and high-dose chemotherapy in children with medulloblastoma or primitive neuroectodermal tumor. *J Clin Oncol*. Nov 15 2004;22(22):4551-4560.

Heckl S, Aschoff A, Kunze S. Radiation-induced cavernous hemangiomas of the brain: a late effect predominantly in children. *Cancer*. Jun 15 2002;94(12):3285-3291.

Hertzberg H, Huk WJ, Ueberall MA, et al. CNS late effects after ALL therapy in childhood. Part I: Neuroradiological findings in long-term survivors of childhood ALL--an evaluation of the interferences between morphology and neuropsychological performance. The German Late Effects Working Group. *Med Pediatr Oncol*. Jun 1997;28(6):387-400.

Kingma A, Mooyaart EL, Kamps WA, Nieuwenhuizen P, Wilmink JT. Magnetic resonance imaging of the brain and neuropsychological evaluation in children treated for acute lymphoblastic leukemia at a young age. *Am J Pediatr Hematol Oncol*. May 1993;15(2):231-238.

Matsumoto K, Takahashi S, Sato A, et al. Leukoencephalopathy in childhood hematopoietic neoplasm caused by moderate-dose methotrexate and prophylactic cranial radiotherapy--an MR analysis. *Int J Radiat Oncol Biol Phys*. Jul 15 1995;32(4):913-918.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
45	≥ 40 Gy to: **Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Cerebrovascular complications** Stroke Moyamoya Occlusive cerebral vasculopathy **Info Link:** Moyamoya syndrome is the complete occlusion of one or more of the three major cerebral vessels with the development of small, immature collateral vessels, which reflect an attempt to revascularize the ischemic portion of the brain.	**Host Factors** Down syndrome **Treatment Factors** Suprasellar radiation **Medical Conditions** Sickle cell disease Neurofibromatosis	**Treatment Factors** Radiation dose ≥ 55 Gy	**HISTORY** **Hemiparesis** **Hemiplegia** **Weakness** **Aphasia** (Yearly) **PHYSICAL** **Neurologic exam** (Yearly)	**Considerations for Further Testing and Intervention** Brain MRI with diffusion-weighted imaging with MR angiography as clinically indicated. Neurology/neurosurgery consultation and follow-up. Physical and occupational therapy as clinically indicated. Note: Revascularization procedures are likely helpful for moyamoya. Aspirin prophylaxis has not yet been shown to be beneficial for moyamoya or occlusive cerebral vasculopathy. **SYSTEM = CNS** **SCORE = 1**

SECTION 45 REFERENCES

Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. *Childs Nerv Syst*. May 2005;21(5):358-364.

Grenier Y, Tomita T, Marymont MH, Byrd S, Burrowes DM. Late postirradiation occlusive vasculopathy in childhood medulloblastoma. Report of two cases. *J Neurosurg*. Sep 1998;89(3):460-464.

Kestle JR, Hoffman HJ, Mock AR. Moyamoya phenomenon after radiation for optic glioma. *J Neurosurg*. Jul 1993;79(1):32-35.

Rudoltz MS, Regine WF, Langston JW, Sanford RA, Kovnar EH, Kun LE. Multiple causes of cerebrovascular events in children with tumors of the parasellar region. *J Neurooncol*. May 1998;37(3):251-261

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
46	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Craniofacial abnormalities**	**Host Factors** Younger age at treatment **Treatment Factors** Higher radiation dose	**Host Factors** Age < 5 years at time of treatment **Treatment Factors** Radiation dose ≥ 30 Gy	**HISTORY** **Psychosocial assessment, with attention to:** **Educational and/or vocational progress** **Depression** **Anxiety** **Post-traumatic stress** **Social withdrawal** (Yearly) **PHYSICAL** **Craniofacial abnormalities** (Yearly)	**Resources** FACES - The National Craniofacial Association www.faces-cranio.org **Considerations for Further Testing and Intervention** Reconstructive craniofacial surgical consultation. Consultation with psychologist in patients with adjustment disorders related to facial asymmetry/deformity. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 46 REFERENCES

Estilo CL, Huryn JM, Kraus DH, et al. 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*. Mar 2003;25(3):215-222.

Kaste SC, Chen G, Fontanesi J, Crom DB, Pratt CB. Orbital development in long-term survivors of retinoblastoma. *J Clin Oncol*. Mar 1997;15(3):1183-1189.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
47	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Chronic sinusitis**	**Treatment Factors** Radiation dose to sinuses ≥ 30 Gy Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Atopic history Hypogammaglobulinemia		**HISTORY** **Rhinorrhea** **Postnasal discharge** (Yearly) **PHYSICAL** **Nasal exam** **Sinuses** (Yearly)	**Considerations for Further Testing and Intervention** CT scan of sinuses as clinically indicated. Otolaryngology consultation as clinically indicated **SYSTEM = Immune** **SCORE = 1**

SECTION 47 REFERENCES

Ellingwood KE, Million RR. Cancer of the nasal cavity and ethmoid/sphenoid sinuses. *Cancer*. Apr 1979;43(4):1517-1526.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
48	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Overweight** Age 2-20 years: BMI for age ≥ 85th - < 95th percentile Age ≥ 21 years: BMI ≥ 25 - 29.9 **Obesity** Age 2-20 years: BMI for age≥ 95th percentile Age ≥ 21 years: BMI ≥ 30 **Info Link:** BMI=wt(kg)/ht(M^2) BMI calculator available on-line at: http://nhlbisupport.com/bmi/ Growth charts for patients < 21 years of age available on-line at: www.cdc.gov/growthcharts	**Host Factors** Younger at treatment **Treatment Factors** Higher cranial radiation dose Combined with corticosteroids **Medical Conditions** Familial dyslipidemia Growth hormone deficiency Hypothyroidism	**Host Factors** Age < 4 years old at time of treatment Female sex **Treatment Factors** Hypothalamic radiation dose ≥ 20 Gy **Medical Conditions** Inability to exercise	**PHYSICAL** **Height** **Weight** **BMI** **Blood pressure** (Yearly) **SCREENING** **Fasting blood glucose** **Fasting serum insulin** **Fasting lipid profile** (Every 2 years in overweight or obese patients. Every 5 years in patients of normal weight. More frequently if indicated based on patient evaluation.)	**Health Links** **Diet and Physical Activity** **Counseling** Counsel regarding obesity-related health risks **Considerations for Further Testing and Intervention** Consider evaluation for other co-morbid conditions including dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance. Nutritional counseling. Endocrine consultation for patients with dyslipidemia or hyperglycemia. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 48 REFERENCES

Brennan BM, Rahim A, Blum WF, Adams JA, Eden OB, Shalet SM. Hyperleptinaemia in young adults following cranial irradiation in childhood: growth hormone deficiency or leptin insensitivity? *Clin Endocrinol (Oxf)*. Feb 1999;50(2):163-169.

Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med*. Jan 14 1993;328(2):87-94.

Dalton VK, Rue M, Silverman LB, et al. Height and weight in children treated for acute lymphoblastic leukemia: relationship to CNS treatment. *J Clin Oncol*. Aug 1 2003;21(15):2953-2960.

Didi M, Didcock E, Davies HA, Ogilvy-Stuart AL, Wales JK, Shalet SM. High incidence of obesity in young adults after treatment of acute lymphoblastic leukemia in childhood. *J Pediatr*. Jul 1995;127(1):63-67.

Lustig RH, Rose SR, Burghen GA, et al. Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr*. Aug 1999;135(2 Pt 1):162-168.

Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. Apr 1 2003;21(7):1359-1365.

Reilly JJ, Ventham JC, Newell J, Aitchison T, Wallace WH, Gibson BE. Risk factors for excess weight gain in children treated for acute lymphoblastic leukaemia. *Int J Obes Relat Metab Disord*. Nov 2000;24(11):1537-1541.

Sklar CA, Mertens AC, Walter A, et al. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. *Med Pediatr Oncol*. Aug 2000;35(2):91-95.

Warner JT, Evans WD, Webb DK, Gregory JW. Body composition of long-term survivors of acute lymphoblastic leukaemia. *Med Pediatr Oncol*. Mar 2002;38(3):165-172.

RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
49	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal** **TBI**	**Metabolic syndrome** **Info Link:** The metabolic syndrome is a clustering of cardiovascular risk factors that may further increase risk for cardiovascular disease. Definitions of metabolic syndrome are evolving, but generally include a combination of obesity with insulin resistance, dyslipidemia, and elevated blood pressure. *Note: Patients who received TBI may develop features of metabolic syndrome without associated obesity.*	**Treatment Factors** Surgery in suprasellar region Prolonged corticosteroid therapy (e.g., for chronic GVHD) **Medical Conditions** Growth hormone deficiency Hypogonadism	**Host Factors** Obesity **Treatment Factors** Cranial radiation dose ≥ 18 Gy	**PHYSICAL** **Height** **Weight** **BMI** **Blood pressure** (Yearly) **SCREENING** **Fasting blood glucose** **Fasting serum insulin** **Fasting lipid profile** (Every 5 years. More frequently if indicated based on patient evaluation.)	**Health Links** **Diet and Physical Activity** **Counseling** Counsel regarding obesity-related health risks **Considerations for Further Testing and Intervention** Consider endocrine consult if insulin resistance/metabolic syndrome is suspected. Nutritional counseling. Cardiology consultation as clinically indicated. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

SECTION 49 REFERENCES

Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. Dec 4 2002;288(21):2709-2716.

Link K, Moell C, Garwicz S, et al. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. *J Clin Endocrinol Metab*. Oct 2004;89(10):5003-5012.

Mohn A, Di Marzio A, Capanna R, Fioritoni G, Chiarelli F. Persistence of impaired pancreatic beta-cell function in children treated for acute lymphoblastic leukaemia. *Lancet*. Jan 10 2004;363(9403):127-128.

Moschovi M, Trimis G, Apostolakou F, Papassotiriou I, Tzortzatou-Stathopoulou F. Serum lipid alterations in acute lymphoblastic leukemia of childhood. *J Pediatr Hematol Oncol*. May 2004;26(5):289-293.

Nuver J, Smit AJ, Postma A, Sleijfer DT, Gietema JA. The metabolic syndrome in long-term cancer survivors, an important target for secondary preventive measures. *Cancer Treat Rev*. Aug 2002;28(4):195-214.

Oeffinger KC, Buchanan GR, Eshelman DA, et al. Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. Oct 2001;23(7):424-430.

Talvensaari KK, Lanning M, Tapanainen P, Knip M. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. *J Clin Endocrinol Metab*. Aug 1996;81(8):3051-3055.

Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. Jun 3 2004;350(23):2362-2374.

RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
50	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal** **TBI**	**Growth hormone deficiency** **Info Link:** Growth charts available on-line at www.cdc.gov/growthcharts	**Host Factors** Younger age at treatment **Treatment Factors** Higher radiation doses Surgery in suprasellar region Pretransplant radiation TBI ≥ 10 Gy in single fraction TBI ≥ 12 Gy fractionated	**Treatment Factors** Radiation dose ≥ 18 Gy Pretransplant cranial radiation TBI given in single fraction	**HISTORY** **Assessment of nutritional status** (Every six months until growth is completed, then yearly) **PHYSICAL** **Height** **Weight** **BMI** (Every six months until growth is completed, then yearly) **Tanner staging** (Every six months until sexually mature)	**Health Links** **Growth Hormone Deficiency** See also: **Hypopituitarism** **Resources** www.magicfoundation.org **Considerations for Further Testing and Intervention** Obtain x-ray for bone age in poorly growing children. Endocrine consultation for: Height below 3rd percentile on growth chart; Drop ≥ 2 percentile rankings on growth chart; Growth velocity < 4-5 cm/year during childhood; Lack of pubertal growth spurt. Evaluate thyroid function in any poorly growing child. Consult with endocrinologist regarding risks/benefits of adult growth hormone replacement therapy. Consider bone density testing in patients who are growth hormone deficient. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 50 REFERENCES

Brownstein CM, Mertens AC, Mitby PA, et al. Factors that affect final height and change in height standard deviation scores in survivors of childhood cancer treated with growth hormone: a report from the childhood cancer survivor study. *J Clin Endocrinol Metab*. Sep 2004;89(9):4422-4427.

Costin G. Effects of low-dose cranial radiation on growth hormone secretory dynamics and hypothalamic-pituitary function. *Am J Dis Child*. Aug 1988;142(8):847-852.

Didcock E, Davies HA, Didi M, Ogilvy Stuart AL, Wales JK, Shalet SM. Pubertal growth in young adult survivors of childhood leukemia. *J Clin Oncol*. Oct 1995;13(10):2503-2507.

Frisk P, Arvidson J, Gustafsson J, Lonnerholm G. Pubertal development and final height after autologous bone marrow transplantation for acute lymphoblastic leukemia. *Bone Marrow Transplant*. Jan 2004;33(2):205-210.

Gleeson HK, Darzy K, Shalet SM. Late endocrine, metabolic and skeletal sequelae following treatment of childhood cancer. *Best Pract Res Clin Endocrinol Metab*. Jun 2002;16(2):335-348.

Merchant TE, Williams T, Smith JM, et al. Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. *Int J Radiat Oncol Biol Phys*. Sep 1 2002;54(1):45-50.

Ogilvy-Stuart AL, Shalet SM. Growth and puberty after growth hormone treatment after irradiation for brain tumours. *Arch Dis Child*. Aug 1995;73(2):141-146.

Packer RJ, Boyett JM, Janss AJ, et al. Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. *J Clin Oncol*. Jan 15 2001;19(2):480-487.

Sklar C, Mertens A, Walter A, et al. Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. *J Pediatr*. Jul 1993;123(1):59-64.

Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1113-1121.

RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
51	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Precocious puberty**	**Host Factors** Female sex Younger age at treatment **Treatment Factors** Radiation doses ≥ 18 Gy		**PHYSICAL** **Height** **Weight** **Tanner stage** **Testicular volume by Prader orchidometry (males only)** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Testosterone (males only)** **Estradiol (females only)** (As clinically indicated in patients with signs of accelerated pubertal progression and growth)	**Health Links** **Precocious Puberty** **Resources** www.magicfoundation.org **Considerations for Further Testing and Intervention** Obtain x-ray for bone age in rapidly growing children. Endocrine consultation for accelerated puberty (puberty in girl < 8 years old or boy < 9 years old). **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 51 REFERENCES

Mills JL, Fears TR, Robison LL, Nicholson HS, Sklar CA, Byrne J. Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia. *J Pediatr*. Oct 1997;131(4):598-602.

Oberfield SE, Soranno D, Nirenberg A, et al. Age at onset of puberty following high-dose central nervous system radiation therapy. *Arch Pediatr Adolesc Med*. Jun 1996;150(6):589-592.

Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. *J Clin Endocrinol Metab*. Jun 1994;78(6):1282-1286.

Quigley C, Cowell C, Jimenez M, et al. Normal or early development of puberty despite gonadal damage in children treated for acute lymphoblastic leukemia. *N Engl J Med*. Jul 20 1989;321(3):143-151.

Sklar CA. Growth and neuroendocrine dysfunction following therapy for childhood cancer. *Pediatr Clin North Am*. Apr 1997;44(2):489-503.

Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1113-1121.

RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
52	≥ 40 Gy to: **Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Hyperprolactinemia**	**Treatment Factors** Higher radiation dose Surgery or tumor in hypothalamic area	**Treatment Factors** Radiation dose ≥ 50 Gy	**HISTORY** **Galactorrhea** **Decreased libido (males)** **Menstrual history (females)** (Yearly) **SCREENING** **Prolactin level** (Males with galactorrhea or decreased libido; Females with galactorrhea or amenorrhea)	**Health Links** **Hyperprolactinemia** **Resources** www.magicfoundation.org **Considerations for Further Testing and Intervention** CT evaluation of sella turcica for pituitary adenoma in patients with hyperprolactinemia. Endocrine consultation for patients with hyperprolactinemia or galactorrhea (or amenorrhea in females). **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 52 REFERENCES

Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med*. Jan 14 1993;328(2):87-94.

Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1113-1121.

RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
53	≥ 40 Gy to: **Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Central hypothyroidism** **Info Link:** Central hypothyroidism includes thyroid-releasing and thyroid-stimulating hormone deficiency	**Treatment Factors** Higher radiation dose		**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** (Yearly; Consider more frequent screening during periods of rapid growth) **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** (Yearly; Consider more frequent screening during periods of rapid growth) **SCREENING** **TSH** **Free T4** (Yearly; Consider more frequent screening during periods of rapid growth)	**Health Links** **Thyroid Problems** See also: **Hypopituitarism** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Consider TSH surge testing. Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 53 REFERENCES

Lando A, Holm K, Nysom K, et al. Thyroid function in survivors of childhood acute lymphoblastic leukaemia: the significance of prophylactic cranial irradiation. *Clin Endocrinol (Oxf)*. Jul 2001;55(1):21-25.

Livesey EA, Brook CG. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours. *Arch Dis Child*. Apr 1989;64(4):593-595.

Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab*. Dec 1999;84(12):4472-4479.

Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Poulsen HS, Muller J. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. *J Clin Endocrinol Metab*. Jan 2003;88(1):136-140.

Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1113-1121.

RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
54	≥ 40 Gy to: **Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Gonadotropin deficiency** **Info Link:** Gonadotropin deficiency includes LH and FSH deficiency.	**Treatment Factors** Higher radiation dose		**MALES:** **HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** **Testicular volume by Prader orchdiometry** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Testosterone** (Baseline at age 14 **and** as clinically indicated in patients with delayed puberty and/or clinical signs and symptoms of testosterone deficiency) **Semen analysis** (As requested by patient and for evaluation of infertility)	**MALES:** **Health Links** **Male Health Issues** See also: **Hypopituitarism** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Consider bone density testing in patients who are gonadotropin deficient. **SYSTEM = Male reproductive** **SCORE = 1**
					FEMALES: **HISTORY** **Pubertal (onset, tempo)** **Menstrual/pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Estradiol** (Baseline at age 13, **and** as clinically indicated in patients with delayed puberty, irregular menses, primary or secondary amenorrhea, or clinical signs and symptoms of estrogen deficiency)	**FEMALES:** **Health Links** Female Health Issues See also: Hypopituitarism **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Consider bone density testing in patients who are gonadotropin deficient. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 54 REFERENCES

Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. *Endocr Relat Cancer*. Dec 2004;11(4):589-602.
Mills JL, Fears TR, Robison LL, Nicholson HS, Sklar CA, Byrne J. Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia. *J Pediatr*. Oct 1997;131(4):598-602.
Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. *J Clin Endocrinol Metab*. Jun 1994;78(6):1282-1286.
Quigley C, Cowell C, Jimenez M, et al. Normal or early development of puberty despite gonadal damage in children treated for acute lymphoblastic leukemia. *N Engl J Med*. Jul 20 1989;321(3):143-151.
Schmiegelow M, Lassen S, Poulsen HS, et al. Gonadal status in male survivors following childhood brain tumors. *J Clin Endocrinol Metab*. Jun 2001;86(6):2446-2452.

RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
55	≥ 40 Gy to: **Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal**	**Central adrenal insufficiency**	**Treatment Factors** Higher radiation dose Surgery or tumor in the suprasellar region	**Treatment Factors** Prior development of another hypothalamic-pituitary endocrinopathy	**HISTORY** **Failure to thrive** **Anorexia** **Dehydration** **Hypoglycemia** **Lethargy** **Unexplained hypotension** (Yearly) **SCREENING** **8:00 a.m. serum cortisol** (Yearly for at least 15 years after treatment and as clinically indicated)	**Health Links** **Central Adrenal Insufficiency** See also: **Hypopituitarism** **Resources** www.magicfoundation.org **Counseling** Counsel regarding corticosteroid replacement therapy and stress dosing. Counsel regarding Medical Alert bracelet. **Considerations for Further Testing and Intervention** Endocrine consultation for further evaluation and replacement steroids **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 55 REFERENCES

Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. *Endocr Relat Cancer*. Dec 2004;11(4):589-602.

Oberfield SE, Nirenberg A, Allen JC, et al. Hypothalamic-pituitary-adrenal function following cranial irradiation. *Horm Res*. 1997;47(1):9-16.

Rose SR, Danish RK, Kearney NS, et al. ACTH deficiency in childhood cancer survivors. *Pediatr Blood Cancer*. Feb 7 2005.

Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Lange M, Poulsen HS, Muller J. Assessment of the hypothalamo-pituitary-adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. *J Clin Endocrinol Metab*. Jul 2003;88(7):3149-3154.

Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1113-1121.

RADIATION

POTENTIAL IMPACT TO EYE

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
56	**Cranial** **Orbital/Eye** **TBI** **Info Link:** Radiation-related ocular complications other than cataracts are generally associated only with orbital/eye radiation or higher dose cranial radiation. However, patients with a history of an ocular tumor (e.g., retinoblastoma) are at higher risk for late-onset ocular complications and should receive ongoing follow-up by an ophthalmologist at least annually, and more frequently if clinically indicated.	**Cataracts**	**Treatment Factors** Radiation dose ≥ 10 Gy TBI ≥ 2 Gy in single fraction TBI ≥ 5 Gy fractionated Radiation combined with - Corticosteroids - Busulfan - Longer interval since treatment	**Treatment Factors** Radiation dose ≥ 15 Gy Fraction dose ≥ 2 Gy TBI ≥ 5 Gy in single fraction TBI ≥ 10 Gy fractionated Cranial/orbital/eye radiation combined with TBI	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** (Yearly) **PHYSICAL** **Visual acuity** **Funduscopic exam to evaluate for lens opacity** (Yearly) **SCREENING** **Evaluation by ophthalmologist** (Yearly for patients with ocular tumors [regardless of radiation dose] and for those who received TBI or ≥ 30 Gy cranial/orbital/eye radiation. Every 3 years for patients without ocular tumors who received <30 Gy.)	**Health Links** **Cataracts** **Considerations for Further Testing and Intervention** Ongoing ophthalmology follow-up for identified problems. Refer patients with visual deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Ocular** **SCORE = 1**

SECTION 56 REFERENCES

Abramson DH, Servodidio CA. Ocular complications due to cancer treatment. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood Cancer: Assessment and Management*. St. Louis: Mosby; 1994:111-131.

Holmstrom G, Borgstrom B, Calissendorff B. Cataract in children after bone marrow transplantation: relation to conditioning regimen. *Acta Ophthalmol Scand*. Apr 2002;80(2):211-215.

Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood*. May 1 2003;101(9):3373-3385.

van Kempen-Harteveld ML, Belkacemi Y, Kal HB, Labopin M, Frassoni F. Dose-effect relationship for cataract induction after single-dose total body irradiation and bone marrow transplantation for acute leukemia. *Int J Radiat Oncol Biol Phys*. Apr 1 2002;52(5):1367-1374.

van Kempen-Harteveld ML, Struikmans H, Kal HB, et al. Cataract after total body irradiation and bone marrow transplantation: degree of visual impairment. *Int J Radiat Oncol Biol Phys*. Apr 1 2002;52(5):1375-1380.

Zierhut D, Lohr F, Schraube P, et al. Cataract incidence after total-body irradiation. *Int J Radiat Oncol Biol Phys*. Jan 1 2000;46(1):131-135.

RADIATION

POTENTIAL IMPACT TO EYE (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
57	≥ 30 Gy to: **Cranial** **Orbital/Eye** **Info Link:** Radiation-related ocular complications other than cataracts are generally associated only with orbital/eye radiation or higher dose cranial radiation. However, patients with a history of an ocular tumor (e.g., retinoblastoma) are at higher risk for late-onset ocular complications and should receive ongoing follow-up by an ophthalmologist at least annually, and more frequently if clinically indicated.	**Ocular toxicity** Orbital hypoplasia Lacrimal duct atrophy Xerophthalmia (keratoconjunctivitis sicca) Keratitis Telangiectasias Retinopathy Optic chiasm neuropathy Enophthalmos Chronic painful eye Maculopathy Papillopathy Glaucoma **Info Link:** Reduced visual acuity may be associated with cataracts, retinal damage, and optic nerve damage.	**Treatment Factors** Higher radiation dose Higher daily fraction dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) [problems related to tearing]	**Host Factors** Chronic GVHD (xerophthalmia only) **Treatment Factors** Fraction dose ≥ 2 Gy	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** **Dry eye** **Persistent eye irritation** **Excessive tearing** **Light sensitivity** **Poor night vision** **Painful eye** (Yearly) **PHYSICAL** **Visual acuity** **Funduscopic exam** (Yearly) **SCREENING** **Evaluation by ophthalmologist** (Yearly)	**Health Links** **Eye Health** **Resources** FACES - The National Craniofacial Association website: www.faces-cranio.org **Considerations for Further Testing and Intervention** Consider every six month ophthalmology evaluation for patients with corneal damage (usually associated with xerophthalmia) or complex ocular problems. Refer patients with visual deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Ocular** **SCORE = 1**

SECTION 57 REFERENCES

Abramson DH, Servodidio CA. Ocular complications due to cancer treatment. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood Cancer: Assessment and Management.* St. Louis: Mosby; 1994:111-131.

Oberlin O, Rey A, Anderson J, et al. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment--results of an international workshop. *J Clin Oncol.* Jan 1 2001;19(1):197-204.

Parsons JT, Bova FJ, Mendenhall WM, Million RR, Fitzgerald CR. Response of the normal eye to high dose radiotherapy. *Oncology (Williston Park).* Jun 1996;10(6):837-847; discussion 847-838, 851-832.

Shields CL, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology.* Nov 2001;108(11):2116-2121.

Zettinig G, Hanselmayer G, Fueger BJ, et al. Long-term impairment of the lacrimal glands after radioiodine therapy: a cross-sectional study. *Eur J Nucl Med Mol Imaging.* Nov 2002;29(11):1428-1432.

RADIATION

POTENTIAL IMPACT TO EAR

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
58	≥ 30 Gy to: **Cranial** **Ear/Infratemporal** **Nasopharyngeal**	**Ototoxicity** Tympanosclerosis Otosclerosis Eustachian tube dysfunction Conductive hearing loss	**Host Factors** Younger age at treatment **Treatment Factors** Higher radiation dose **Medical Conditions** Chronic otitis Chronic cerumen impaction	**Treatment Factors** Dose ≥ 50 Gy	**HISTORY** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** (Yearly) **PHYSICAL** **Otoscopic exam** (Yearly) **SCREENING** **Complete pure tone audiogram or brainstem auditory evoked response [BAER, ABR]** (Yearly after completion of therapy for 5 years [for patients <10 years old, continue yearly until age 10], then every 5 years. If hearing loss is detected, test at least yearly or as recommended by audiologist. If clinical suspicion of hearing loss at any time, test as clinically indicated. If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions [OAEs].) **Info Link:** Complete pure tone audiogram should include testing of both ears: (1) Air conduction from 250 to 8000 Hz (2) Bone conduction if air conduction thresholds exceed bone by 15dB at any frequency (3) Speech discrimination evaluation. OAEs measure outer hair cell function only. Because carboplatin selectively damages inner hair cells, patients treated with carboplatin should not be evaluated with OAEs.	**Health Links** **Hearing Loss** **Educational Issues** **Considerations for Further Testing and Intervention** Audiology consultation for patients with progressive hearing loss. Otolaryngology consultation for patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Speech and language therapy for children with hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources. Consider specialized evaluation for specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**
		Sensorineural hearing loss Tinnitus	**Host Factors** Younger age at treatment CNS tumor CSF shunting **Treatment Factors** Higher radiation dose Conventional (non-conformal) radiation	**Treatment Factors** Radiation administered prior to platinum chemotherapy Combined with other ototoxic agents such as: - Cisplatin - Carboplatin in myeloablative doses - Aminoglycosides		

SECTION 58 REFERENCES

Freilich RJ, Kraus DH, Budnick AS, Bayer LA, Finlay JL. Hearing loss in children with brain tumors treated with cisplatin and carboplatin-based high-dose chemotherapy with autologous bone marrow rescue. *Med Pediatr Oncol*. Feb 1996;26(2):95-100.

Huang E, Teh BS, Strother DR, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. *Int J Radiat Oncol Biol Phys*. Mar 1 2002;52(3):599-605.

Johannesen TB, Rasmussen K, Winther FO, Halvorsen U, Lote K. Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. *Int J Radiat Oncol Biol Phys*. May 1 2002;53(1):86-90.

Kortmann RD, Kuhl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. *Int J Radiat Oncol Biol Phys*. Jan 15 2000;46(2):269-279.

Landier W, Merchant T. Adverse effects of cancer treatment on hearing. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. Survivors of Childhood and Adolescent Cancer: *A Multidisciplinary Approach, Second Edition*. Heidelberg, Germany: Springer-Verlag; 2005:109-123.

Merchant TE, Gould CJ, Xiong X, et al. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. *Int J Radiat Oncol Biol Phys*. Mar 15 2004;58(4):1194-1207.

Ondrey FG, Greig JR, Herscher L. Radiation dose to otologic structures during head and neck cancer radiation therapy. *Laryngoscope*. Feb 2000;110(2 Pt 1):217-221.

Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. Dec 1 2000;48(5):1489-1495.

Schell MJ, McHaney VA, Green AA, et al. Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. *J Clin Oncol*. Jun 1989;7(6):754-760.

Shearer PD. Hearing impairment In: Wallace H, Green D, eds. *Late Effects of Childhood Cancer*. London: Arnold; 2004: 49-54.

RADIATION

POTENTIAL IMPACT TO ORAL CAVITY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
59	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle**	**Xerostomia** **Salivary gland dysfunction**	**Treatment Factors** Head and neck radiation involving the parotid gland Higher radiation doses Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Salivary gland dose ≥ 30 Gy **Medical Conditions** Chronic GVHD	**HISTORY** **Xerostomia** (Yearly) **PHYSICAL** **Oral exam** (Yearly) **SCREENING** **Dental exam and cleaning** (Every six months)	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine); Regular dental care including fluoride applications **SYSTEM = Dental** **SCORE = 1**

SECTION 59 REFERENCES

Antin JH. Clinical practice. Long-term care after hematopoietic-cell transplantation in adults. *N Engl J Med*. Jul 4 2002;347(1):36-42.

Chao KS, Deasy JO, Markman J, et al. 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*. Mar 15 2001;49(4):907-916.

Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. May 15 1991;21(1):109-122.

Guchelaar HJ, Vermes A, Meerwaldt JH. Radiation-induced xerostomia: pathophysiology, clinical course and supportive treatment. *Support Care Cancer*. Jul 1997;5(4):281-288

RADIATION

POTENTIAL IMPACT TO ORAL CAVITY (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
60	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Dental abnormalities** Tooth/root agenesis Microdontia Root thinning/shortening Enamel dysplasia Periodontal disease Dental caries Malocclusion Temporomandibular joint dysfunction	**Host Factors** Younger age at treatment Gorlin's syndrome (nevoid basal cell carcinoma syndrome) **Treatment Factors** Higher radiation dose	**Host Factors** Age < 5 years at time of treatment **Treatment Factors** Dose ≥ 10 Gy	**PHYSICAL** **Oral exam** (Yearly) **SCREENING** **Dental exam and cleaning** (Every six months)	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Regular dental care including fluoride applications. Consultation with orthodontist experienced in management of irradiated childhood cancer survivors. Baseline panorex prior to dental procedures to evaluate root development. **SYSTEM = Dental** **SCORE = 1**

SECTION 60 REFERENCES

Goho C. Chemoradiation therapy: effect on dental development. *Pediatr Dent*. Jan-Feb 1993;15(1):6-12.

Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. *Med Pediatr Oncol*. Aug 1995;25(2):96-101.

Kaste SC, Hopkins KP, Jones D, Crom D, Greenwald CA, Santana VM. Dental abnormalities in children treated for acute lymphoblastic leukemia. *Leukemia*. Jun 1997;11(6):792-796.

Maguire A, Welbury RR. Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development. *Dent Update*. Jun 1996;23(5):188-194.

Raney RB, Asmar L, Vassilopoulou-Sellin R, et al. 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. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. *Med Pediatr Oncol*. Oct 1999;33(4):362-371.

Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. *Cancer*. Dec 15 1990;66(12):2645-2652

RADIATION

POTENTIAL IMPACT TO ORAL CAVITY (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
61	≥ 40 Gy to: **Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle**	**Osteoradionecrosis**	**Treatment Factors** Radiation dose to bone ≥ 45 Gy	**Treatment Factors** Radiation dose to bone ≥ 50 Gy	**HISTORY** **Impaired or delayed healing following dental work** **Persistent jaw pain or swelling** **Trismus** (As clinically indicated) **PHYSICAL** **Impaired wound healing** **Jaw swelling** **Trismus** (As clinically indicated)	**Health Links** **Osteoradionecrosis** **Considerations for Further Testing and Intervention** Imaging studies (x-ray, CT scan and/or MRI) may assist in making diagnosis. Surgical biopsy may be needed to confirm diagnosis. Consider hyperbaric oxygen treatments. **SYSTEM = Dental** **SCORE = 1**

SECTION 61 REFERENCES

Ashamalla HL, Ames JW, Uri A, Winkler P. Hyperbaric oxygen in the management of osteoradionecrosis. *Med Pediatr Oncol*. Jul 1996;27(1):48-53.

Duggal MS, Curzon ME, Bailey CC, Lewis IJ, Prendergast M. Dental parameters in the long-term survivors of childhood cancer compared with siblings. *Oral Oncol*. Sep 1997;33(5):348-353.

Estilo CL, Huryn JM, Kraus DH, et al. 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*. Mar 2003;25(3):215-222.

Nasman M, Forsberg CM, Dahllof G. Long-term dental development in children after treatment for malignant disease. *Eur J Orthod*. Apr 1997;19(2):151-159.

Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. Dec 1 2000;48(5):1489-1495

RADIATION

POTENTIAL IMPACT TO NECK/THYROID

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
62	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Thyroid nodules**	**Host Factors** Younger age at treatment Female sex **Treatment Factors** Higher radiation dose Thyroid gland directly in radiation field TBI	**Treatment Factors** Radiation dose ≥ 25 Gy	**PHYSICAL** **Thyroid exam** (Yearly)	**Health Links** **Thyroid Problems** **Considerations for Further Testing and Intervention** Ultrasound and FNA for evaluation of palpable nodule(s). Endocrine and/or surgical consultation for diagnostic biopsy or thyroidectomy. **SYSTEM = SMN** **SCORE = 1**

SECTION 62 REFERENCES

Black P, Straaten A, Gutjahr P. Secondary thyroid carcinoma after treatment for childhood cancer. *Med Pediatr Oncol*. Aug 1998;31(2):91-95.

Constine LS, Donaldson SS, McDougall IR, Cox RS, Link MP, Kaplan HS. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer*. Feb 15 1984;53(4):878-883.

DeGroot LJ. Effects of irradiation on the thyroid gland. *Endocrinol Metab Clin North Am*. Sep 1993;22(3):607-615.

Schneider AB, Shore-Freedman E, Weinstein RA. Radiation-induced thyroid and other head and neck tumors: occurrence of multiple tumors and analysis of risk factors. *J Clin Endocrinol Metab*. Jul 1986;63(1):107-112.

Sigurdson AJ, Ronckers CM, Mertens AC, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet*. Jun 28 2005;365(9476):2014-2023.

Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. Sep 2000;85(9):3227-3232.

RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
63	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Thyroid cancer**	**Host Factors** Younger age at treatment Female sex **Treatment Factors** ≥ 5 years after irradiation Thyroid gland directly in radiation field TBI Risk increased up to 30 Gy with a downturn of risk after 30 Gy		**PHYSICAL** **Thyroid exam** (Yearly)	**Health Links** **Thyroid Problems** **Considerations for Further Testing and Intervention** Ultrasound and FNA for evaluation of palpable nodule(s). Surgical consultation for resection. Nuclear medicine consultation for ablation of residual disease. Endocrine consultation for postoperative medical management. **SYSTEM = SMN** **SCORE = 1**

SECTION 63 REFERENCES

De Groot LJ. Effects of irradiation on the thyroid gland. *Endocrinol Metab Clin North Am*. Sep 1993;22(3):607-615.

Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1165-1170.

Hegedus L. Thyroid ultrasonography as a screening tool for thyroid disease. *Thyroid*. Nov 2004;14(11):879-880.

Inskip PD. Thyroid cancer after radiotherapy for childhood cancer. *Med Pediatr Oncol*. May 2001;36(5):568-573.

Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, Orecchia R. Radiotherapy-induced thyroid disorders. *Cancer Treat Rev*. Jun 2004;30(4):369-384.

Martinek A, Dvorackova J, Honka M, Horacek J, Klvana P. Importance of guided fine needle aspiration cytology (FNAC) for the diagnostics of thyroid nodules - own experience. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. Jul 2004;148(1):45-50.

Ron E, Saftlas AF. Head and neck radiation carcinogenesis: epidemiologic evidence. *Otolaryngol Head Neck Surg*. Nov 1996;115(5):403-408.

Schneider AB, Fogelfeld L. Radiation-induced endocrine tumors. *Cancer Treat Res*. 1997;89:141-161.

Sigurdson AJ, Ronckers CM, Mertens AC, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet*. Jun 28 2005;365(9476):2014-2023.

Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. Sep 2000;85(9):3227-3232.

RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
64	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Hypothyroidism**	**Host Factors** Female sex **Treatment Factors** Radiation dose ≥ 10 Gy Thyroid gland directly in radiation field TBI	**Treatment Factors** Radiation dose ≥ 20 Gy	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** (Yearly; Consider more frequent screening during periods of rapid growth) **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** (Yearly; Consider more frequent screening during periods of rapid growth) **SCREENING** **TSH** **Free T4** (Yearly; Consider more frequent screening during periods of rapid growth)	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 64 REFERENCES

Chin D, Sklar C, Donahue B, et al. Thyroid dysfunction as a late effect in survivors of pediatric medulloblastoma/primitive neuroectodermal tumors: a comparison of hyperfractionated versus conventional radiotherapy. *Cancer*. Aug 15 1997;80(4):798-804.

Constine LS, Donaldson SS, McDougall IR, Cox RS, Link MP, Kaplan HS. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer*. Feb 15 1984;53(4):878-883.

DeGroot LJ. Effects of irradiation on the thyroid gland. *Endocrinol Metab Clin North Am*. Sep 1993;22(3):607-615.

Katsanis E, Shapiro RS, Robison LL, et al. Thyroid dysfunction following bone marrow transplantation: long-term follow-up of 80 pediatric patients. *Bone Marrow Transplant*. May 1990;5(5):335-340.

Ogilvy-Stuart AL, Shalet SM, Gattamaneni HR. Thyroid function after treatment of brain tumors in children. *J Pediatr*. Nov 1991;119(5):733-737.

Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. Sep 2000;85(9):3227-3232.

RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
65	≥ 40 Gy to: **Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle**	**Hyperthyroidism**	**Treatment Factors** Higher radiation dose		**HISTORY** **Heat intolerance** **Tachycardia** **Palpitations** **Weight loss** **Emotional lability** **Muscular weakness** **Hyperphagia** (Yearly) **PHYSICAL** **Eyes** **Skin** **Thyroid** **Cardiac** **Neurologic** (Yearly) **SCREENING** **TSH** **Free T4** (Yearly)	**Health Links** **Thyroid Problems** **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 65 REFERENCES

Chin D, Sklar C, Donahue B, et al. Thyroid dysfunction as a late effect in survivors of pediatric medulloblastoma/primitive neuroectodermal tumors: a comparison of hyperfractionated versus conventional radiotherapy. *Cancer*. Aug 15 1997;80(4):798-804.

Constine LS, Donaldson SS, McDougall IR, Cox RS, Link MP, Kaplan HS. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer*. Feb 15 1984;53(4):878-883.

DeGroot LJ. Effects of irradiation on the thyroid gland. *Endocrinol Metab Clin North Am*. Sep 1993;22(3):607-615.

Katsanis E, Shapiro RS, Robison LL, et al. Thyroid dysfunction following bone marrow transplantation: long-term follow-up of 80 pediatric patients. *Bone Marrow Transplant*. May 1990;5(5):335-340.

Ogilvy-Stuart AL, Shalet SM, Gattamaneni HR. Thyroid function after treatment of brain tumors in children. *J Pediatr*. Nov 1991;119(5):733-737.

Sanders JE. Endocrine complications of high-dose therapy with stem cell transplantation. *Pediatr Transplant*. Jun 2004;8 Suppl 5:39-50.

Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. Aug 1 2001;6:G17-22.

Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. Sep 2000;85(9):3227-3232.

Sklar CA, Kim TH, Ramsay NK. Thyroid dysfunction among long-term survivors of bone marrow transplantation. *Am J Med*. Nov 1982;73(5):688-694.

RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
66	≥ 40 Gy to: **Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle**	**Carotid artery disease**			**HISTORY** **Memory impairment** (Yearly) **PHYSICAL** **Diminished carotid pulses** **Carotid bruits** **Abnormal neurologic exam (compromise of blood flow to brain)** (Yearly)	**Considerations for Further Testing and Intervention** Doppler ultrasound of carotid vessels as clinically indicated. MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated. Consider color Doppler 10 years after completion of radiation therapy to the neck as a baseline; refer to cardiologist if abnormal. **SYSTEM = Cardiovascular** **SCORE = 2A**

SECTION 66 REFERENCES

Grenier Y, Tomita T, Marymont MH, Byrd S, Burrowes DM. Late postirradiation occlusive vasculopathy in childhood medulloblastoma. Report of two cases. *J Neurosurg*. Sep 1998;89(3):460-464.

Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *JAMA*. Dec 3 2003;290(21):2831-2837.

Larsen RL, Barber G, Heise CT, August CS. Exercise assessment of cardiac function in children and young adults before and after bone marrow transplantation. *Pediatrics*. Apr 1992;89(4 Pt 2):722-729.

Liesner RJ, Leiper AD, Hann IM, Chessells JM. Late effects of intensive treatment for acute myeloid leukemia and myelodysplasia in childhood. *J Clin Oncol*. May 1994;12(5):916-924.

Rovelli A, Pezzini C, Silvestri D, Tana F, Galli MA, Uderzo C. Cardiac and respiratory function after bone marrow transplantation in children with leukaemia. *Bone Marrow Transplant*. Oct 1995;16(4):571-576

RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
67	≥ 40 Gy to: **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle**	**Subclavian artery disease**			**PHYSICAL** **Diminished brachial and radial pulses** **Pallor of upper extremities** **Coolness of skin** **Unequal blood pressure** (Yearly)	**Considerations for Further Testing and Intervention** Doppler ultrasound of subclavian vessels as clinically indicated. MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated. Consider color Doppler 10 years after completion of radiation therapy to the neck as a baseline; refer to cardiologist if abnormal. **SYSTEM = Cardiovascular** **SCORE = 2A**

SECTION 67 REFERENCES

Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *JAMA*. Dec 3 2003;290(21):2831-2837.

RADIATION

POTENTIAL IMPACT TO BREAST

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
68 (Female)	≥ 20 Gy to: **Mantle** **Mini-Mantle** **Mediastinal** **Chest (thorax)** **Axilla**	**Breast cancer**	**Host Factors** Family history of breast cancer **Treatment Factors** Higher radiation dose Longer time since radiation (≥ 5 years) **Info Link** There is currently a deficiency in the literature regarding whether or not TBI is a risk factor for the development of breast cancer. Monitoring of patients who received TBI should be determined on an individual basis.	**Host Factors** Female gender	**PHYSICAL** **Breast exam** (Yearly beginning at puberty until age 25, then every six months) **SCREENING** **Mammogram** (Beginning 8 years after radiation or at age 25, whichever occurs last) **Info Link:** Mammography is currently limited in its ability to evaluate the premenopausal breast. The role of MRI is evolving for screening of other populations at high risk for breast cancer (e.g., premenopausal known or likely carriers of gene mutation of known penetrance).	**Health Links** **Breast Cancer** **Counseling** Teach breast self-exam and counsel to perform monthly beginning at puberty. **Considerations for Further Testing and Intervention** Surgical consultation for diagnostic procedure in patients with breast mass or suspicious radiographic finding. Decisions regarding the use of HRT should be based on current literature and should take into consideration the risk/benefit ratio for individual patients. **SYSTEM = SMN** **SCORE = 1**

SECTION 68 REFERENCES

Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med*. Mar 21 1996;334(12):745-751.

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Goss PE, Sierra S. Current perspectives on radiation-induced breast cancer. *J Clin Oncol*. Jan 1998;16(1):338-347.

Guibout C, Adjadj E, Rubino C, et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol*. Jan 1 2005;23(1):197-204.

Kaste SC, Hudson MM, Jones DJ, et al. Breast masses in women treated for childhood cancer: incidence and screening guidelines. *Cancer*. Feb 15 1998;82(4):784-792.

Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med*. Oct 19 2004;141(8):590-597.

Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol*. Jun 2000;18(12):2435-2443.

Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA*. Jul 23 2003;290(4):465-475.

van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst*. Jul 2 2003;95(13):971-980.

Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT. Management of breast cancer after Hodgkin's disease. *J Clin Oncol*. Feb 2000;18(4):765-772.

RADIATION

POTENTIAL IMPACT TO BREAST (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
69 (Female)	**Mantle** **Mini-Mantle** **Mediastinal** **Chest (thorax)** **Whole lung** **Axilla** **TBI**	**Breast tissue hypoplasia**	**Host Factors** Prepubertal at time of breast irradiation **Treatment Factors** Higher radiation dose		**PHYSICAL** **Breast exam** (Yearly)	**Considerations for Further Testing and Intervention** Surgical consultation for breast reconstruction after completion of growth. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 69 REFERENCES

Furst CJ, Lundell M, Ahlback SO, Holm LE. Breast hypoplasia following irradiation of the female breast in infancy and early childhood. *Acta Oncol*. 1989;28(4):519-523.

Johnston KA, Vowels MR, Carroll S. Failure to lactate: an unexpected late effect of cranial radiation. *Med Pediatr Oncol* 2001;37(3):169.

Macklis RM, Oltikar A, Sallan SE. Wilms' tumor patients with pulmonary metastases. *Int J Radiat Oncol Biol Phys*. Oct 1991;21(5):1187-1193.

RADIATION

POTENTIAL IMPACT TO LUNGS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
70	**Mantle** **Mediastinal** **Chest (thorax)** **Whole lung** **TBI**	**Pulmonary toxicity** Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	**Host Factors** Younger age at irradiation **Treatment Factors** Radiation dose ≥ 10 Gy Chest radiation combined with TBI Radiation combined with: - Bleomycin - Busulfan - Carmustine (BCNU) - Lomustine (CCNU) - Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** Radiation dose ≥ 15 Gy TBI ≥ 6 Gy in single fraction TBI ≥ 12 Gy fractionated	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **PHYSICAL** **Pulmonary exam** (Yearly) **SCREENING** **Chest x-ray** **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: www.smokefree.gov **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Due to the potential pulmonary toxicity of this therapy, patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations. **SYSTEM = Pulmonary** **SCORE = 1**

SECTION 70 REFERENCES

Hinkle AS, Proukou C, Chen Y. Pulmonary effects of antineoplastic therapy. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach, Second Edition.* Heidelberg, Germany: Springer-Verlag; 2005:161-180.

Lund MB, Kongerud J, Nome O, et al. Lung function impairment in long-term survivors of Hodgkin's disease. *Ann Oncol.* May 1995;6(5):495-501.

Mertens AC, Yasui Y, Liu Y, et al. Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. *Cancer.* Dec 1 2002;95(11):2431-2441.

Nysom K, Holm K, Hertz H, Hesse B. Risk factors for reduced pulmonary function after malignant lymphoma in childhood. *Med Pediatr Oncol.* Apr 1998;30(4):240-248.

Nysom K, Holm K, Olsen JH, Hertz H, Hesse B. Pulmonary function after treatment for acute lymphoblastic leukaemia in childhood. *Br J Cancer.* Jul 1998;78(1):21-27.

Stolp B, Assistant Medical Director Divers Alert Network, Director Anesthesiology Emergency Airway Services, Durham, N.C. Risks associated with SCUBA diving in childhood cancer survivors. Personal communication to Landier W, Bhatia S Aug 23, 2002.

RADIATION

POTENTIAL IMPACT TO HEART

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
71	**Mantle** **Mediastinal** **Chest (thorax)** **Axilla** **Spine (thoracic)** **Whole abdomen** **All upper abdominal fields**	**Cardiac toxicity** Congestive heart failure Cardiomyopathy Pericarditis Pericardial fibrosis Valvular disease Myocardial infarction Arrhythmia Atherosclerotic heart disease	**Host Factors** Younger age at irradiation Family history of dyslipidemia Coronary artery disease **Treatment Factors** Radiation dose ≥ 20 Gy to chest TBI Combined with radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Combined with other cardiotoxic chemotherapy - Anthracyclines - Cyclophosphamide conditioning for HCT - Amsacrine **Medical Conditions** Hypertension Obesity Dyslipidemia Diabetes mellitus Congenital heart disease Febrile illness Pregnancy Premature ovarian failure (untreated) **Health Behaviors** Smoking Isometric exercise Drug use (e.g., cocaine, diet pills, ephedra)	**Host Factors** Female sex Black/ of African descent Younger than age 5 years at time of treatment **Treatment Factors** Anteriorly-weighted radiation fields Lack of subcarinal shielding Doses ≥ 30 Gy in patients who have received anthracyclines Doses ≥ 40 Gy in patients who have not received anthracyclines Longer time since treatment	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 years: Abdominal symptoms (nausea, vomiting)** (Yearly) **Info Link:** Exertional intolerance is uncommon in young patients (< 25 years). Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in young patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** (Yearly) **SCREENING** **Fasting glucose and lipid profile** (Every 3 to 5 years. If abnormal, refer for ongoing management.) **EKG (include evaluation of QTc interval)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.) **ECHO** (Baseline at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose - *see table at left*.)	**Health Links** **Heart Health** **Diet and Physical Activity** **Resources** A downloadable wallet card is available from the AHA website for patients requiring endocarditis prophylaxis: www.americanheart.org/downloadable/heart/1023826501754walletcard.pdf **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure, and heart-healthy diet. Counsel regarding endocarditis prophylaxis if valvular abnormalities present. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. Limited high repetition weight lifting (i.e., lifting a lighter weight with ease no more than 15 to 20 times in a row) is much less stressful to the heart and is more likely to be safe. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation for patients with subclinical abnormalities on screening evaluations or with left ventricular dysfunction, dysrhythmia or prolonged QTc interval. Additional cardiology evaluation for patients who are pregnant or planning pregnancy who: (1) received ≥ 30 Gy chest radiation, or (2) received chest radiation in combination with cardiotoxic chemotherapy (anthracyclines or high-dose cyclophosphamide). Evaluation to include echocardiogram before and periodically during pregnancy (especially during third trimester) and monitoring during labor and delivery due to risk of cardiac failure. Consider cardiology consultation (5 to 10 years after radiation) to evaluate risk for coronary artery disease in patients who received ≥ 40 Gy chest radiation alone or ≥ 30 Gy chest radiation plus anthracycline. Consider excess risk of isometric exercise program in any high-risk patient defined as needing screening every 1 or 2 years. **SYSTEM = Cardiovascular** **SCORE = 1**

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM

Age at Treatment*	Radiation Dose	Anthracycline Dose†	Recommended Frequency
< 5 years old	Any	None	Every 2 years
		Any	Every year
≥ 5 years old	<30 Gy	None	Every 5 years
	≥30 Gy	None	Every 2 years
	Any	< 300 mg/m²	Every 2 years
		≥ 300 mg/m²	Every year
Any age with serial decrease in function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)

†Based on equivalent mg of doxorubicin/daunorubicin

SECTION 71 REFERENCES

Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. *Crit Rev Oncol Hematol*. Jan 2003;45(1):55-75.

Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol*. Aug 1 2004;22(15):3139-3148.

Eames GM, Crosson J, Steinberger J, et al. Cardiovascular function in children following bone marrow transplant: a cross-sectional study. *Bone Marrow Transplant*. Jan 1997;19(1):61-66.

Glanzmann C, Kaufmann P, Jenni R, Hess OM, Huguenin P. Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol*. Jan 1998;46(1):51-62.

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*. Apr 1 2001;19(7):1926-1934.

Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol*. Jul 1993;11(7):1208-1215.

Hertenstein B, Stefanic M, Schmeiser T, et al. Cardiac toxicity of bone marrow transplantation: predictive value of cardiologic evaluation before transplant. *J Clin Oncol*. May 1994;12(5):998-1004.

Hogarty AN, Leahey A, Zhao H, et al. Longitudinal evaluation of cardiopulmonary performance during exercise after bone marrow transplantation in children. *J Pediatr*. Mar 2000;136(3):311-317.

Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA*. Dec 3 2003;290(21):2831-2837.

Jakacki RI, Goldwein JW, Larsen RL, Barber G, Silber JH. Cardiac dysfunction following spinal irradiation during childhood. *J Clin Oncol*. Jun 1993;11(6):1033-1038.

Lonnerholm G, Arvidson J, Andersson LG, Carlson K, Jonzon A, Sunnegardh J. Myocardial function after autologous bone marrow transplantation in children: a prospective long-term study. *Acta Paediatr*. Feb 1999;88(2):186-192.

Pihkala J, Saarinen UM, Lundstrom U, et al. Effects of bone marrow transplantation on myocardial function in children. *Bone Marrow Transplant*. Feb 1994;13(2):149-155.

RADIATION

POTENTIAL IMPACT TO SPLEEN

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
72	≥ 40 Gy to: **Spleen (entire)** **Whole abdomen** **Left Upper quadrant** **Inverted Y**	**Functional asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., Haemophilus influenzae, streptococcus pneumoniae, meningococcus)	**Treatment Factors** Higher radiation dose to entire spleen		**PHYSICAL** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** (When febrile T ≥ 101ºF) **SCREENING** **Blood culture** (When febrile T ≥ 101°F)	**Health Links** **Splenic Precautions** **Counseling** Medical alert bracelet/card noting functional asplenia; Counsel to avoid malaria and tick bites if living in or visiting endemic areas **Considerations for Further Testing and Intervention** In patients with T ≥ 101°F (38.3° C) or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC; toxic clinical appearance; fever ≥ 104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines. Pneumovax booster in patients ≥10 years old at ≥ 5 years after previous dose (AAP-CIDP Recommendations, 2003). **SYSTEM = Immune** **SCORE = 1**

SECTION 72 REFERENCES

Immunization in special clinical circumstances: asplenic children. In: Pickering LK, ed. *Red Book 2003: Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2003.

Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. *Eur J Haematol*. Nov 2003;71(5):319-326.

Coleman CN, McDougall IR, Dailey MO, Ager P, Bush S, Kaplan HS. Functional hyposplenia after splenic irradiation for Hodgkin's disease. *Ann Intern Med*. Jan 1982;96(1):44-47.

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
73	≥ 30 Gy to: **Cervical (neck)** **Spine (cervical, thoracic)** **Supraclavicular** **Mantle** **Mini-Mantle** **Mediastinal** **Chest (thorax)** **Whole abdomen** **All upper abdominal fields**	**Esophageal stricture**	**Treatment Factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, actinomycin) **Medical Conditions** Gastroesophageal reflux	**Treatment Factors** Radiation dose ≥ 40 Gy	**HISTORY** **Dysphagia** **Heartburn** (Yearly)	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Surgical and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 73 REFERENCES

Mahboubi S, Silber JH. Radiation-induced esophageal strictures in children with cancer. *Eur Radiol.* 1997;7(1):119-122.

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
74	≥ 30 Gy to: **Whole abdomen** **All upper abdominal fields**	**Hepatic fibrosis** **Cirrhosis**	**Treatment Factors** Higher radiation dose **Medical Conditions** Chronic hepatitis History of VOD **Health Behaviors** Alcohol use	**Treatment Factors** Dose ≥ 40 Gy to at least 1/3 of liver volume Dose 20-30 Gy to entire liver	**PHYSICAL** **Jaundice** **Spider angiomas** **Palmar erythema** **Xanthomata** **Hepatomegaly** **Splenomegaly** (Yearly) **SCREENING** **ALT** **AST** **Bilirubin** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.)	**Health Links** **Liver Health** **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 74 REFERENCES

Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. May 15 1991;21(1):109-122.

Jirtle RL, Anscher MS, Alati T. Radiation sensitivity of the liver. *Advances Rad Biol*. 1990;14:269-311.

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
75	≥ 30 Gy to: **Whole abdomen** **All upper abdominal fields**	**Cholelithiasis**	**Host Factors** Ileal conduit Obesity Pregnancy Family history of cholelithiasis **Treatment Factors** Abdominal surgery Abdominal radiation TPN		**HISTORY** **Colicky abdominal pain related to fatty food intake** **Excessive flatulence** (Yearly and PRN) **PHYSICAL** **RUQ or epigastric tenderness** **Positive Murphy's sign** (Yearly and PRN)	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Consider gallbladder ultrasound in patients with chronic abdominal pain **SYSTEM = GI/Hepatic** **SCORE = 2B**

SECTION 75 REFERENCES

Mahmoud H, Schell M, Pui CH. Cholelithiasis after treatment for childhood cancer. *Cancer*. Mar 1 1991;67(5):1439-1442.

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
76	≥ 30 Gy to: **Whole abdomen** **All upper abdominal fields** **Pelvic** **Spine (thoracic, lumbar, sacral)**	**Bowel obstruction**	**Treatment Factors** Higher radiation dose to bowel Abdominal surgery **Info Link** Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery	**Treatment Factors** Radiation dose ≥ 45 Gy (Obstruction may occur in people who received lower doses of abdominal radiation during childhood)	**HISTORY** **Abdominal pain** **Emesis** **Distention** **Vomiting** **Constipation** (With clinical symptoms of obstruction) **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** (With clinical symptoms of obstruction)	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Obtain KUB in patients with clinical symptoms of obstruction. Surgical consultation in patients unresponsive to medical management. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 76 REFERENCES

Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. May 15 1991;21(1):109-122.

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
77	≥ 30 Gy to: **Whole abdomen** **All upper abdominal fields** **Pelvic** **Spine (thoracic, lumbar, sacral)**	**Chronic enterocolitis** **Fistula** **Strictures**	**Treatment Factors** Higher radiation dose to bowel Abdominal surgery	**Treatment Factors** Radiation dose ≥ 45 Gy	**HISTORY** **Nausea** **Vomiting** **Abdominal pain** **Diarrhea** (Yearly)	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Serum protein and albumin yearly in patients with chronic diarrhea or fistula. Surgical and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 77 REFERENCES

Donaldson SS, Jundt S, Ricour C, Sarrazin D, Lemerle J, Schweisguth O. Radiation enteritis in children. A retrospective review, clinicopathologic correlation, and dietary management. *Cancer*. Apr 1975;35(4): 1167-1178.

Heyn R, Raney RB, Jr., Hays DM, et al. Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. *J Clin Oncol*. Apr 1992;10(4):614-623.

Raney B, Jr., Heyn R, Hays DM, et al. 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*. Apr 1 1993;71(7):2387-2394.

RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
78	≥ 30 Gy to: **Whole abdomen** **All upper abdominal fields** **Pelvic** **Spine (thoracic, lumbar, sacral)**	**Colorectal cancer** **Info Link:** Reports of colorectal cancer in cohorts of long-term survivors suggest that radiation likely increases risk, but the median age of onset is not as well established as that of secondary breast cancer following chest radiation. The expert panel agreed that early onset of screening is likely beneficial, and that a prudent course would be to initiate screening for colorectal cancer for those at highest risk (abdominal, pelvic, and/or spinal radiation ≥ 30 Gy) at age 35, or 10 years post radiation, whichever occurs last. Surveillance should be done via colonoscopy as per recommendations for populations at highest risk, with information from the first colonoscopy informing the frequency of follow-up testing.	**Host Factors** Current age ≥ 50 years **Treatment Factors** Higher radiation dose to bowel Higher daily dose fraction Combined with chemotherapy (especially alkylators) **Medical Conditions** Obesity **Health Behaviors** High fat/low fiber diet	**Host Factors** Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps, or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps in first degree relative	**SCREENING** **Colonoscopy** (Every 5 years [minimum] beginning at 10 years after radiation or at age 35 years [whichever occurs last]; more frequently if indicated based on colonoscopy results; Per the ACS, begin screening earlier for the following high-risk groups - HNPCC: at puberty; FAP: at age 21 years; IBD: 8 years after diagnosis of IBD; Information from the first colonoscopy will inform frequency of follow-up testing)	**Health Links** **Colorectal Cancer** **Considerations for Further Testing and Intervention** Surgical and/or oncology consultation as needed. **SYSTEM = SMN** **SCORE = 2A**

SECTION 78 REFERENCES

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol*. Jun 2000;18(12):2435-2443.

Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol*. Feb 2000;18(3):498-509

RADIATION

POTENTIAL IMPACT TO URINARY TRACT

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
79	**Whole abdomen** **All upper abdominal fields** **TBI** **Info Link:** Includes all upper abdominal fields except Paraaortic	**Renal toxicity** Renal insufficiency Hypertension	**Host Factors** Bilateral Wilms tumor Mononephric **Treatment Factors** Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Radiation dose ≥ 10 Gy TBI combined with radiation to the kidney Combined with other nephrotoxic agents such as: - Cisplatin - Carboplatin - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants **Medical Conditions** Diabetes mellitus Hypertension Nephrectomy	**Treatment Factors** Radiation dose ≥ 15 Gy TBI ≥ 6 Gy in single fraction TBI ≥ 12 Gy fractionated	**PHYSICAL** **Blood pressure** (Yearly) **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** (Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated.) **Urinalysis** (Yearly)	**Health Links** **Kidney Health** See also: **Single Kidney Health** **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 1**

SECTION 79 REFERENCES

Cassady JR. Clinical radiation nephropathy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1249-1256.

Fels LM, Bokemeyer C, van Rhee J, Schmoll HJ, Stolte H. Evaluation of late nephrotoxicity in long-term survivors of Hodgkin's disease. *Oncology*. Jan-Feb 1996;53(1):73-78.

Frisk P, Bratteby LE, Carlson K, Lonnerholm G. Renal function after autologous bone marrow transplantation in children: a long-term prospective study. *Bone Marrow Transplant*. Jan 2002;29(2):129-136.

Keane WF, Crosson JT, Staley NA, Anderson WR, Shapiro FL. Radiation-induced renal disease. A clinicopathologic study. *Am J Med*. Jan 1976;60(1):127-137.

Kumar M, Kedar A, Neiberger RE. Kidney function in long-term pediatric survivors of acute lymphoblastic leukemia following allogeneic bone marrow transplantation. *Pediatr Hematol Oncol*. Jul-Aug 1996;13(4):375-379.

Ritchey ML, Green DM, Thomas PR, et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. *Med Pediatr Oncol*. Feb 1996;26(2):75-80.

RADIATION

POTENTIAL IMPACT TO URINARY TRACT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
80	≥ 30 Gy to: **Whole abdomen** **Pelvic** **Spine (sacral)**	**Hemorrhagic cystitis**	**Treatment Factors** Higher radiation dose (≥ 30 Gy to entire bladder; ≥ 60 Gy to portion of bladder)	**Treatment Factors** Combined with cyclophosphamide and/or ifosfamide	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly) **SCREENING** **Urinalysis** (Yearly)	**Health Links** **Bladder Health** **Counseling** Counsel to promptly report dysuria or gross hematuria **Considerations for Further Testing and Intervention** Urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as ≥ 5 RBC/HFP on at least 2 occasions). Nephrology or Urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/creatinine ratio. Urology referral for patients with culture negative macroscopic hematuria. **SYSTEM = Urinary** **SCORE = 2A**

SECTION 80 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.

Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1257-1280.

Piver MS, Rose PG. Long-term follow-up and complications of infants with vulvovaginal embryonal rhabdomyosarcoma treated with surgery, radiation therapy, and chemotherapy. *Obstet Gynecol*. Mar 1988;71(3 Pt 2):435-437.

Raney B, Jr., Heyn R, Hays DM, et al. 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*. Apr 1 1993;71(7):2387-2394.

Stillwell TJ, Benson RC, Jr. Cyclophosphamide-induced hemorrhagic cystitis. A review of 100 patients. *Cancer*. Feb 1 1988;61(3):451-457.

Stillwell TJ, Benson RC, Jr., Burgert EO, Jr. Cyclophosphamide-induced hemorrhagic cystitis in Ewing's sarcoma. *J Clin Oncol*. Jan 1988;6(1):76-82.

Yeung CK, Ward HC, Ransley PG, Duffy PG, Pritchard J. Bladder and kidney function after cure of pelvic rhabdomyosarcoma in childhood. *Br J Cancer*. Nov 1994;70(5):1000-1003.

RADIATION

POTENTIAL IMPACT TO URINARY TRACT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
81	≥ 30 Gy to: **Whole abdomen** **Pelvic** **Spine (sacral)**	**Urinary tract toxicity** Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis	**Treatment Factors** Higher cumulative radiation dose (≥ 45 Gy) Radiation to entire bladder Combined with: - Cyclophosphamide - Ifosfamide - Vincristine		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly) **SCREENING** **Urinalysis** (Yearly)	**Health Links** **Bladder Health** **Considerations for Further Testing and Intervention** Urologic consultation for patients with incontinence or dysfunctional voiding. **SYSTEM = Urinary** **SCORE = 1**

SECTION 81 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.

Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. Mar 30 1995;31(5):1257-1280.

Piver MS, Rose PG. Long-term follow-up and complications of infants with vulvovaginal embryonal rhabdomyosarcoma treated with surgery, radiation therapy, and chemotherapy. *Obstet Gynecol*. Mar 1988;71(3 Pt 2):435-437.

Raney B, Jr., Heyn R, Hays DM, et al. 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*. Apr 1 1993;71(7):2387-2394.

Yeung CK, Ward HC, Ransley PG, Duffy PG, Pritchard J. Bladder and kidney function after cure of pelvic rhabdomyosarcoma in childhood. *Br J Cancer*. Nov 1994;70(5):1000-1003.

RADIATION

POTENTIAL IMPACT TO URINARY TRACT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
82	**Whole abdomen** **Pelvic** **Spine (sacral)** **Info Link:** Applies to sacral spine at doses ≥ 30 Gy only.	**Bladder malignancy**	**Treatment Factors** Radiation to pelvis Combined with: - Cyclophosphamide - Ifosfamide **Health Behaviors** Alcohol use Smoking		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly) **SCREENING** **Urinalysis** (Yearly)	**Health Links** **Bladder Health** **Counseling** Counsel to promptly report dysuria or gross hematuria **Considerations for Further Testing and Intervention** Urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as ≥ 5 RBC/HFP on at least 2 occasions). Nephrology or Urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/creatinine ratio. Urology referral for patients with culture negative macroscopic hematuria. **SYSTEM = SMN** **SCORE = 2A**

SECTION 82 REFERENCES

Kersun LS, Wimmer RS, Hoot AC, Meadows AT. Secondary malignant neoplasms of the bladder after cyclophosphamide treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer*. Mar 2004;42(3):289-291.

Pedersen-Bjergaard J, Ersboll J, Hansen VL, et al. Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med*. Apr 21 1988;318(16):1028-1032.

Travis LB, Curtis RE, Glimelius B, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst*. Apr 5 1995;87(7):524-530.

RADIATION

POTENTIAL IMPACT TO FEMALE REPRODUCTIVE SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
83 (Female)	**Whole abdomen** **Pelvic** **Spine (lumbar, sacral)** **TBI** **Info Link:** Applies to all pelvic fields except iliac/inguinal. Applies to lumbar and sacral spine at doses ≥ 25 Gy.	**Uterine vascular insufficiency** (resulting in adverse pregnancy outcomes, such as spontaneous abortion, neonatal death, low-birth weight infant, fetal malposition, and premature labor) **Info Link:** 10% of girls with Wilms tumor have congenital uterine anomalies.	**Host Factors** Females with Wilms tumor and associated müllerian anomalies **Treatment Factors** Higher radiation dose to pelvis	**Host Factors** Prepubertal at treatment **Treatment Factors** Radiation dose ≥ 30 Gy TBI	**HISTORY** **Pregnancy** **Childbirth history** (Yearly and as clinically indicated)	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Considerations for Further Testing and Intervention** Consider high-level ultrasound evaluation of genitourinary tract after pubertal development as clinically indicated in patients contemplating pregnancy. High-risk obstetrical care during pregnancy. **SYSTEM = Female reproductive** **SCORE = 2B**

SECTION 83 REFERENCES

Blatt J. Pregnancy outcome in long-term survivors of childhood cancer. *Med Pediatr Oncol*. Jul 1999;33(1):29-33.

Byrne J. Infertility and premature menopause in childhood cancer survivors. *Med Pediatr Oncol*. Jul 1999;33(1):24-28.

Byrne J, Mulvihill JJ, Connelly RR, et al. Reproductive problems and birth defects in survivors of Wilms' tumor and their relatives. *Med Pediatr Oncol*. 1988;16(4):233-240.

Byrne J, Nicholson HS. Excess risk for Mullerian duct anomalies in girls with Wilms tumor. *Med Pediatr Oncol*. Apr 2002;38(4):258-259.

Critchley HO. Factors of importance for implantation and problems after treatment for childhood cancer. *Med Pediatr Oncol*. Jul 1999;33(1):9-14.

Green DM, Peabody EM, Nan B, Peterson S, Kalapurakal JA, Breslow NE. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol*. May 15 2002;20(10):2506-2513.

Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. *Hosp Med*. Aug 2000;61(8):550-557.

RADIATION

POTENTIAL IMPACT TO FEMALE REPRODUCTIVE SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
84 (Female)	**Whole abdomen** **Pelvic** **Spine (lumbar, sacral)** **TBI** **Info Link:** Applies to lumbar and sacral spine at doses ≥ 25 Gy only.	**Gonadal dysfunction (ovarian)** Delayed/arrested puberty Premature menopause Infertility	**Host Factors** Older age at irradiation **Treatment Factors** Prepubertal female: Radiation dose ≥10 Gy Pubertal female: Radiation dose ≥ 5 Gy Combined with alkylating agent chemotherapy Longer time since treatment	**Treatment Factors** Prepubertal female: Radiation dose ≥15 Gy Pubertal female: Radiation dose ≥10 Gy Combined with cyclophosphamide conditioning for HCT	**HISTORY** **Pubertal (onset, tempo)** **Menstrual/pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Estradiol** (Baseline at age 13, **and** as clinically indicated in patients with delayed puberty, irregular menses or primary or secondary amenorrhea, clinical signs and symptoms of estrogen deficiency)	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to radiation. Recovery of fertility may occur years after therapy. Counsel regarding risks and benefits of HRT. **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed/arrested puberty or persistently abnormal hormone levels. Gynecology or endocrinology consultation for HRT. Consider evaluation for conditions exacerbated by hypogonadism (e.g., osteopenia/osteoporosis). Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 84 REFERENCES

Bath LE, Wallace WH, Critchley HO. Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. *BJOG*. Feb 2002;109(2):107-114.

Hamre MR, Robison LL, Nesbit ME, et al. Effects of radiation on ovarian function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Childrens Cancer Study Group. *J Clin Oncol*. Nov 1987;5(11):1759-1765.

Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. *Endocrinol Metab Clin North* Am. Dec 1998;27(4):927-943.

Livesey EA, Brook CG. Gonadal dysfunction after treatment of intracranial tumours. *Arch Dis Child*. May 1988;63(5):495-500.

Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys*. Mar 15 2000;46(5):1239-1246.

Papadakis V, Vlachopapadopoulou E, Van Syckle K, et al. Gonadal function in young patients successfully treated for Hodgkin disease. *Med Pediatr Oncol*. May 1999;32(5):366-372.

Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol*. Jul 1999;33(1):2-8.

Stillman RJ, Schinfeld JS, Schiff I, et al. Ovarian failure in long-term survivors of childhood malignancy. *Am J Obstet Gynecol*. Jan 1981;139(1):62-66.

Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. *Hosp Med*. Aug 2000;61(8):550-557

RADIATION

POTENTIAL IMPACT TO FEMALE REPRODUCTIVE SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
85 (Female)	**Pelvic**	**Vaginal fibrosis/stenosis**	**Host Factors** Vaginal tumor or pelvic tumor adjacent to vagina **Treatment Factors** Prepubertal female: Radiation dose ≥ 25 Gy Postpubertal female: Radiation dose ≥ 50 Gy **Medical Conditions** Chronic GVHD	**Treatment Factors** Prepubertal female: Radiation dose ≥ 35 Gy Postpubertal female: Radiation dose ≥ 55 Gy	**HISTORY** **Psychosocial assessment** **Dyspareunia** **Vulvar pain** **Post-coital bleeding** **Difficulty with tampon insertion** (Yearly)	**Considerations for Further Testing and Intervention** Gynecologic consultation for management. Psychological consultation in patients with emotional difficulties. **SYSTEM = Female reproductive** **SCORE = 2A**

SECTION 85 REFERENCES

Flamant F, Gerbaulet A, Nihoul-Fekete C, Valteau-Couanet D, Chassagne D, Lemerle J. Long-term sequelae of conservative treatment by surgery, brachytherapy, and chemotherapy for vulval and vaginal rhab domyosarcoma in children. *J Clin Oncol*. Nov 1990;8(11):1847-1853.

Spunt SL, Sweeney TA, Hudson MM, Billups CA, Krasin MJ, Hester AL. Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. *J Clin Oncol*. Oct 1 2005;23(28):7143-7151.

RADIATION

POTENTIAL IMPACT TO MALE REPRODUCTIVE SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
86 (Male)	**Pelvic** **Testicular** **TBI**	**Gonadal dysfunction (testicular):** **Germ cell failure** Oligospermia Azoospermia Infertility	**Treatment Factors** Radiation dose to testes: - 1 to 3 Gy: Azoospermia may be reversible - 3 to 6 Gy: Azoospermia possibly reversible (but unlikely)	**Treatment Factors** Radiation dose to testes ≥ 6 Gy: Azoospermia likely permanent	**SCREENING** **Semen analysis** (As requested by patient and for evaluation of infertility. Periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years post therapy.)	**Health Links** **Male Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to radiation. Recovery of fertility may occur years after therapy. **Considerations for Further Testing and Intervention** Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies. Testing for Inhibin B can be considered in conjunction with FSH as an indicator of germ cell function. **SYSTEM = Male reproductive** **SCORE = 1**

SECTION 86 REFERENCES

Bordallo MA, Guimaraes MM, Pessoa CH, et al. Decreased serum inhibin B/FSH ratio as a marker of Sertoli cell function in male survivors after chemotherapy in childhood and adolescence. *J Pediatr Endocrinol Metab*. Jun 2004;17(6):879-887.

Goldman S, Johnson FL. Effects of chemotherapy and irradiation on the gonads. *Endocrinol Metab Clin North Am*. Sep 1993;22(3):617-629.

Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. *Endocrinol Metab Clin North Am*. Dec 1998;27(4):927-943.

Kinsella TJ. Effects of radiation therapy and chemotherapy on testicular function. *Prog Clin Biol Res*. 1989;302:157-171; discussion 172-157.

Rowley MJ, Leach DR, Warner GA, Heller CG. Effect of graded doses of ionizing radiation on the human testis. *Radiat Res*. Sep 1974;59(3):665-678.

Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol*. Jul 1999;33(1):2-8.

Sklar CA, Robison LL, Nesbit ME, et al. 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*. Dec 1990;8(12):1981-1987.

Simon B, Lee SJ, Partridge AH, Runowicz CD. Preserving fertility after cancer. *CA Cancer J Clin*. Jul-Aug 2005;55(4):211-228; quiz 263-214.

Wallace WH, Thomson AB. Preservation of fertility in children treated for cancer. *Arch Dis Child*. Jun 2003;88(6):493-496.

Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. *Hosp Med*. Aug 2000;61(8):550-557.

RADIATION

POTENTIAL IMPACT TO MALE REPRODUCTIVE SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
87 (Male)	≥ 20 Gy to: **Pelvic** **Testicular**	**Gonadal dysfunction (testicular):** **Leydig cell dysfunction** Delayed/arrested puberty Hypogonadism	**Treatment Factors** Testicular irradiation combined with head/brain irradiation	**Treatment Factors** Combined with: - Alkylating agents - Cyclophosphamide conditioning for HCT	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** **Testicular volume by Prader orchdiometry** (Yearly until sexually mature) **SCREENING** **FSH, LH, testosterone** (Baseline at age 14, **and** as clinically indicated in patients with delayed puberty or clinical signs and symptoms of testosterone deficiency)	**Health Links** **Male Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Urology or endocrinology consultation for HRT. Consider evaluation for conditions exacerbated by hypogonadism (e.g., osteopenia/osteoporosis). **SYSTEM = Male reproductive** **SCORE = 1**

SECTION 87 REFERENCES

Goldman S, Johnson FL. Effects of chemotherapy and irradiation on the gonads. *Endocrinol Metab Clin North Am*. Sep 1993;22(3):617-629.

Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. *Endocrinol Metab Clin North Am*. Dec 1998;27(4):927-943.

Kinsella TJ. Effects of radiation therapy and chemotherapy on testicular function. *Prog Clin Biol Res*. 1989;302:157-171; discussion 172-157.

Rowley MJ, Leach DR, Warner GA, Heller CG. Effect of graded doses of ionizing radiation on the human testis. *Radiat Res*. Sep 1974;59(3):665-678.

Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol*. Jul 1999;33(1):2-8.

Sklar CA, Robison LL, Nesbit ME, et al. 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*. Dec 1990;8(12):1981-1987.

RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
88	**All neck fields** **All chest fields** **Whole abdomen** **All upper abdominal fields** **All extremity fields** **Pelvic** **All spinal fields** **Info Link:** Applies to spine at doses ≥ 12 Gy only.	**Musculoskeletal growth problems** Hypoplasia Fibrosis Reduced or uneven growth Shortened trunk height (trunk radiation) Limb length discrepancy (extremity radiation)	**Host Factors** Younger age at treatment **Treatment Factors** Higher cumulative radiation dose Larger radiation treatment field Higher radiation dose per fraction	**Host Factors** Prepubertal at treatment **Treatment Factors** Epiphysis in treatment field Dose ≥ 20 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Height** **Weight** (Yearly) **Sitting height** (Yearly for patients who had trunk radiation) **Limb lengths** (Yearly for patients who had extremity radiation)	**Counseling** Counsel regarding increased risk of fractures in weight-bearing irradiated bones **Considerations for Further Testing and Intervention** Orthopedic consultation for any deficit noted in growing child. Consider plastic surgery consult for reconstruction. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 88 REFERENCES

Donaldson SS. Pediatric patients: tolerance levels and effects of treatment. In: Vaeth JM, Meyer JL, eds. *Frontiers of Radiation Therapy and Oncology*. Vol 23. New York, NY: Karger; 1989:390-407.

Fletcher BD. Effects of pediatric cancer therapy on the musculoskeletal system. *Pediatr Radiol*. Aug 1997;27(8):623-636.

Hogeboom CJ, Grosser SC, Guthrie KA, Thomas PR, D'Angio GJ, Breslow NE. Stature loss following treatment for Wilms tumor. *Med Pediatr Oncol*. Feb 2001;36(2):295-304.

Katzman H, Waugh T, Berdon W. Skeletal changes following irradiation of childhood tumors. *J Bone Joint Surg Am*. Jul 1969;51(5):825-842.

Merchant TE, Nguyen L, Nguyen D, Wu S, Hudson MM, Kaste SC. Differential attenuation of clavicle growth after asymmetric mantle radiotherapy. *Int J Radiat Oncol Biol Phys*. Jun 1 2004;59(2):556-561.

Noorda EM, Somers R, van Leeuwen FE, Vulsma T, Behrendt H. Adult height and age at menarche in childhood cancer survivors. *Eur J Cancer*. Mar 2001;37(5):605-612.

Probert JC, Parker BR. The effects of radiation therapy on bone growth. *Radiology*. Jan 1975;114(1):155-162.

Probert JC, Parker BR, Kaplan HS. Growth retardation in children after megavoltage irradiation of the spine. *Cancer*. Sep 1973;32(3):634-639.

RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
89	**Mantle** **Mini-Mantle** **Mediastinal** **Whole lung** **Chest (thorax)** **Whole abdomen** **All upper abdominal fields** **Pelvic** **Spine (lumbar, sacral, thoracic)** **Info Link:** Applies to spine at doses ≥ 12 Gy only.	**Scoliosis**	**Host Factors** Younger age at irradiation Paraspinal malignancies **Treatment Factors** Hemithoracic or abdominal radiation Hemithoracic, abdominal or spinal surgery Radiation of only a portion of (rather than whole) vertebral body **Info Link** With contemporary treatment approaches, scoliosis is infrequently seen as a consequence of radiation unless the patient has also undergone surgery to the hemithorax, abdomen or spine	**Treatment Factors** Radiation doses ≥ 20 Gy (lower doses for infants) Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Spine exam for scoliosis** (Yearly until growth completed. May need more frequent assessment during puberty.)	**Health Links** **Scoliosis and Kyphosis** **Considerations for Further Testing and Intervention** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on radiographic exam. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 89 REFERENCES

Marcus RB, DiCaprio MR, Lindskog DM, McGrath BE, Gamble K, Scarborough M. Musculoskeletal, Integument, Breast. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach, Second Edition*. Heidelberg, Germany: Springer-Verlag; 2005:262-269.

Paulino AC, Mayr NA, Simon JH, Buatti JM. Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. *Int J Radiat Oncol Biol Phys*. Mar 15 2002;52(4):1025-1031.

Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys*. Mar 15 2000;46(5):1239-1246.

RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
90	**Mantle** **Mini-Mantle** **Mediastinal** **Whole lung** **Chest (thorax)** **Whole abdomen** **All upper abdominal fields** **Spine (thoracic)** **Info Link:** Applies to thoracic spine at doses ≥ 30 Gy only.	**Kyphosis**	**Host Factors** Younger age at irradiation Paraspinal malignancies Neurofibromatosis	**Treatment Factors** Radiation doses ≥ 20 Gy (lower doses for infants) Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Spine exam for kyphosis** (Yearly until growth completed. May need more frequent assessment during puberty.)	**Health Links** **Scoliosis and Kyphosis** **Considerations for Further Testing and Intervention** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on radiographic exam **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 90 REFERENCES

Marcus RB, DiCaprio MR, Lindskog DM, McGrath BE, Gamble K, Scarborough M. Musculoskeletal, Integument, Breast. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. *Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach, Second Edition*. Heidelberg, Germany: Springer-Verlag; 2005:262-269.

Paulino AC, Mayr NA, Simon JH, Buatti JM. Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. *Int J Radiat Oncol Biol Phys*. Mar 15 2002;52(4):1025-1031.

Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys*. Mar 15 2000;46(5):1239-1246.

RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
91	≥ 40 Gy to: **All neck fields** **All chest fields** **Whole abdomen** **All upper abdominal fields** **Pelvic** **All spinal fields** **All extremity fields**	**Radiation-induced fracture**	**Treatment Factors** History of surgery to cortex of bone	**Treatment Factors** Radiation dose ≥ 50 Gy to bone	**PHYSICAL** **Pain, swelling, deformity of bone** (As Indicated)	**Considerations for Further Testing and Intervention** Radiograph of affected bone as clinically indicated. Orthopedic evaluation as clinically indicated. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 91 REFERENCES

Paulino AC. Late effects of radiotherapy for pediatric extremity sarcomas. *Int J Radiat Oncol Biol Phys*. Sep 1 2004;60(1):265-274.

Wagner LM, Neel MD, Pappo AS, et al. Fractures in pediatric Ewing sarcoma. *J Pediatr Hematol Oncol*. Dec 2001;23(9):568-571.

RADIATION

TBI

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
38 TBI	**All Radiation Fields** (Including TBI) **Info Link:** General factors influencing radiation toxicity include daily fraction size, cumulative dose, age of patient at irradiation and type of radiation used. Toxicity may not be manifest until growth is completed or patient ages.	**Secondary benign or malignant neoplasm** Occurring in or near radiation field **Info Link:** Patients with bilateral or familial retinoblastoma (implying a germline mutation) are at increased risk for developing second malignant neoplasms	**Host Factors** Cancer predisposing mutation (e.g., p53, RB1, NF1) Younger age at treatment **Treatment Factors** High cumulative radiation dose Large radiation treatment volumes Alkylating agent exposure	**Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Inspection and palpation of skin and soft tissues in irradiated field(s)** (Yearly) **SCREENING** **Other evaluations based on treatment volumes** (See recommendations for specific fields)	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** There is currently a deficiency in the literature regarding whether or not TBI is a risk factor for the development of breast cancer. Monitoring for breast cancer in females who received TBI should be determined on an individual basis. Surgical and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 38 TBI REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Forrest DL, Nevill TJ, Naiman SC, et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. *Bone Marrow Transplant*. Nov 2003;32(9):915-923.

Howe R, Micallef IN, Inwards DJ, et al. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. *Bone Marrow Transplant*. Aug 2003;32(3):317-324.

Kolb HJ, Socie G, Duell T, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Ann Intern Med*. Nov 16 1999;131(10):738-744.

Menu-Branthomme A, Rubino C, Shamsaldin A, et al. Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. *Int J Cancer*. May 20 2004;110(1):87-93.

Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst*. Apr 18 2001;93(8):618-629.

Rowlings PA, Curtis RE, Passweg JR, et al. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *J Clin Oncol*. Oct 1999;17(10):3122-3127.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
39 TBI	**All Radiation Fields** (Including TBI)	**Dysplastic nevi** **Skin cancer** Basal cell carcinoma Squamous cell carcinoma Melanoma	**Host Factors** Gorlin's syndrome (nevoid basal cell carcinoma syndrome)	**Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**HISTORY** **Skin lesions** **Changing moles (asymmetry, bleeding, increasing size, borders)** (Yearly) **PHYSICAL** **Dermatologic exam of irradiated fields** (Yearly)	**Health Links** **Skin Health** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Dermatology consultation for evaluation and monitoring of atypical nevi. Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 39 TBI REFERENCES

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.

Cancer Prevention and Early Detection Facts and Figures: American Cancer Society; 2005.

Curtis RE, Metayer C, Rizzo JD, et al. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. *Blood*. May 15 2005;105(10):3802-3811.

Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. *J Natl Cancer Inst*. Dec 18 1996;88(24):1848-1853.

Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Jun 1 2005;23(16):3733-3741.

Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol*. May 2001;36(5):549-554

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
42 TBI	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal** **TBI**	**Brain tumor** (benign or malignant)	**Host Factors** Younger age at treatment Neurofibromatosis **Treatment Factors** Higher radiation dose	**Host Factors** Age < 6 years at time of treatment Ataxia telangiectasia	**HISTORY** **Headaches** **Vomiting** **Cognitive, motor or sensory deficits** **Seizures and other neurologic symptoms** (Yearly) **PHYSICAL** **Neurologic exam** (Yearly)	**Considerations for Further Testing and Intervention** Brain MRI as clinically indicated for symptomatic patients. Consider brain MRI every other year for patients with neurofibromatosis beginning 2 years after radiation therapy. Neurosurgical consultation for tissue diagnosis and/or resection. Neuro-oncology consultation for medical management. **SYSTEM = SMN** **SCORE = 1**

SECTION 42 TBI REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.

Socie G, Curtis RE, Deeg HJ, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol*. Jan 2000;18(2):348-357.

Witherspoon RP, Fisher LD, Schoch G, et al. Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med*. Sep 21 1989;321(12):784-789.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
43 TBI	**Cranial** **Ear/Infratemporal** **TBI**	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change **Info Link:** Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. *Note: New deficits may emerge over time.*	**Host Factors** Younger age at treatment Primary CNS tumor CNS leukemia/lymphoma Relapsed leukemia/lymphoma treated with CNS-directed therapy Head/neck tumors with brain in radiation field **Treatment Factors** Radiation in combination with: - Dexamethasone - TBI - Methotrexate (IT, IO, high-dose IV) - Cytarabine (high-dose IV) Higher radiation dose Larger radiation field Greater cortical volumes Cranial radiation in combination with TBI Longer elapsed time since therapy	**Host Factors** Age < 3 years at time of treatment Female sex Supratentorial tumor Premorbid or family history of learning or attention problems	**HISTORY** **Educational and/or vocational progress** (Yearly) **SCREENING** **Referral for formal neuropsychological evaluation** (Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress)	**Health Links** **Educational Issues** **Considerations for Further Testing and Intervention** Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Refer patients with neurocognitive deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Consider use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution - lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

SECTION 43 TBI REFERENCES

Chou RH, Wong GB, Kramer JH, et al. Toxicities of total-body irradiation for pediatric bone marrow transplantation. *Int J Radiat Oncol Biol Phys.* Mar 1 1996;34(4):843-851.

Felder-Puig R, Peters C, Matthes-Martin S, et al. Psychosocial adjustment of pediatric patients after allogeneic stem cell transplantation. *Bone Marrow Transplant.* Jul 1999;24(1):75-80.

Kupst MJ, Penati B, Debban B, et al. Cognitive and psychosocial functioning of pediatric hematopoietic stem cell transplant patients: a prospective longitudinal study. *Bone Marrow Transplant.* Nov 2002;30(9):609-617.

Phipps S, Dunavant M, Srivastava DK, Bowman L, Mulhern RK. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. *J Clin Oncol.* Mar 2000;18(5):1004-1011.

Simms S, Kazak AE, Gannon T, Goldwein J, Bunin N. Neuropsychological outcome of children undergoing bone marrow transplantation. *Bone Marrow Transplant.* Jul 1998;22(2):181-184.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
49 TBI	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal** **TBI**	**Metabolic syndrome** **Info Link:** The metabolic syndrome is a clustering of cardiovascular risk factors that may further increase risk for cardiovascular disease. Definitions of metabolic syndrome are evolving, but generally include a combination of obesity with insulin resistance, dyslipidemia, and elevated blood pressure. *Note: Patients who received TBI may develop features of metabolic syndrome without associated obesity*	**Treatment Factors** Surgery in suprasellar region Prolonged corticosteroid therapy (e.g., for chronic GVHD) **Medical Conditions** Growth hormone deficiency Hypogonadism	**Host Factors** Obesity **Treatment Factors** Cranial radiation dose ≥ 18 Gy	**PHYSICAL** **Height** **Weight** **BMI** **Blood pressure** (Yearly) **SCREENING** **Fasting blood glucose** **Fasting serum insulin** **Fasting lipid profile** (Every 5 years. More frequently if indicated based on patient evaluation.)	**Health Links** **Diet and Physical Activity** **Counseling** Counsel regarding obesity-related health risks **Considerations for Further Testing and Intervention** Consider endocrine consult if insulin resistance/metabolic syndrome is suspected. Nutritional counseling. Cardiology consultation as clinically indicated. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

SECTION 49 TBI REFERENCES

Hoffmeister PA, Storer BE, Sanders JE. Diabetes mellitus in long-term survivors of pediatric hematopoietic cell transplantation. *J Pediatr Hematol Oncol*. Feb 2004;26(2):81-90.

Lorini R, Cortona L, Scaramuzza A, et al. Hyperinsulinemia in children and adolescents after bone marrow transplantation. *Bone Marrow Transplant*. Jun 1995;15(6):873-877.

Smedmyr B, Wibell L, Simonsson B, Oberg G. Impaired glucose tolerance after autologous bone marrow transplantation. *Bone Marrow Transplant*. Aug 1990;6(2):89-92.

Taskinen M, Saarinen-Pihkala UM, Hovi L, Lipsanen-Nyman M. Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. *Lancet*. Sep 16 2000;356(9234):993-997.

Traggiai C, Stanhope R, Nussey S, Leiper AD. Diabetes mellitus after bone marrow transplantation during childhood. *Med Pediatr Oncol*. Feb 2003;40(2):128-129.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
50 TBI	**Cranial** **Orbital/Eye** **Ear/Infratemporal** **Nasopharyngeal** **TBI**	**Growth hormone deficiency** **Info Link:** Growth charts available on-line at www.cdc.gov/growthcharts	**Host Factors** Younger age at treatment **Treatment Factors** Higher radiation doses Surgery in suprasellar region Pretransplant radiation TBI ≥ 10 Gy in single fraction TBI ≥ 12 Gy fractionated	**Treatment Factors** Radiation dose ≥ 18 Gy Pretransplant cranial radiation TBI given in single fraction	**HISTORY** **Assessment of nutritional status** (Every six months until growth is completed, then yearly) **PHYSICAL** **Height** **Weight** **BMI** (Every six months until growth is completed, then yearly) **Tanner staging** (Every six months until sexually mature)	**Health Links** **Growth Hormone Deficiency** See also: **Hypopituitarism** **Resources** www.magicfoundation.org **Considerations for Further Testing and Intervention** Obtain x-ray for bone age in poorly growing children. Endocrine consultation for: Height below 3rd percentile on growth chart; Drop ≥ 2 percentile rankings on growth chart; Growth velocity < 4-5 cm/year during childhood; Lack of pubertal growth spurt. Evaluate thyroid function in any poorly growing child. Consult with endocrinologist regarding risks/benefits of adult growth hormone replacement therapy. Consider bone density testing in patients who are growth hormone deficient. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 50 TBI REFERENCES

Cohen A, Rovelli A, Bakker B, et al. 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*. Jun 15 1999;93(12):4109-4115.

Giorgiani G, Bozzola M, Locatelli F, et al. 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*. Jul 15 1995;86(2):825-831.

Huma Z, Boulad F, Black P, Heller G, Sklar C. Growth in children after bone marrow transplantation for acute leukemia. *Blood*. Jul 15 1995;86(2):819-824.

Sanders JE, Guthrie KA, Hoffmeister PA, Woolfrey AE, Carpenter PA, Appelbaum FR. Final adult height of patients who received hematopoietic cell transplantation in childhood. *Blood*. Feb 1 2005;105(3):1348-1354.

Sanders JE, Pritchard S, Mahoney P, et al. Growth and development following marrow transplantation for leukemia. *Blood*. Nov 1986;68(5):1129-1135.

Wingard JR, Plotnick LP, Freemer CS, et al. Growth in children after bone marrow transplantation: busulfan plus cyclophosphamide versus cyclophosphamide plus total body irradiation. *Blood*. Feb 15 1992;79(4):1068-1073.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
56 TBI	**Cranial** **Orbital/Eye** **TBI** **Info Link:** Radiation-related ocular complications other than cataracts are generally associated only with orbital/eye radiation or higher dose cranial radiation. However, patients with a history of an ocular tumor (e.g., retinoblastoma) are at higher risk for late-onset ocular complications and should receive ongoing follow-up by an ophthalmologist at least annually, and more frequently if clinically indicated.	**Cataracts**	**Treatment Factors** Radiation dose ≥ 10 Gy TBI ≥ 2 Gy in single fraction TBI ≥ 5 Gy fractionated Radiation combined with - Corticosteroids - Busulfan - Longer interval since treatment	**Treatment Factors** Radiation dose ≥ 15 Gy Fraction dose ≥ 2 Gy TBI ≥ 5 Gy in single fraction TBI ≥ 10 Gy fractionated Cranial/orbital/eye radiation combined with TBI	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** (Yearly) **PHYSICAL** **Visual acuity** **Funduscopic exam to evaluate for lens opacity** (Yearly) **SCREENING** **Evaluation by ophthalmologist** (Yearly for patients with ocular tumors [regardless of radiation dose] and for those who received TBI or ≥ 30 Gy cranial/orbital/eye radiation. Every 3 years for patients without ocular tumors who received < 30 Gy.)	**Health Links** **Cataracts** **Considerations for Further Testing and Intervention** Ongoing ophthalmology follow-up for identified problems. Refer patients with visual deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Ocular** **SCORE = 1**

SECTION 56 TBI REFERENCES

Holmstrom G, Borgstrom B, Calissendorff B. Cataract in children after bone marrow transplantation: relation to conditioning regimen. *Acta Ophthalmol Scand*. Apr 2002;80(2):211-215.

Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood*. May 1 2003;101(9):3373-3385.

van Kempen-Harteveld ML, Belkacemi Y, Kal HB, Labopin M, Frassoni F. Dose-effect relationship for cataract induction after single-dose total body irradiation and bone marrow transplantation for acute leukemia. *Int J Radiat Oncol Biol Phys*. Apr 1 2002;52(5):1367-1374.

van Kempen-Harteveld ML, Struikmans H, Kal HB, et al. Cataract after total body irradiation and bone marrow transplantation: degree of visual impairment. *Int J Radiat Oncol Biol Phys*. Apr 1 2002;52(5):1375-1380.

Zierhut D, Lohr F, Schraube P, et al. Cataract incidence after total-body irradiation. *Int J Radiat Oncol Biol Phys*. Jan 1 2000;46(1):131-135.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
60 TBI	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Dental abnormalities** Tooth/root agenesis Microdontia Root thinning/shortening Enamel dysplasia Periodontal disease Dental caries Malocclusion Temporomandibular joint dysfunction	**Host Factors** Younger age at treatment Gorlin's syndrome (nevoid basal cell carcinoma syndrome) **Treatment Factors** Higher radiation dose	**Host Factors** Age < 5 years at time of treatment **Treatment Factors** Dose ≥ 10 Gy	**PHYSICAL** **Oral exam** (Yearly) **SCREENING** **Dental exam and cleaning** (Every six months)	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Regular dental care including fluoride applications. Consultation with orthodontist experienced in management of irradiated childhood cancer survivors. Baseline panorex prior to dental procedures to evaluate root development. **SYSTEM = Dental** **SCORE = 1**

SECTION 60 TBI REFERENCES

Dahllof G, Bagesund M, Remberger M, Ringden O. Risk factors for salivary dysfunction in children 1 year after bone marrow transplantation. *Oral Oncol*. Sep 1997;33(5):327-331.

Dahllof G, Bagesund M, Ringden O. Impact of conditioning regimens on salivary function, caries-associated microorganisms and dental caries in children after bone marrow transplantation. A 4-year longitudinal study. *Bone Marrow Transplant*. Sep 1997;20(6):479-483.

Dahllof G, Jonsson A, Ulmner M, Huggare J. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. *Am J Orthod Dentofacial Orthop*. Nov 2001;120(5):459-465.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
62 TBI	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Thyroid nodules**	**Host Factors** Younger age at treatment Female sex **Treatment Factors** Higher radiation dose Thyroid gland directly in radiation field TBI	**Treatment Factors** Radiation dose ≥ 25 Gy	**PHYSICAL** **Thyroid exam** (Yearly)	**Health Links** **Thyroid Problems** **Considerations for Further Testing and Intervention** Ultrasound and FNA for evaluation of palpable nodule(s). Endocrine and/or surgical consultation for diagnostic biopsy or thyroidectomy. **SYSTEM = SMN** **SCORE = 1**

SECTION 62 TBI REFERENCES

Faraci M, Barra S, Cohen A, et al. Very late nonfatal consequences of fractionated TBI in children undergoing bone marrow transplant. *Int J Radiat Oncol Biol Phys.* Dec 1 2005;63(5):1568-1575.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
63 TBI	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Thyroid cancer**	**Host Factors** Younger age at treatment Female sex **Treatment Factors** ≥ 5 years after irradiation Thyroid gland directly in radiation field TBI Risk increased up to 30 Gy with a downturn of risk after 30 Gy		**PHYSICAL** **Thyroid exam** (Yearly)	**Health Links** **Thyroid Problems** **Considerations for Further Testing and Intervention** Ultrasound and FNA for evaluation of palpable nodule(s). Surgical consultation for resection. Nuclear medicine consultation for ablation of residual disease. Endocrine consultation for postoperative medical management. **SYSTEM = SMN** **SCORE = 1**

SECTION 63 TBI REFERENCES

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.
Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. *N Engl J Med*. Mar 27 1997;336(13):897-904.
Socie G, Curtis RE, Deeg HJ, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol*. Jan 2000;18(2):348-357.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
64 TBI	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Spine (cervical)** **Cervical (neck)** **Supraclavicular** **Mantle** **Mini-Mantle** **TBI**	**Hypothyroidism**	**Host Factors** Female sex **Treatment Factors** Radiation dose ≥ 10 Gy Thyroid gland directly in radiation field TBI	**Treatment Factors** Radiation dose ≥ 20 Gy	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** (Yearly; Consider more frequent screening during periods of rapid growth) **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** (Yearly; Consider more frequent screening during periods of rapid growth) **SCREENING** **TSH** **Free T4** (Yearly; Consider more frequent screening during periods of rapid growth)	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 64 TBI REFERENCES

Katsanis E, Shapiro RS, Robison LL, et al. Thyroid dysfunction following bone marrow transplantation: long-term follow-up of 80 pediatric patients. *Bone Marrow Transplant*. May 1990;5(5):335-340.

Sanders JE. Endocrine complications of high-dose therapy with stem cell transplantation. *Pediatr Transplant*. Jun 2004;8 Suppl 5:39-50.

Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. Aug 1 2001;6:G17-22.

Sklar CA, Kim TH, Ramsay NK. Thyroid dysfunction among long-term survivors of bone marrow transplantation. *Am J Med*. Nov 1982;73(5):688-694.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
69 TBI (Female)	**Mantle** **Mini-Mantle** **Mediastinal** **Chest (thorax)** **Whole lung** **Axilla** **TBI**	**Breast tissue hypoplasia**	**Host Factors** Prepubertal at time of breast irradiation **Treatment Factors** Higher radiation dose		**PHYSICAL** **Breast exam** (Yearly)	**Considerations for Further Testing and Intervention** Surgical consultation for breast reconstruction after completion of growth. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 69 TBI REFERENCES

Furst CJ, Lundell M, Ahlback SO, Holm LE. Breast hypoplasia following irradiation of the female breast in infancy and early childhood. *Acta Oncol*. 1989;28(4):519-523.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
70 TBI	**Mantle** **Mediastinal** **Chest (thorax)** **Whole lung** **TBI**	**Pulmonary toxicity** Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	**Host Factors** Younger age at irradiation **Treatment Factors** Radiation dose ≥ 10 Gy Chest radiation combined with TBI Radiation combined with: - Bleomycin - Busulfan - Carmustine (BCNU) - Lomustine (CCNU) - Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** Radiation dose ≥ 15 Gy TBI ≥ 6 Gy in single fraction TBI ≥ 12 Gy fractionated	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **PHYSICAL** **Pulmonary exam** (Yearly) **SCREENING** **Chest x-ray** **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: www.smokefree.gov **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Due to the potential pulmonary toxicity of this therapy, patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations. **SYSTEM = Pulmonary** **SCORE = 1**

SECTION 70 TBI REFERENCES

Fanfulla F, Locatelli F, Zoia MC, et al. Pulmonary complications and respiratory function changes after bone marrow transplantation in children. *Eur Respir J.* Oct 1997;10(10):2301-2306.

Frankovich J, Donaldson SS, Lee Y, Wong RM, Amylon M, Verneris MR. High-dose therapy and autologous hematopoietic cell transplantation in children with primary refractory and relapsed Hodgkin's disease: atopy predicts idiopathic diffuse lung injury syndromes. *Biol Blood Marrow Transplant.* 2001;7(1):49-57.

Gore EM, Lawton CA, Ash RC, Lipchik RJ. Pulmonary function changes in long-term survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys.* Aug 1 1996;36(1):67-75.

Griese M, Rampf U, Hofmann D, Fuhrer M, Reinhardt D, Bender-Gotze C. Pulmonary complications after bone marrow transplantation in children: twenty-four years of experience in a single pediatric center. *Pediatr Pulmonol.* Nov 2000;30(5):393-401.

Kader HA, Khanna S, Hutchinson RM, Aukett RJ, Archer J. Pulmonary complications of bone marrow transplantation: the impact of variations in total body irradiation parameters. *Clin Oncol (R Coll Radiol).* 1994;6(2):96-101.

Nenadov Beck M, Meresse V, Hartmann O, Gaultier C. Long-term pulmonary sequelae after autologous bone marrow transplantation in children without total body irradiation. *Bone Marrow Transplant.* Dec 1995;16(6):771-775.

Nysom K, Holm K, Hesse B, et al. Lung function after allogeneic bone marrow transplantation for leukaemia or lymphoma. *Arch Dis Child.* May 1996;74(5):432-436.

Palmas A, Tefferi A, Myers JL, et al. Late-onset noninfectious pulmonary complications after allogeneic bone marrow transplantation. *Br J Haematol.* Mar 1998;100(4):680-687.

Stolp B, Assistant Medical Director Divers Alert Network, Director Anesthesiology Emergency Airway Services, Durham, N.C. Risks associated with SCUBA diving in childhood cancer survivors. Personal communication to Landier W, Bhatia S Aug 23, 2002.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
79 TBI	**Whole abdomen** **All upper abdominal fields** **TBI** **Info Link:** Includes all upper abdominal fields except Paraaortic	**Renal toxicity** Renal insufficiency Hypertension	**Host Factors** Bilateral Wilms tumor Mononephric **Treatment Factors** Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Radiation dose ≥ 10 Gy TBI combined with radiation to the kidney Combined with other nephrotoxic agents such as: - Cisplatin - Carboplatin - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants **Medical Conditions** Diabetes mellitus Hypertension Nephrectomy	**Treatment Factors** Radiation dose ≥ 15 Gy TBI ≥ 6 Gy in single fraction TBI ≥ 12 Gy fractionated	**PHYSICAL** **Blood pressure** (Yearly) **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** (Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated.) **Urinalysis** (Yearly)	**Health Links** **Kidney Health** See also: **Single Kidney Health** **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 1**

SECTION 79 TBI REFERENCES

Lawton CA, Cohen EP, Murray KJ, et al. Long-term results of selective renal shielding in patients undergoing total body irradiation in preparation for bone marrow transplantation. *Bone Marrow Transplant.* Dec 1997;20(12):1069-1074.

Miralbell R, Bieri S, Mermillod B, et al. Renal toxicity after allogeneic bone marrow transplantation: the combined effects of total-body irradiation and graft-versus-host disease. *J Clin Oncol.* Feb 1996;14(2):579-585.

Tarbell NJ, Guinan EC, Niemeyer C, Mauch P, Sallan SE, Weinstein HJ. Late onset of renal dysfunction in survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys.* Jul 1988;15(1):99-104.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
83 TBI (Female)	**Whole abdomen** **Pelvic** **Spine (lumbar, sacral)** **TBI** **Info Link:** Applies to all pelvic fields except iliac/inguinal. Applies to lumbar and sacral spine at doses ≥ 25 Gy.	**Uterine vascular insufficiency** (resulting in adverse pregnancy outcomes, such as spontaneous abortion, neonatal death, low-birth weight infant, fetal malposition, and premature labor) **Info Link:** 10% of girls with Wilms tumor have congenital uterine anomalies.	**Host Factors** Females with Wilms tumor and associated müllerian anomalies **Treatment Factors** Higher radiation dose to pelvis	**Host Factors** Prepubertal at treatment **Treatment Factors** Radiation dose ≥ 30 Gy TBI	**HISTORY** **Pregnancy** **Childbirth history** (Yearly and as clinically indicated)	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Considerations for Further Testing and Intervention** Consider high-level ultrasound evaluation of genitourinary tract after pubertal development as clinically indicated in patients contemplating pregnancy. High-risk obstetrical care during pregnancy. **SYSTEM = Female reproductive** **SCORE = 2B**

SECTION 83 TBI REFERENCES

Gulati SC, Van Poznak C. Pregnancy after bone marrow transplantation. *J Clin Oncol*. May 1998;16(5):1978-1985.

Sanders JE, Hawley J, Levy W, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood*. Apr 1 1996;87(7):3045-3052.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
84 TBI (Female)	**Whole abdomen** **Pelvic** **Spine (lumbar, sacral)** **TBI** **Info Link:** Applies to lumbar and sacral spine at doses ≥ 25 Gy only.	**Gonadal dysfunction (ovarian)** Delayed/arrested puberty Premature menopause Infertility	**Host Factors** Older age at irradiation **Treatment Factors** Prepubertal female: Radiation dose ≥10 Gy Pubertal female: Radiation dose ≥ 5 Gy Combined with alkylating agent chemotherapy Longer time since treatment	**Treatment Factors** Prepubertal female: Radiation dose ≥15 Gy Pubertal female: Radiation dose ≥10 Gy Combined with cyclophosphamide conditioning for HCT	**HISTORY** **Pubertal (onset, tempo)** **Menstrual/pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Estradiol** (Baseline at age 13, **and** as clinically indicated in patients with delayed puberty, irregular menses or primary or secondary amenorrhea, clinical signs and symptoms of estrogen deficiency)	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to radiation. Recovery of fertility may occur years after therapy. Counsel regarding risks and benefits of HRT. **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed/arrested puberty or persistently abnormal hormone levels. Gynecology or endocrinology consultation for HRT. Consider evaluation for conditions exacerbated by hypogonadism (e.g., osteopenia/osteoporosis). Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 84 TBI REFERENCES

Couto-Silva AC, Trivin C, Thibaud E, Esperou H, Michon J, Brauner R. Factors affecting gonadal function after bone marrow transplantation during childhood. *Bone Marrow Transplant*. Jul 2001;28(1):67-75.

Grigg AP, McLachlan R, Zaja J, Szer J. Reproductive status in long-term bone marrow transplant survivors receiving busulfan-cyclophosphamide (120 mg/kg). *Bone Marrow Transplant*. Nov 2000;26(10):1089-1095.

Sanders JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. The Long-term Follow-up Team. *Bone Marrow Transplant*. 1991;8 Suppl 1:2-4.

Sarafoglou K, Boulad F, Gillio A, Sklar C. Gonadal function after bone marrow transplantation for acute leukemia during childhood. *J Pediatr*. Feb 1997;130(2):210-216.

Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. Aug 1 2001;6:G17-22.

Thibaud E, Rodriguez-Macias K, Trivin C, Esperou H, Michon J, Brauner R. Ovarian function after bone marrow transplantation during childhood. *Bone Marrow Transplant*. Feb 1998;21(3):287-290.

RADIATION

TBI (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
86 TBI (Male)	**Pelvic** **Testicular** **TBI**	**Gonadal dysfunction (testicular):** **Germ cell failure** Oligospermia Azoospermia Infertility	**Treatment Factors** Radiation dose to testes: - 1 to 3 Gy: Azoospermia may be reversible - 3 to 6 Gy: Azoospermia possibly reversible (but unlikely)	**Treatment Factors** Radiation dose to testes ≥ 6 Gy: Azoospermia likely permanent	**SCREENING** **Semen analysis** (As requested by patient and for evaluation of infertility. Periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years post therapy.)	**Health Links** **Male Health Issues** **Resources** American Society for Reproductive Medicine: www.asrm.org Fertile Hope: www.fertilehope.org **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to radiation. Recovery of fertility may occur years after therapy. **Considerations for Further Testing and Intervention** Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies. Testing for Inhibin B can be considered in conjunction with FSH as an indicator of germ cell function. **SYSTEM = Male reproductive** **SCORE = 1**

SECTION 86 TBI REFERENCES

Anserini P, Chiodi S, Spinelli S, et al. Semen analysis following allogeneic bone marrow transplantation. Additional data for evidence-based counselling. *Bone Marrow Transplant*. Oct 2002;30(7):447-451.

Couto-Silva AC, Trivin C, Thibaud E, Esperou H, Michon J, Brauner R. Factors affecting gonadal function after bone marrow transplantation during childhood. *Bone Marrow Transplant*. Jul 2001;28(1):67-75.

Grigg AP, McLachlan R, Zaja J, Szer J. Reproductive status in long-term bone marrow transplant survivors receiving busulfan-cyclophosphamide (120 mg/kg). *Bone Marrow Transplant*. Nov 2000;26(10):1089-1095.

Jacob A, Barker H, Goodman A, Holmes J. Recovery of spermatogenesis following bone marrow transplantation. *Bone Marrow Transplant*. Aug 1998;22(3):277-279.

Sanders JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. The Long-term Follow-up Team. *Bone Marrow Transplant*. 1991;8 Suppl 1:2-4.

Sarafoglou K, Boulad F, Gillio A, Sklar C. Gonadal function after bone marrow transplantation for acute leukemia during childhood. *J Pediatr*. Feb 1997;130(2):210-216.

Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. Aug 1 2001;6:G17-22.

HEMATOPOIETIC CELL TRANSPLANT

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
92	**Hematopoietic Cell Transplant (HCT)** **Info Link:** Complications after hematopoietic cell transplantation have multifactorial etiology: prior therapy for primary malignancy; intensity of transplant conditioning; stem cell product (e.g., marrow, cord blood, peripheral stem cells); donor (e.g., autologous, allogeneic, unrelated); quality of donor to recipient match; complication of transplant process (immunosuppression and GVHD); complications in the post-transplant period; underlying disease; host genetic factors; lifestyle behaviors. This section includes late treatment complications that may be observed in hematopoietic cell transplant recipients not covered elsewhere in these guidelines. Refer to other sections of these guidelines for specific details related to late complications of radiation and of specific chemotherapeutic agents.	**Acute myeloid leukemia** **Myelodysplasia**	**Treatment Factors** Radiation therapy Stem cell mobilization with etoposide Alkylating agent chemotherapy Epipodophyllotoxins Anthracyclines Autologous transplant	**Host Factors** Older age **Treatment Factors** Autologous transplant for non-Hodgkin's and Hodgkin's lymphoma	**HISTORY** **Fatigue** **Bleeding** **Easy bruising** (Yearly up to 10 years after transplant) **PHYSICAL** **Dermatologic exam (pallor, petechiae, purpura)** (Yearly up to 10 years after transplant) **SCREENING** **CBC/differential** (Yearly up to 10 years after transplant)	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Counsel to promptly report fatigue, pallor, petechiae, or bone pain. **Considerations for Further Testing and Intervention** Bone marrow exam as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 92 REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Ramsay NK, Steinbuch M, et al. Malignant neoplasms following bone marrow transplantation. *Blood*. May 1 1996;87(9):3633-3639.

Del Canizo M, Amigo M, Hernandez JM, et al. Incidence and characterization of secondary myelodysplastic syndromes following autologous transplantation. *Haematologica*. Apr 2000;85(4):403-409.

Forrest DL, Nevill TJ, Naiman SC, et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. *Bone Marrow Transplant*. Nov 2003;32(9):915-923.

Hosing C, Munsell M, Yazji S, et al. Risk of therapy-related myelodysplastic syndrome/acute leukemia following high-dose therapy and autologous bone marrow transplantation for non-Hodgkin's lymphoma. *Ann Oncol*. Mar 2002;13(3):450-459.

Howe R, Micallef IN, Inwards DJ, et al. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. *Bone Marrow Transplant*. Aug 2003;32(3):317-324.

Kolb HJ, Socie G, Duell T, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Ann Intern Med*. Nov 16 1999;131(10):738-744.

Krishnan A, Bhatia S, Slovak ML, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood*. Mar 1 2000;95(5):1588-1593.

Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. *Blood*. Jun 15 1994;83(12):3780-3786.

Stone RM, Neuberg D, Soiffer R, et al. Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol*. Dec 1994;12(12):2535-2542

HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
93	**Hematopoietic Cell Transplant (HCT)**	**Solid tumors**	**Host Factors** Younger age at transplant Fanconi's anemia **Treatment Factors** Radiation therapy **Medical Conditions** Hepatitis C infection Chronic GVHD Human papilloma virus infection (females)	**Treatment Factors** TBI	**PHYSICAL** **Evaluation for benign or malignant neoplasms** (Yearly)	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Females with cGVHD appear to be at increased risk for cervical cancer and should, at minimum, have pelvic exams and PAP testing according to ACS recommendations (see Section 138) with more aggressive monitoring as clinically indicated. Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 93 REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.

Bhatia S, Ramsay NK, Steinbuch M, et al. Malignant neoplasms following bone marrow transplantation. *Blood*. May 1 1996;87(9):3633-3639.

Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. *N Engl J Med*. Mar 27 1997;336(13):897-904.

Forrest DL, Nevill TJ, Naiman SC, et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. *Bone Marrow Transplant*. Nov 2003;32(9):915-923.

Kolb HJ, Socie G, Duell T, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Ann Intern Med*. Nov 16 1999;131(10):738-744.

Lishner M, Patterson B, Kandel R, et al. Cutaneous and mucosal neoplasms in bone marrow transplant recipients. *Cancer*. Feb 1 1990;65(3):473-476.

Socie G, Curtis RE, Deeg HJ, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol*. Jan 2000;18(2):348-357.

Witherspoon RP, Fisher LD, Schoch G, et al. Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med*. Sep 21 1989;321(12):784-789.

HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
94	**Hematopoietic Cell Transplant (HCT)**	**Lymphoma**	**Medical Conditions** Chronic GVHD	**Medical Conditions** Chronic hepatitis C with siderosis and steatosis	**PHYSICAL** **Lymphadenopathy** **Splenomegaly** (Yearly)	**Considerations for Further Testing and Intervention** Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 94 REFERENCES

Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol*. Apr 1 2003;21(7):1352-1358.

Bhatia S, Ramsay NK, Steinbuch M, et al. Malignant neoplasms following bone marrow transplantation. *Blood*. May 1 1996;87(9):3633-3639.

Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood*. Oct 1 1999;94(7):2208-2216.

Forrest DL, Nevill TJ, Naiman SC, et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. *Bone Marrow Transplant*. Nov 2003;32(9):915-923.

Rowlings PA, Curtis RE, Passweg JR, et al. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *J Clin Oncol*. Oct 1999;17(10):3122-3127.

Socie G, Curtis RE, Deeg HJ, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol*. Jan 2000;18(2):348-357.

Witherspoon RP, Fisher LD, Schoch G, et al. Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med*. Sep 21 1989;321(12):784-789.

HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
95	**Hematopoietic Cell Transplant (HCT)**	**Hepatic toxicity** Chronic hepatitis Cirrhosis Iron overload	**Treatment Factors** History of multiple transfusions Radiation to the liver Antimetabolite therapy **Medical Conditions** Chronic GVHD Viral hepatitis History of VOD **Health Behaviors** Alcohol use	**Medical Conditions** Chronic hepatitis C with siderosis and steatosis	**SCREENING** **ALT** **AST** **Bilirubin** **Ferritin** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.)	**Health Links** **Liver Health** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Note: *PCR testing for HCV may be required in immunosuppressed patients who are negative for antibody*. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction or known hepatitis. Hepatitis A and B immunizations in patients lacking immunity. Consider liver biopsy in patients with persistent elevation of ferritin (based on clinical context and magnitude of elevation). Consider phlebotomy or chelation therapy for treatment of iron overload. Consider erythropoietin in patients with iron overload and low hemoglobin. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 95 REFERENCES

McKay PJ, Murphy JA, Cameron S, et al. Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. *Bone Marrow Transplant*. Jan 1996;17(1):63-66.

Ohata K, Hamasaki K, Toriyama K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer*. Jun 15 2003;97(12):3036-3043.

Paul IM, Sanders J, Ruggiero F, Andrews T, Ungar D, Eyster ME. Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. *Blood*. Jun 1 1999;93(11):3672-3677.

Peffault de Latour R, Levy V, Asselah T, et al. Long-term outcome of hepatitis C infection after bone marrow transplantation. *Blood*. Mar 1 2004;103(5):1618-1624.

Strasser SI, Myerson D, Spurgeon CL, et al. Hepatitis C virus infection and bone marrow transplantation: a cohort study with 10-year follow-up. *Hepatology*. Jun 1999;29(6):1893-1899.

Strasser SI, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood*. May 15 1999;93(10):3259-3266.

HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
96	**Hematopoietic Cell Transplant (HCT)**	**Osteonecrosis** (Avascular Necrosis) **Info Link:** Osteonecrosis typically occurs during the acute treatment phase, may progress over time or resolve. Multifocal osteonecrosis is significantly more common (3:1) than unifocal.	**Host Factors** Age ≥ 10 years at time of transplant **Treatment Factors** Corticosteroids (dexamethasone effect is more potent than prednisone) TBI High-dose radiation to any bone Allogeneic HCT > autologous	**Treatment Factors** Prolonged corticosteroid therapy (e.g., for chronic GVHD) **Medical Conditions** Chronic GVHD	**HISTORY** **Joint pain** **Swelling** **Immobility** **Limited range of motion** (Yearly) **PHYSICAL** **Musculoskeletal exam** (Yearly)	**Health Links** **Osteonecrosis** **Considerations for Further Testing and Intervention** MRI as clinically indicated in patients with history suggestive of osteonecrosis (should be done soon after symptom onset). Orthopedic consultation in patients with positive imaging and/or symptoms of osteonecrosis. Physical therapy evaluation (for non-pharmacologic pain management, range of motion, strengthening, stretching, functional mobility). **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 96 REFERENCES

Fink JC, Leisenring WM, Sullivan KM, Sherrard DJ, Weiss NS. Avascular necrosis following bone marrow transplantation: a case-control study. *Bone*. Jan 1998;22(1):67-71.

Kaste SC, Shidler TJ, Tong X, et al. Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. *Bone Marrow Transplant*. Feb 2004;33(4):435-441.

Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. Sep 15 2000;18(18):3262-3272.

Tauchmanova L, De Rosa G, Serio B, et al. Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: a single center experience and a review. *Cancer*. May 15 2003;97(10):2453-2461.

HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
97	**Hematopoietic Cell Transplant (HCT)**	**Osteopenia** **Osteoporosis** Osteopenia is defined as bone mineral density ≥ 1 and < 2.5 SD below mean Osteoporosis is defined as bone mineral density ≥ 2.5 SD below mean **Info Link:** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density (BMD) of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the YOUNG-NORMAL MEAN BMD. A T-score of ≥ 2.5 standard deviations BELOW the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. There are not defined standards for referral or treatment of low BMD in children.	**Host Factors** Both genders are at risk **Treatment Factors** Methotrexate Corticosteroids Cranial radiation **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use	**Host Factors** Older age at time of treatment **Treatment Factors** Prolonged corticosteroid therapy (e.g., for chronic GVHD)	**SCREENING** **Bone density evaluation (DEXA or quantitative CT)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated.) **Info Link:** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	**Health Links** **Bone Health** **Resources** National Osteoporosis Foundation website: www.nof.org **Considerations for Further Testing and Intervention** Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency, correction of chronic metabolic acidosis that could accelerate bone loss). Endocrine consultation for patients with osteoporosis or history of multiple fractures for pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators). **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 97 REFERENCES

Baker KS, Gurney JG, Ness KK, et al. Late effects in survivors of chronic myeloid leukemia treated with hematopoietic cell transplantation: results from the Bone Marrow Transplant Survivor Study. *Blood*. Sep 15 2004;104(6):1898-1906.

Bhatia S, Ramsay NK, Weisdorf D, Griffiths H, Robison LL. Bone mineral density in patients undergoing bone marrow transplantation for myeloid malignancies. *Bone Marrow Transplant*. Jul 1998;22(1):87-90.

Kaste SC, Chesney RW, Hudson MM, Lustig RH, Rose SR, Carbone LD. Bone mineral status during and after therapy of childhood cancer: an increasing population with multiple risk factors for impaired bone health. *J Bone Miner Res*. Dec 1999;14(12):2010-2014.

Kaste SC, Shidler TJ, Tong X, et al. Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. *Bone Marrow Transplant*. Feb 2004;33(4):435-441.

Nysom K, Holm K, Michaelsen KF, et al. Bone mass after allogeneic BMT for childhood leukaemia or lymphoma. *Bone Marrow Transplant*. Jan 2000;25(2):191-196.

Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg*. May 2004;62(5):527-534.

Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. Aug 1 2001;6:G17-22.

Stern JM, Chesnut CH, 3rd, Bruemmer B, et al. Bone density loss during treatment of chronic GVHD. *Bone Marrow Transplant*. Mar 1996;17(3):395-400.

HEMATOPOIETIC CELL TRANSPLANT

WITH CHRONIC GVHD

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
98	**HCT with Chronic GVHD**	**Dermatologic toxicity** Permanent alopecia Nail dysplasia Vitiligo Scleroderma **Info Link:** More common with active cGVHD; effects may persist after cGVHD resolves.			**PHYSICAL** **Hair (alopecia)** **Nail (hypoplasia)** **Skin (vitiligo, scleroderma)** (Yearly)	**Health Links** **Skin Health** **SYSTEM = Dermatologic** **SCORE = 1**

SECTION 98 REFERENCES

Antin JH. Clinical practice. Long-term care after hematopoietic-cell transplantation in adults. *N Engl J Med*. Jul 4 2002;347(1):36-42.

HEMATOPOIETIC CELL TRANSPLANT

WITH CHRONIC GVHD (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
99	**HCT with Chronic GVHD**	**Xerophthalmia (keratoconjunctivitis sicca)** **Info Link:** More common with active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Cranial radiation Eye radiation Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Radiation dose to eye ≥ 30 Gy Radiation fraction ≥ 2 Gy	**HISTORY** **Dry eyes (burning, itching, foreign body sensation, inflammation)** (Yearly) **PHYSICAL** **Eye exam** (Yearly)	**Health Links** **Eye Health** **Considerations for Further Testing and Intervention** Supportive care with artificial tears. Schirmer's testing as clinically indicated. Ongoing ophthalmology follow-up for identified problems. Consider every six month ophthalmology evaluation for patients with corneal damage. **SYSTEM = Ocular** **SCORE = 1**

SECTION 99 REFERENCES

Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood*. May 1 2003;101(9):3373-3385.

Tichelli A, Duell T, Weiss M, et al. Late-onset keratoconjunctivitis sicca syndrome after bone marrow transplantation: incidence and risk factors. European Group or Blood and Marrow Transplantation (EBMT) Working Party on Late Effects. *Bone Marrow Transplant*. Jun 1996;17(6):1105-1111.

Ng JS, Lam DS, Li CK, et al. Ocular complications of pediatric bone marrow transplantation. *Ophthalmology*. Jan 1999;106(1):160-164.

Suh DW, Ruttum MS, Stuckenschneider BJ, Mieler WF, Kivlin JD. Ocular findings after bone marrow transplantation in a pediatric population. *Ophthalmology*. Aug 1999;106(8):1564-1570.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
100	**HCT with Chronic GVHD**	**Xerostomia** **Salivary gland dysfunction** **Dental caries** **Periodontal disease** **Oral cancer** **Info Link:** More common with active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Head and neck radiation involving the parotid gland Higher radiation doses Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Salivary gland radiation dose ≥ 30 Gy	**HISTORY** **Xerostomia** (Yearly) **PHYSICAL** **Oral exam** (Yearly) **SCREENING** **Dental exam and cleaning** (Every six months)	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine). Regular dental care including fluoride applications and regular screening for intraoral malignancy. **SYSTEM = Dental** **SCORE = 1**

SECTION 100 REFERENCES

Dahllof G, Bagesund M, Remberger M, Ringden O. Risk factors for salivary dysfunction in children 1 year after bone marrow transplantation. *Oral Oncol*. Sep 1997;33(5):327- 331.

Dahllof G, Bagesund M, Ringden O. Impact of conditioning regimens on salivary function, caries-associated microorganisms and dental caries in children after bone marrow transplantation. A 4-year longitudinal study. *Bone Marrow Transplant*. Sep 1997;20(6):479-483.

Dahllof G, Jonsson A, Ulmner M, Huggare J. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. *Am J Orthod Dentofacial Orthop*. Nov 2001;120(5):459-465.

Duggal MS, Curzon ME, Bailey CC, Lewis IJ, Prendergast M. Dental parameters in the long-term survivors of childhood cancer compared with siblings. *Oral Oncol*. Sep 1997;33(5):348-353.

Guchelaar HJ, Vermes A, Meerwaldt JH. Radiation-induced xerostomia: pathophysiology, clinical course and supportive treatment. *Support Care Cancer*. Jul 1997;5(4):281-288.

Makkonen TA, Edelman L, Forsten L. Salivary flow and caries prevention in patients receiving radiotherapy. *Proc Finn Dent Soc*. 1986;82(2):93-100.

Maxymiw WG, Wood RE. The role of dentistry in patients undergoing bone marrow transplantation. *Br Dent J*. Oct 7 1989;167(7):229-234.

HEMATOPOIETIC CELL TRANSPLANT

WITH CHRONIC GVHD (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
101	**HCT with Chronic GVHD**	**Pulmonary toxicity** Bronchiolitis obliterans Chronic bronchitis Bronchiectasis **Info Link:** More common with active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Chest radiation TBI Pulmonary toxic chemotherapy: - Bleomycin - Busulfan - Carmustine (BCNU) - Lomustine (CCNU)	**Medical Conditions** Prolonged immunosuppression related to cGVHD and its treatment	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **PHYSICAL** **Pulmonary exam** (Yearly) **SCREENING** **Chest x-ray** **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: www.smokefree.gov **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations. **SYSTEM = Pulmonary** **SCORE = 1**

SECTION 101 REFERENCES

Cerveri I, Fulgoni P, Giorgiani G, et al. Lung function abnormalities after bone marrow transplantation in children: has the trend recently changed? *Chest*. Dec 2001;120(6):1900-1906.

Cerveri I, Zoia MC, Fulgoni P, et al. Late pulmonary sequelae after childhood bone marrow transplantation. *Thorax*. Feb 1999;54(2):131-135.

Fanfulla F, Locatelli F, Zoia MC, et al. Pulmonary complications and respiratory function changes after bone marrow transplantation in children. *Eur Respir J*. Oct 1997;10(10):2301-2306.

Gore EM, Lawton CA, Ash RC, Lipchik RJ. Pulmonary function changes in long-term survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys*. Aug 1 1996;36(1):67-75.

Griese M, Rampf U, Hofmann D, Fuhrer M, Reinhardt D, Bender-Gotze C. Pulmonary complications after bone marrow transplantation in children: twenty-four years of experience in a single pediatric center. *Pediatr Pulmonol*. Nov 2000;30(5):393-401.

Kader HA, Khanna S, Hutchinson RM, Aukett RJ, Archer J. Pulmonary complications of bone marrow transplantation: the impact of variations in total body irradiation parameters. *Clin Oncol (R Coll Radiol)*. 1994;6(2):96-101.

Nenadov Beck M, Meresse V, Hartmann O, Gaultier C. Long-term pulmonary sequelae after autologous bone marrow transplantation in children without total body irradiation. *Bone Marrow Transplant*. Dec 1995;16(6):771-775.

Nysom K, Holm K, Hesse B, et al. Lung function after allogeneic bone marrow transplantation for leukaemia or lymphoma. *Arch Dis Child*. May 1996;74(5):432-436.

Stolp B, Assistant Medical Director Divers Alert Network, Director Anesthesiology Emergency Airway Services, Durham, N.C. Risks associated with SCUBA diving in childhood cancer survivors. Personal communication to Landier W, Bhatia S Aug 23, 2002

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
102	**HCT with Chronic GVHD**	**Immunologic complications** Secretory IgA deficiency Hypogammaglobulinemia Chronic infections (e.g., conjunctivitis, sinusitis, and bronchitis associated with chronic GVHD) **Info Link:** Related to cGVHD; effects may persist or resolve over time.		**Host Factors** Low CD4 T-cell count **Medical Conditions** Prolonged immunosuppression related to cGVHD and its treatment	**HISTORY** **Chronic conjunctivitis** **Chronic sinusitis** **Chronic bronchitis** (Yearly) **PHYSICAL** **Eye exam** **Nasal exam** **Pulmonary exam** (Yearly)	**Considerations for Further Testing and Intervention** Consider PCP and anti-fungal prophylaxis in patients with active cGVHD for duration of immunosuppressive therapy. Immunology or infectious diseases consultation for assistance with management of chronic infections **SYSTEM = Immune** **SCORE = 1**

SECTION 102 REFERENCES

Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. *Eur J Haematol*. Nov 2003;71(5):319-326.

Engelhard D, Cordonnier C, Shaw PJ, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *Br J Haematol*. May 2002;117(2):444-450.

Maury S, Mary JY, Rabian C, et al. Prolonged immune deficiency following allogeneic stem cell transplantation: risk factors and complications in adult patients. *Br J Haematol*. Dec 2001;115(3):630-641.

Nordoy T, Kolstad A, Endresen P, et al. Persistent changes in the immune system 4-10 years after ABMT. *Bone Marrow Transplant*. Oct 1999;24(8):873-878.

Storek J, Dawson MA, Storer B, et al. Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. *Blood*. Jun 1 2001;97(11):3380-3389.

Storek J, Gooley T, Witherspoon RP, Sullivan KM, Storb R. Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. *Am J Hematol*. Feb 1997;54(2):131-138.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
103	**HCT with Chronic GVHD**	**Functional asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., Haemophilus influenzae, streptococcus pneumoniae, meningococcus) **Info Link:** This section applies only to patients who have active cGVHD	**Treatment Factors** Splenic radiation Ongoing immunosuppression	**Host Factors** Hypogammaglobulinemia	**PHYSICAL** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** (When febrile T ≥ 101ºF) **SCREENING** **Blood culture** (When febrile T ≥ 101ºF)	**Health Links** **Splenic precautions** **Considerations for Further Testing and Intervention** Consider antibiotic prophylaxis for encapsulated organisms and bacteremia/endocarditis prophylaxis for duration of immunosuppressive therapy for chronic GVHD (see Dajani AS et al. Circulation 1997 for endocarditis prophylaxis dosing recommendations per the AHA). In patients with T ≥ 101°F (38.3° C) or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC; toxic clinical appearance; fever ≥ 104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines. Pneumovax booster in patients ≥10 years old at ≥ 5 years after previous dose (AAP-CIDP Recommendations, 2003). **SYSTEM = Immune** **SCORE = 1**

SECTION 103 REFERENCES

Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. *Eur J Haematol*. Nov 2003;71(5):319-326.

Engelhard D, Cordonnier C, Shaw PJ, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *Br J Haematol*. May 2002;117(2):444-450.

Picardi M, Selleri C, Rotoli B. Spleen sizing by ultrasound scan and risk of pneumococcal infection in patients with chronic GVHD: preliminary observations. *Bone Marrow Transplant*. Jul 1999;24(2):173-177. -138.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
104	**HCT with Chronic GVHD**	**Esophageal stricture** **Info Link:** Related to cGVHD; generally not reversible over time.	**Treatment Factors** Radiation involving the esophagus Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Gastroesophageal reflux	**Treatment Factors** Radiation dose ≥ 40 Gy	**HISTORY** **Dysphagia** **Heartburn** (Yearly)	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Surgery and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 104 REFERENCES

Memoli D, Spitzer TR, Cottler-Fox M, Cahill R, Benjamin S, Deeg HJ. Acute esophageal stricture after bone marrow transplantation. *Bone Marrow Transplant*. Sep 1988;3(5):513-516.
Stemmelin GR, Pest P, Peters RA, Ceresetto JM, Shanley CM, Bullorsky EO. Severe esophageal stricture after autologous bone marrow transplant. *Bone Marrow Transplant*. Jun 1995;15(6):1001-1002.
Williams M. Gastrointestinal manifestations of graft-versus-host disease: diagnosis and management. *AACN Clin Issues*. Nov 1999;10(4):500-506.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
105 (Female)	**HCT with Chronic GVHD**	**Vaginal fibrosis/stenosis** **Info Link:** Related to cGVHD; generally not reversible over time.	**Treatment Factors** Pelvic radiation		**HISTORY** **Psychosocial assessment** **Dyspareunia** **Vulvar pain** **Post-coital bleeding** **Difficulty with tampon insertion** (Yearly)	**Considerations for Further Testing and Intervention** Gynecologic consultation for management. Psychological consultation in patients with emotional difficulties. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 105 REFERENCES

DeLord C, Treleaven J, Shepherd J, Saso R, Powles RL. Vaginal stenosis following allogeneic bone marrow transplantation for acute myeloid leukaemia. *Bone Marrow Transplant*. Mar 1999;23(5):523-525.
Hayes EC, Rock JA. Treatment of vaginal agglutination associated with chronic graft-versus-host disease. *Fertil Steril*. Nov 2002;78(5):1125-1126.
Spinelli S, Chiodi S, Costantini S, et al. Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. *Haematologica*. Oct 2003;88(10):1163-1168.
Spiryda LB, Laufer MR, Soiffer RJ, Antin JA. Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. *Biol Blood Marrow Transplant*. Dec 2003;9(12):760-765.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
106	**HCT with Chronic GVHD**	**Joint contractures** **Info Link:** Related to cGVHD; generally not reversible over time.			**PHYSICAL** **Musculoskeletal exam** (Yearly)	**Considerations for Further Testing and Intervention** Consultation with physical therapy, rehabilitation medicine/physiatrist. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 106 REFERENCES

Antin JH. Clinical practice. Long-term care after hematopoietic-cell transplantation in adults. *N Engl J Med*. Jul 4 2002;347(1):36-42.

Beredjiklian PK, Drummond DS, Dormans JP, Davidson RS, Brock GT, August C. Orthopaedic manifestations of chronic graft-versus-host disease. *J Pediatr Orthop*. Sep-Oct 1998;18(5):572-575.

Flowers ME, Parker PM, Johnston LJ, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood*. Jul 15 2002;100(2):415-419.

SURGERY

AMPUTATION

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
107	**Amputation**	**Amputation-related complications** Impaired cosmesis Functional and activity limitations Residual limb integrity problems Phantom pain Neuropathic pain Musculoskeletal pain Increased energy expenditure Impaired quality of life and functional status Psychological maladjustment	**Host Factors** Skeletally immature/ growing children **Treatment Factors** Site of amputation: Hemipelvectomy > Trans-femur amputation > Trans-tibia amputation **Medical Conditions** Obesity Diabetes Poor residual limb healing		**HISTORY** **Phantom pain** **Functional and activity limitations** (Yearly) **PHYSICAL** **Residual limb integrity** (Yearly) **SCREENING** **Prosthetic evaluation** (Every six months until skeletally mature, then yearly thereafter)	**Health Links** **Amputation** **Counseling** Counsel regarding skin checks, signs of poor prosthetic fit, residual limb and prosthetic hygiene, physical fitness, and importance of maintaining a healthy weight and lifestyle. **Considerations for Further Testing and Intervention** Physical therapy consultation as needed per changing physical status such as weight gain or gait training with a new prosthesis, and for non-pharmacological pain management. Occupational therapy consultation as needed to assist with activities of daily living. Psychological/social work consultation to assist with emotional difficulties related to body image, marriage, pregnancy, parenting, employment, insurance and depression. Vocational counseling/training to identify vocations that will not produce/exacerbate functional limitations. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 107 REFERENCES

Aulivola B, Hile CN, Hamdan AD, et al. Major lower extremity amputation: outcome of a modern series. *Arch Surg*. Apr 2004;139(4):395-399; discussion 399.

Eiser C. Quality of life implications as a consequence of surgery: limb salvage, primary and secondary amputation. *Sarcoma*. 2001;5(4):189-195.

Eiser C. Quality of life in survivors of a primary bone tumor: a systematic review. *Sarcoma*. 1999;4:183-190.

Nagarajan R, Neglia JP, Clohisy DR, et al. Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors: a report from the childhood cancer survivor study. *Cancer*. May 15 2003;97(10):2554-2564.

Renard AJ, Veth RP, Schreuder HW, van Loon CJ, Koops HS, van Horn JR. Function and complications after ablative and limb-salvage therapy in lower extremity sarcoma of bone. *J Surg Oncol*. Apr 2000;73(4):198-205.

Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. A long-term oncological, functional, and quality-of-life study. *J Bone Joint Surg Am*. May 1994;76(5):649-656.

SURGERY

CENTRAL VENOUS CATHETER

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
108	**Central venous catheter**	**Thrombosis** **Vascular insufficiency** **Infection of retained cuff or line tract**			**HISTORY** **Tenderness or swelling at previous catheter site** (Yearly and as clinically indicated) **PHYSICAL** **Venous stasis** **Swelling** **Tenderness at previous catheter site** (Yearly and as clinically indicated)	**SYSTEM = Cardiovascular** **SCORE = 1**

SECTION 108 REFERENCES

Wilimas JA, Hudson M, Rao B, Luo X, Lott L, Kaste SC. Late vascular occlusion of central lines in pediatric malignancies. *Pediatrics*. Feb 1998;101(2):E7.

SURGERY

CYSTECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
109	**Cystectomy** **Info Link:** All potential late effects for pelvic surgery apply to Cystectomy (see also sections 126-129).	**Cystectomy-related complications** Chronic urinary tract infection Renal dysfunction Vesicoureteral reflux Hydronephrosis Reservoir calculi Spontaneous neobladder perforation Vitamin B12/folate/carotene deficiency **Info Link:** Reservoir calculi are stones in the neobladder (a reservoir for urine usually constructed of ileum/colon)			**SCREENING** **Urology evaluation** (Yearly)	**Health Links** **Cystectomy** **Kidney Health** **SYSTEM = Urinary** **SCORE =** **Chronic urinary tract infection: 1** **Renal dysfunction: 1** **Vesicoureteral reflux: 1** **Hydronephrosis: 1** **Spontaneous neobladder perforation: 1** **Reservoir calculi: 2A** **Vitamin B12/folate/carotene deficiency: 2B**

SECTION 109 REFERENCES

DeFoor W, Tackett L, Minevich E, Wacksman J, Sheldon C. Risk factors for spontaneous bladder perforation after augmentation cystoplasty. *Urology*. Oct 2003;62(4):737-741.

Hautmann RE, de Petriconi R, Gottfried HW, Kleinschmidt K, Mattes R, Paiss T. The ileal neobladder: complications and functional results in 363 patients after 11 years of followup. *J Urol*. Feb 1999;161(2):422-427; discussion 427-428.

Hensle TW, Bingham J, Lam J, Shabsigh A. Preventing reservoir calculi after augmentation cystoplasty and continent urinary diversion: the influence of an irrigation protocol. *BJU Int*. Mar 2004;93(4):585-587.

Jahnson S, Pedersen J. Cystectomy and urinary diversion during twenty years--complications and metabolic implications. *Eur Urol*. 1993;24(3):343-349.

Kaefer M, Tobin MS, Hendren WH, et al. Continent urinary diversion: the Children's Hospital experience. *J Urol*. Apr 1997;157(4):1394-1399.

Kalloo NB, Jeffs RD, Gearhart JP. Long-term nutritional consequences of bowel segment use for lower urinary tract reconstruction in pediatric patients. *Urology*. Dec 1997;50(6):967-971.

Raney B, Jr., Heyn R, Hays DM, et al. 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*. Apr 1 1993;71(7):2387-2394.

Sim HG, Lau WK, Cheng CW. A twelve-year review of radical cystectomies in Singapore General Hospital. *Ann Acad Med Singapore*. Sep 2002;31(5):645-650.

SURGERY

ENUCLEATION

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
110	**Enucleation**	**Impaired cosmesis** **Poor prosthetic fit** **Orbital hypoplasia**	**Host Factors** Younger age at enucleation **Treatment Factors** Combined with radiation		**SCREENING** **Evaluation by ocularist** **Evaluation by ophthalmologist** (Yearly)	**Health Links** **Eye Health** **Considerations for Further Testing and Intervention** Psychological consultation in patients with emotional difficulties related to cosmetic and visual impairment. Vocational rehabilitation referral as indicated. **SYSTEM = Ocular** **SCORE = 1**

SECTION 110 REFERENCES

Kaste SC, Chen G, Fontanesi J, Crom DB, Pratt CB. Orbital development in long-term survivors of retinoblastoma. *J Clin Oncol*. Mar 1997;15(3):1183-1189.

SURGERY

HYSTERECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
111 (Female)	**Hysterectomy** **Info Link:** For patients who also underwent oophorectomy, see also: Section 123 (unilateral oophorectomy) or Section 124 (bilateral oophorectomy)	**Pelvic floor dysfunction** **Urinary incontinence** **Sexual dysfunction**			**HISTORY** **Psychosocial assessment** **Abdominal pain** **Urinary leakage** **Dyspareunia** (Yearly)	**Health Links** **Female Health Issues** **Counseling** Counsel patients with ovaries regarding potential for biologic parenthood using gestational surrogate. **Considerations for Further Testing and Intervention** Reproductive endocrinology consultation for patients wishing to pursue pregnancy via gestational surrogate. **SYSTEM = Female reproductive** **SCORE = 2A**

SECTION 111 REFERENCES

Abdel-Fattah M, Barrington J, Yousef M, Mostafa A. Effect of total abdominal hysterectomy on pelvic floor function. *Obstet Gynecol Surv*. Apr 2004;59(4):299-304.

Brown JS, Sawaya G, Thom DH, Grady D. Hysterectomy and urinary incontinence: a systematic review. *Lancet*. Aug 12 2000;356(9229):535-539.

Dragisic KG, Milad MP. Sexual functioning and patient expectations of sexual functioning after hysterectomy. *Am J Obstet Gynecol*. May 2004;190(5):1416-1418.

SURGERY

LAPAROTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
112	**Laparotomy**	**Adhesions** **Bowel obstruction**	**Treatment Factors** Combined with radiation		**HISTORY** **Abdominal pain** **Emesis** **Distention** **Vomiting** **Constipation** (With clinical symptoms of obstruction) **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** (With clinical symptoms of obstruction)	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** KUB as clinically indicated for suspected obstruction. Surgical consultation for patients unresponsive to medical management. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 112 REFERENCES

Jockovich M, Mendenhall NP, Sombeck MD, Talbert JL, Copeland EM, 3rd, Bland KI. Long-term complications of laparotomy in Hodgkin's disease. *Ann Surg*. Jun 1994;219(6):615-621; discussion 621-614.

Kaiser CW. Complications from staging laparotomy for Hodgkin disease. *J Surg Oncol*. 1981;16(4):319-325.

Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys*. Mar 15 2000;46(5):1239-1246.

Ritchey ML, Green DM, Thomas PR, et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. *Med Pediatr Oncol*. Feb 1996;26(2):75-80.

SURGERY

LIMB SPARING PROCEDURE

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
113	**Limb sparing procedure**	**Complications related to limb sparing procedure** Functional and activity limitations Contractures Chronic infection Chronic pain Limb length discrepancy Musculoskeletal pain Increased energy expenditure Fibrosis Prosthetic malfunction (loosening, non-union, fracture) requiring revision, replacement or amputation Prosthetic revision required due to growth Impaired quality of life Complications with pregnancy/delivery (in female patients with internal hemipelvectomy)	**Host Factors** Younger age at surgery Rapid growth spurt **Treatment Factors** Tibial endoprosthesis **Medical Conditions** Endoprosthetic infection Obesity **Health Behaviors** High level of physical activity (associated with higher risk loosening) Low level of physical activity (associated with higher risk of contractures or functional limitations)	**Treatment Factors** Radiation to extremity **Medical Conditions** Poor healing Infection of reconstruction	**HISTORY** **Functional and activity limitations** (Yearly and as clinically indicated) **PHYSICAL** **Residual limb integrity** (Yearly and as clinically indicated) **SCREENING** **Radiograph** (Yearly) **Evaluation by orthopedic surgeon** (Every six months until skeletally mature, then yearly)	**Health Links** **Limb Sparing Procedures** **Counseling** Counsel regarding need for antibiotic prophylaxis prior to dental and invasive procedures. **Considerations for Further Testing and Intervention** Antibiotic prophylaxis prior to dental and invasive procedures. Physical therapy consultation As needed per changes in functional status (such as post-lengthening, revisions, life changes such as pregnancy), and for non-pharmacological pain management. Consider psychological consultation as needed to assist with emotional difficulties related to body image, marriage, pregnancy, parenting, employment, insurance and depression. Vocational counseling/training to identify vocations that will not produce/exacerbate functional limitations. **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 113 REFERENCES

Chihara IG, Osada H, Iitsuka Y, Masuda K, Sekiya S. Pregnancy after limb-sparing hemipelvectomy for Ewing's sarcoma. A case report and review of the literature. *Gynecol Obstet Invest*. 2003;56(4):218-220.

Davis AM, Sennik S, Griffin AM, et al. Predictors of functional outcomes following limb salvage surgery for lower-extremity soft tissue sarcoma. *J Surg Oncol*. Apr 2000;73(4):206-211.

Eiser C. Quality of life implications as a consequence of surgery: limb salvage, primary and secondary amputation. *Sarcoma*. 2001;5(4):189-195.

Jeys LM, Grimer RJ, Carter SR, Tillman RM. Risk of amputation following limb salvage surgery with endoprosthetic replacement, in a consecutive series of 1261 patients. *Int Orthop*. 2003;27(3):160-163.

Nagarajan R, Neglia JP, Clohisy DR, Robison LL. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? *J Clin Oncol*. Nov 15 2002;20(22):4493-4501.

Nagarajan R, Neglia JP, Clohisy DR, et al. Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors: a report from the childhood cancer survivor study. *Cancer*. May 15 2003;97(10):2554-2564.

Renard AJ, Veth RP, Schreuder HW, van Loon CJ, Koops HS, van Horn JR. Function and complications after ablative and limb-salvage therapy in lower extremity sarcoma of bone. *J Surg Oncol*. Apr 2000;73(4):198-205.

Tunn PU, Schmidt-Peter P, Pomraenke D, Hohenberger P. Osteosarcoma in children: long-term functional analysis. *Clin Orthop Relat Res*. Apr 2004(421):212-217.

Veenstra KM, Sprangers MA, van der Eyken JW, Taminiau AH. Quality of life in survivors with a Van Ness-Borggreve rotationplasty after bone tumour resection. *J Surg Oncol*. Apr 2000;73(4):192-197.

Yonemoto T, Tatezaki S, Ishii T, Hagiwara Y. Marriage and fertility in long-term survivors of high grade osteosarcoma. *Am J Clin Oncol*. Oct 2003;26(5):513-516.

SURGERY

NEPHRECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
114	**Nephrectomy**	**Renal toxicity** Proteinuria Hyperfiltration Renal insufficiency **Hydrocele** (males only)	**Treatment Factors** Combined with other nephrotoxic therapy, such as: - Cisplatin - Carboplatin - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants - Methotrexate - Radiation impacting the kidneys		**PHYSICAL** **Blood pressure** (Yearly) **Testicular exam to evaluate for hydrocele** (Yearly for males) **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** (Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated.) **Urinalysis** (Yearly)	**Health Links** **Single Kidney Health** See also: **Kidney Health** **Counseling** Discuss contact sports, bicycle safety (e.g., avoiding handlebar injuries), and proper use of seatbelts (i.e., wearing lapbelts around hips, not waist). Counsel to use NSAIDS with caution. **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 1**

SECTION 114 REFERENCES

Bailey S, Roberts A, Brock C, et al. Nephrotoxicity in survivors of Wilms' tumours in the North of England. *Br J Cancer*. Nov 4 2002;87(10):1092-1098.

Finklestein JZ, Norkool P, Green DM, Breslow N, D'Angio GJ. Diastolic hypertension in Wilms' tumor survivors: a late effect of treatment? A report from the National Wilms' Tumor Study Group. *Am J Clin Oncol*. Jun 1993;16(3):201-205.

Gerstenbluth RE, Spirnak JP, Elder JS. Sports participation and high grade renal injuries in children. *J Urol*. Dec 2002;168(6):2575-2578.

Ginsberg JP, Hobbie WL, Ogle SK, Canning DA, Meadows AT. Prevalence of and risk factors for hydrocele in survivors of Wilms tumor. *Pediatr Blood Cancer*. Apr 2004;42(4):361-363.

Mitus A, Tefft M, Fellers FX. Long-term follow-up of renal functions of 108 children who underwent nephrectomy for malignant disease. *Pediatrics*. Dec 1969;44(6):912-921.

Mpofu C, Mann JR. Urinary protein/creatinine index in follow up of patients with Wilms' tumour after nephrectomy. *Arch Dis Child*. Dec 1992;67(12):1462-1466.

Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys*. Mar 15 2000;46(5):1239-1246.

Ritchey ML, Green DM, Thomas PR, et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. *Med Pediatr Oncol*. Feb 1996;26(2):75-80.

Sharp DS, Ross JH, Kay R. Attitudes of pediatric urologists regarding sports participation by children with a solitary kidney. *J Urol*. Oct 2002;168(4 Pt 2):1811-1814; discussion 1815.

Srinivas M, Agarwala S, Padhy AK, et al. Somatic growth and renal function after unilateral nephrectomy for Wilms' tumor. *Pediatr Surg Int*. Dec 1998;14(3):185-188.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
115	**Neurosurgery - Brain**	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change **Info Link:** Neurocognitive deficits vary with extent of surgery and postoperative complications. In general, mild delays occur in most areas of neuropsychological function compared to healthy children. Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New deficits may emerge over time. Neurosensory deficits (i.e., vision, hearing) due to tumor or its therapy may complicate neurocognitive outcomes.	**Host Factors** Younger age at treatment Primary CNS tumor **Treatment Factors** Extent and location of resection Longer elapsed time since therapy In combination with: - TBI - Cranial radiation - Methotrexate (IT, IO, high-dose IV) - Cytarabine (high-dose IV)	**Host Factors** Age < 3 years at time of treatment Supratentorial tumor Predisposing family history of learning or attention problems **Treatment Factors** Radiation dose ≥ 24 Gy to whole brain Radiation dose ≥ 40 Gy to local fields **Medical Conditions** Posterior fossa syndrome CNS infection	**HISTORY** **Educational and/or vocational progress** (Yearly) **SCREENING** **Referral for formal neuropsychological evaluation** (Baseline at entry into long-term follow-up. Periodically as clinically indicated for patients with evidence of impaired educational or vocational progress.)	**Health Links** **Educational Issues** **Considerations for Further Testing and Intervention** Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Refer patients with neurocognitive deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Consider use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution - lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

SECTION 115 REFERENCES

Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. *J Pediatr Psychol*. Jan-Feb 2005;30(1):65-78.

Carpentieri SC, Waber DP, Pomeroy SL, et al. Neuropsychological functioning after surgery in children treated for brain tumor. *Neurosurgery*. Jun 2003;52(6):1348-1356; discussion 1356-1347.

Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol*. Jul 2004;5(7):399-408.

Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Med Pediatr Oncol*. Jan 2003;40(1):26-34.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
116	**Neurosurgery - Brain**	**Motor and/or sensory deficits** Paralysis Movement disorders Ataxia Eye problems (ocular nerve palsy, gaze paresis, nystagmus, papilledema, optic atrophy)	**Host Factors** Primary CNS tumor **Medical Conditions** Hydrocephalus	**Host Factors** Optic pathway tumor Hypothalamic tumor Suprasellar tumor (eye problems)	**SCREENING** **Evaluation by neurologist** (Yearly, until 2 to 3 years after surgery or stable; continue to monitor if symptoms persist) **Evaluation by physiatrist/rehabilitation medicine specialist** (Yearly, or more frequently as clinically indicated in patients with motor dysfunction)	**Considerations for Further Testing and Intervention** Speech, physical, and occupational therapy in patients with persistent deficits. Consider consultations with nutrition, endocrine, and psychiatry (for obsessive-compulsive behaviors) in patients with hypothalamic-pituitary axis tumors. Ophthalmology evaluation as clinically indicated. **SYSTEM = CNS** **SCORE = 1**

SECTION 116 REFERENCES

Cassidy L, Stirling R, May K, Picton S, Doran R. Ophthalmic complications of childhood medulloblastoma. *Med Pediatr Oncol*. Jan 2000;34(1):43-47.

Doxey D, Bruce D, Sklar F, Swift D, Shapiro K. Posterior fossa syndrome: identifiable risk factors and irreversible complications. *Pediatr Neurosurg*. Sep 1999;31(3):131-136.

Morris EB, Laningham FH, Sandlund JT, Khan RB. Posterior reversible encephalopathy syndrome in children with cancer. *Pediatr Blood Cancer*. Nov 29 2005.

Mulhern RK, Palmer SL. Neurocognitive late effects in pediatric cancer. *Curr Probl Cancer*. Jul-Aug 2003;27(4):177-197.

Sonderkaer S, Schmiegelow M, Carstensen H, Nielsen LB, Muller J, Schmiegelow K. Long-term neurological outcome of childhood brain tumors treated by surgery only. *J Clin Oncol*. Apr 1 2003;21(7):1347-1351

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
117	**Neurosurgery - Brain**	**Seizures**	**Host Factors** Primary CNS tumor **Treatment Factors** Methotrexate (IV, IT, IO)		**SCREENING** **Evaluation by neurologist** (Every six months for patients with seizure disorder)	**SYSTEM = CNS** **SCORE = 1**

SECTION 117 REFERENCES

Khan RB, Marshman KC, Mulhern RK. Atonic seizures in survivors of childhood cancer. *J Child Neurol*. Jun 2003;18(6):397-400.
Khan RB, Hunt DL, Boop FA, et al. Seizures in children with primary brain tumors: incidence and long-term outcome. *Epilepsy Res*. May 2005;64(3):85-91.
Morris EB, Laningham FH, Sandlund JT, Khan RB. Posterior reversible encephalopathy syndrome in children with cancer. *Pediatr Blood Cancer*. Nov 29 2005.
Mulhern RK, Palmer SL. Neurocognitive late effects in pediatric cancer. *Curr Probl Cancer*. Jul-Aug 2003;27(4):177-197.
Sonderkaer S, Schmiegelow M, Carstensen H, Nielsen LB, Muller J, Schmiegelow K. Long-term neurological outcome of childhood brain tumors treated by surgery only. *J Clin Oncol*. Apr 1 2003;21(7):1347-1351.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
118	**Neurosurgery - Brain**	**Hydrocephalus** **Shunt malfunction**	**Host Factors** Primary CNS tumor		**SCREENING** **Abdominal x-ray** (After pubertal growth spurt for patients with shunts to assure distal shunt tubing in peritoneum) **Evaluation by neurosurgeon** (Yearly for patients with shunts)	**Counseling** Education patient/family regarding potential symptoms of shunt malfunction. **SYSTEM = CNS** **SCORE = 1**

SECTION 118 REFERENCES

Dias MS, Albright AL. Management of hydrocephalus complicating childhood posterior fossa tumors. *Pediatr Neurosci.* 1989;15(6):283-289; discussion 290.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
119	**Neurosurgery - Spinal cord**	**Neurogenic bladder** **Urinary incontinence**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation dose ≥ 45 Gy to lumbar and/or sacral spine and/or cauda equina	**Host Factors** Injury above the level of the sacrum **Treatment Factors** Radiation dose ≥ 50 Gy to lumbar and/or sacral spine and/or cauda equina	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly)	**Health Links** **Neurogenic Bladder** **Counseling** Counsel regarding adequate fluid intake, regular voiding, seeking medical attention for symptoms of voiding dysfunction or urinary tract infection, and compliance with recommended bladder catheterization regimen. **Considerations for Further Testing and Intervention** Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections. **SYSTEM = CNS** **SCORE = 1**

SECTION 119 REFERENCES

Fowler C. *Neurology of Bowel, Bladder, and Sexual Dysfunction* Vol 23: Elsevier; 1999.

Hoover M, Bowman LC, Crawford SE, et al. Long-term outcome of patients with intraspinal neuroblastoma. *Med Pediatr Oncol.* May 1999;32(5):353-359.

Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumors occurrring during the neonatal period. *Pediatr Surg Int.* 1996;10(5-6):366-370.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
120	**Neurosurgery - Spinal cord**	**Neurogenic bowel** **Fecal incontinence**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation dose ≥ 50 Gy to bladder, pelvis, or spine	**Host Factors** Injury above the level of the sacrum	**HISTORY** **Chronic constipation** **Fecal soiling** (Yearly) **PHYSICAL** **Rectal exam** (As clinically indicated)	**Counseling** Counsel regarding benefits of adherence to bowel regimen, including adequate hydration, fiber, laxatives/enemas as clinically indicated. **Considerations for Further Testing and Intervention** GI consultation to establish bowel regimen for patients with chronic impaction or fecal soiling. **SYSTEM = CNS** **SCORE = 1**

SECTION 120 REFERENCES

Fowler C. *Neurology of Bowel, Bladder, and Sexual Dysfunction* Vol 23: Elsevier; 1999.

Hoover M, Bowman LC, Crawford SE, et al. Long-term outcome of patients with intraspinal neuroblastoma. *Med Pediatr Oncol.* May 1999;32(5):353-359.

Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumors occurrring during the neonatal period. *Pediatr Surg Int.* 1996;10(5-6):366-370.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
121 (Male)	**Neurosurgery - Spinal cord**	**Sexual dysfunction (Male)** Erectile dysfunction	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation to bladder, pelvis, or spine **Medical Conditions** Hypogonadism	**Host Factors** Injury above the level of the sacrum **Treatment Factors** Radiation dose ≥ 55 Gy to penile bulb in adult Radiation dose ≥ 45 Gy in prepubertal child	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use impacting sexual function** (Yearly)	**Health Links** **Male Health Issues** **Resources** www.urologychannel.com **Considerations for Further Testing and Intervention** Urologic consultation in patients with positive history. **SYSTEM = CNS** **SCORE = 2A**
121 (Female)	**Neurosurgery - Spinal cord**	**Sexual dysfunction (Female)**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation to bladder, pelvis, or spine **Medical Conditions** Hypogonadism Vaginal fibrosis/stenosis Chronic GVHD	**Host Factors** Injury above the level of the sacrum	**HISTORY** **Dyspareunia** **Altered or diminished sensation, loss of sensation** **Medication use impacting sexual function** (Yearly)	**SYSTEM = CNS** **SCORE = 2A**

SECTION 121 REFERENCES

Fowler C. *Neurology of Bowel, Bladder, and Sexual Dysfunction* Vol 23: Elsevier; 1999.

Hoover M, Bowman LC, Crawford SE, et al. Long-term outcome of patients with intraspinal neuroblastoma. *Med Pediatr Oncol.* May 1999;32(5):353-359.

Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumors occurrring during the neonatal period. *Pediatr Surg Int.* 1996;10(5-6):366-370.

SURGERY

OOPHOROPEXY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
122 (Female)	**Oophoropexy** **Info Link:** If shielding from radiation was incomplete: See also Section 84 (ovarian dysfunction related to radiation)	**Oophoropexy-related complications** Inability to conceive despite normal ovarian function Dyspareunia Symptomatic ovarian cysts Bowel obstruction Pelvic adhesions	**Treatment Factors** Ovarian radiation Tubo-ovarian dislocation, especially with lateral ovarian transposition		**HISTORY** **Abdominal pain** **Pelvic pain** **Dyspareunia** **Inability to conceive despite normal ovarian function** (Yearly)	**Considerations for Further Testing and Intervention** Gynecologic consultation for patients with positive history and/or physical findings. **SYSTEM = Female reproductive** **SCORE = 2A**

SECTION 122 REFERENCES

Chambers SK, Chambers JT, Kier R, Peschel RE. Sequelae of lateral ovarian transposition in irradiated cervical cancer patients. *Int J Radiat Oncol Biol Phys*. Jun 1991;20(6):1305-1308.

Damewood MD, Hesla HS, Lowen M, Schultz MJ. Induction of ovulation and pregnancy following lateral oophoropexy for Hodgkin's disease. *Int J Gynaecol Obstet*. Dec 1990;33(4):369-371.

Hadar H, Loven D, Herskovitz P, Bairey O, Yagoda A, Levavi H. An evaluation of lateral and medial transposition of the ovaries out of radiation fields. *Cancer*. Jul 15 1994;74(2):774-779.

Thibaud E, Ramirez M, Brauner R, et al. Preservation of ovarian function by ovarian transposition performed before pelvic irradiation during childhood. *J Pediatr*. Dec 1992;121(6):880-884.

SURGERY

OOPHORECTOMY (UNILATERAL)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
123 (Female)	**Oophorectomy (unilateral)**	**Premature menopause** **Info Link:** Evidence for premature menopause following unilateral oophorectomy is limited and has been extrapolated from the adult literature.	**Health Behaviors** Smoking	**Treatment Factors** Combined with: - Pelvic radiation - Alkylating agents - TBI	**HISTORY** **Pubertal (onset, tempo)** **Menstrual/pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** (Yearly until sexually mature) **SCREENING** **FSH** **LH** **Estradiol** (Baseline at age 13 **and** as clinically indicated in patients with delayed puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency)	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine (www.asrm.org) Fertile Hope (www.fertilehope.org) **Counseling** Counsel currently menstruating women to be cautious about delaying childbearing. Counsel regarding need for contraception. **Considerations for Further Testing and Intervention** Refer to reproductive endocrinology for counseling regarding oocyte cryopreservation in patients wishing to preserve options for future fertility. **SYSTEM = Female reproductive** **SCORE = 2A**

SECTION 123 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.

Lass A. The fertility potential of women with a single ovary. *Hum Reprod Update*. Sep-Oct 1999;5(5):546-550.

Schover LR. Sexuality and fertility after cancer. *Hematology (Am Soc Hematol Educ Program)*. 2005:523-527.

Tangir J, Zelterman D, Ma W, Schwartz PE. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. *Obstet Gynecol*. Feb 2003;101(2):251-257.

SURGERY

OOPHORECTOMY (BILATERAL)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
124 (Female)	**Oophorectomy (bilateral)**	**Hypogonadism** **Infertility**			**SCREENING** **Gynecologic or endocrinologic consultation for initiation of hormonal replacement therapy** (At age 11)	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine (www.asrm.org) Fertile Hope (www.fertilehope.org) **Counseling** Counsel regarding benefits of HRT in promoting pubertal progression, bone and cardiovascular health. Counsel women regarding pregnancy potential with donor eggs (if uterus is intact). **Considerations for Further Testing and Intervention** Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Reproductive endocrinology referral regarding assisted reproductive technologies. **SYSTEM = Female reproductive** **SCORE = 1**

SECTION 124 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.

Schover LR. Sexuality and fertility after cancer. *Hematology (Am Soc Hematol Educ Program)*. 2005:523-527.

Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med*. Sep 7 2000;343(10):682-688.

Tangir J, Zelterman D, Ma W, Schwartz PE. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. *Obstet Gynecol*. Feb 2003;101(2):251-257.

SURGERY

ORCHIECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
125 (Male)	**Orchiectomy**	**Hypogonadism** **Infertility**	**Treatment Factors** Unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents	**Treatment Factors** Bilateral orchiectomy	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use impacting sexual function** (Yearly) **PHYSICAL** **Tanner stage** **Testicular volume by Prader orchdiometry** (Yearly until sexually mature) **SCREENING** **Semen analysis** (As requested by patient for evaluation of infertility) **FSH, LH, testosterone** (For patient with bilateral orchiectomy, refer to endocrinology at about age 11. For patients with unilateral orchiectomy, obtain as clinically indicated for delayed puberty or signs and symptoms of testosterone deficiency.)	**Health Links** **Male Health Issues** **Counseling** For patients with single testis - counsel to wear athletic supporter with protective cup during athletic activities. **Considerations for Further Testing and Intervention** Refer to endocrinologist for bilateral orchiectomy, delayed puberty, or persistently abnormal hormone levels. Consider surgical placement of testicular prosthesis. **SYSTEM = Male reproductive** **SCORE = 1**

SECTION 125 REFERENCES

Herr HW, Bar-Chama N, O'Sullivan M, Sogani PC. Paternity in men with stage I testis tumors on surveillance. *J Clin Oncol.* Feb 1998;16(2):733-734.

Jacobsen KD, Fossa SD, Bjoro TP, Aass N, Heilo A, Stenwig AE. Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. *Eur Urol.* Sep 2002;42(3):229-238; discussion 237-228.

Lee PA, Coughlin MT. The single testis: paternity after presentation as unilateral cryptorchidism. *J Urol.* Oct 2002;168(4 Pt 2):1680-1682; discussion 1682-1683.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
126	**Pelvic surgery** **Info Link:** For patients with cystectomy: See also Section 109	**Urinary incontinence** **Urinary tract obstruction** **Info Link:** Urinary tract obstruction related to retroperitoneal fibrosis	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Retroperitoneal node dissection Extensive pelvic dissection (e.g., bilateral ureteral re-implantation, retroperitoneal tumor resection): Radiation to the bladder, pelvis, and/or lumbar-sacral spine		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** (Yearly)	**Counseling** Counsel regarding adequate fluid intake, regular voiding, seeking medical attention for symptoms of voiding dysfunction or urinary tract infection, compliance with recommended bladder catheterization regimen. **Considerations for Further Testing and Intervention** Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections. **SYSTEM = Urinary** **SCORE = 1**

SECTION 126 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.

Heyn R, Raney RB, Jr., Hays DM, et al. Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. *J Clin Oncol*. Apr 1992;10(4):614-623.

Koyle MA, Hatch DA, Furness PD, 3rd, Lovell MA, Odom LF, Kurzrock EA. Long-term urological complications in survivors younger than 15 months of advanced stage abdominal neuroblastoma. *J Urol*. Oct 2001;166(4):1455-1458.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
127	**Pelvic surgery**	**Fecal incontinence**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation to the bladder, pelvis, or spine		**HISTORY** **Chronic constipation, fecal soiling** (Yearly) **PHYSICAL** **Rectal exam** (As clinically indicated)	**Counseling** Counsel regarding benefits of adherence to bowel regimen, including adequate hydration, fiber, laxatives/enemas as clinically indicated. **Considerations for Further Testing and Intervention** GI consultation to establish bowel regimen for patients with chronic impaction or fecal soiling. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 127 REFERENCES

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.
Hoover M, Bowman LC, Crawford SE, et al. Long-term outcome of patients with intraspinal neuroblastoma. *Med Pediatr Oncol*. May 1999;32(5):353-359.
Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumors occurrring during the neonatal period. *Pediatr Surg Int*. 1996;10(5-6):366-370.
Mosiello G, Gatti C, De Gennaro M, et al. Neurovesical dysfunction in children after treating pelvic neoplasms. *BJU Int*. Aug 2003;92(3):289-292.
Rao S, Azmy A, Carachi R. Neonatal tumours: a single-centre experience. *Pediatr Surg Int*. Sep 2002;18(5-6):306-309.

SURGERY

PELVIC SURGERY (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
128 (Male)	**Pelvic surgery**	**Sexual dysfunction (Male)** Retrograde ejaculation Anejaculation Erectile dysfunction	**Treatment Factors** Retroperitoneal node dissection Retroperitoneal tumor resection Cystectomy Radical prostatectomy Tumor adjacent to spine Radiation to bladder, pelvis, or spine **Medical Conditions** Hypogonadism	**Host Factors** Extensive presacral tumor resection or dissection Radiation dose ≥ 55 Gy to penile bulb in adult and ≥ 45 Gy in prepubertal child	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use impacting sexual function** **Quality of ejaculate (frothy white urine with first void after intercourse suggests retrograde ejaculation)** (Yearly)	**Health Links** **Male Health Issues** **Resources** www.urologychannel.com **Considerations for Further Testing and Intervention** Urologic consultation in patients with positive history and/or physical exam findings. **SYSTEM = Male reproductive** **SCORE = 2A**
128 (Female)	**Pelvic surgery**	**Sexual dysfunction (Female)**	**Host Factors** Chronic GVHD Hypogonadism Tumor adjacent to spine **Medical Conditions** Radiation to bladder, pelvis, or spine		**HISTORY** **Dyspareunia** **Altered or diminished sensation, loss of sensation** **Medication use impacting sexual function** (Yearly)	**SYSTEM = Female reproductive** **SCORE = 2A**

SECTION 128 REFERENCES

(Male)

Fossa SD. Long-term sequelae after cancer therapy--survivorship after treatment for testicular cancer. *Acta Oncol*. 2004;43(2):134-141.

Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. *J Pediatr Hematol Oncol*. Mar-Apr 1999;21(2):115-122.

Hartmann JT, Albrecht C, Schmoll HJ, Kuczyk MA, Kollmannsberger C, Bokemeyer C. Long-term effects on sexual function and fertility after treatment of testicular cancer. *Br J Cancer*. May 1999;80(5-6):801-807.

Jacobsen KD, Ous S, Waehre H, et al. Ejaculation in testicular cancer patients after post-chemotherapy retroperitoneal lymph node dissection. *Br J Cancer*. Apr 1999;80(1-2):249-255.

(Female)

Burton KA, Wallace WH, Critchley HO. Female reproductive potential post-treatment for childhood cancer. *Hosp Med*. Sep 2002;63(9):522-527.

El-Toukhy TA, Hefni M, Davies A, Mahadevan S. The effect of different types of hysterectomy on urinary and sexual functions: a prospective study. *J Obstet Gynaecol*. Jun 2004;24(4):420-425.

Schover LR. Sexuality and fertility after cancer. *Hematology (Am Soc Hematol Educ Program)*. 2005:523-527.

Spunt SL, Sweeney TA, Hudson MM, Billups CA, Krasin MJ, Hester AL. Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. *J Clin Oncol*. Oct 1 2005;23(28):7143-7151.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
129 (Male)	**Pelvic surgery**	**Hydrocele**	**Treatment Factors** Retroperitoneal node dissection		**PHYSICAL** **Testicular exam to evaluate for hydrocele** (Yearly)	**Considerations for Further Testing and Intervention** Urologic consultation for patients with hydrocele. **SYSTEM = Urinary** **SCORE = 1**

SECTION 129 REFERENCES

Ginsberg JP, Hobbie WL, Ogle SK, Canning DA, Meadows AT. Prevalence of and risk factors for hydrocele in survivors of Wilms tumor. *Pediatr Blood Cancer*. Apr 2004;42(4):361-363.

SURGERY

PULMONARY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
130	**Pulmonary lobectomy** **Pulmonary metastasectomy** **Pulmonary wedge resection**	**Pulmonary dysfunction**	**Treatment Factors** Combined with pulmonary toxic therapy - Bleomycin - Busulfan - Carmustine (BCNU) - Lomustine (CCNU) **Medical Conditions** Atopic history **Health Behaviors** Smoking	**Treatment Factors** Combined with: - Chest radiation - TBI	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** (Yearly) **PHYSICAL** **Pulmonary exam** (Yearly) **SCREENING** **Chest x-ray** **PFTs (including DLCO and spirometry)** (Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction.)	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: www.smokefree.gov **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs and/or CXR, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for patients with symptomatic pulmonary dysfunction; Influenza and pneumococcal vaccinations **SYSTEM = Pulmonary** **SCORE = 2A**

SECTION 130 REFERENCES

Berend N, Woolcock AJ, Marlin GE. Effects of lobectomy on lung function. *Thorax*. Feb 1980;35(2):145-150.

Bolliger CT, Jordan P, Soler M, et al. Pulmonary function and exercise capacity after lung resection. *Eur Respir J*. Mar 1996;9(3):415-421.

Pelletier C, Lapointe L, LeBlanc P. Effects of lung resection on pulmonary function and exercise capacity. *Thorax*. Jul 1990;45(7):497-502.

Stolp B, Assistant Medical Director Divers Alert Network, Director Anesthesiology Emergency Airway Services, Durham, N.C. Risks associated with SCUBA diving in childhood cancer survivors. Personal communication to Landier W, Bhatia S Aug 23, 2002.

SURGERY

SPLENECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
131	**Splenectomy**	**Asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., Haemophilus influenzae, streptococcus pneumoniae, meningococcus)			**PHYSICAL** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** (When febrile T ≥ 101ºF) **SCREENING** **Blood culture** (When febrile T ≥ 101ºF)	**Health Links** **Splenic Precautions** **Counseling** Medical alert bracelet/card noting asplenia. Counsel to avoid malaria and tick bites if living in or visiting endemic areas **Considerations for Further Testing and Intervention** In patients with T ≥101°F (38.3° C) or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC; toxic clinical appearance; fever ≥ 104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines. Pneumovax booster in patients ≥10 years old at ≥ 5 years after previous dose (AAP-CIDP Recommendations, 2003). **SYSTEM = Immune** **SCORE = 1**

SECTION 131 REFERENCES

Immunization in special clinical circumstances: asplenic children. In: Pickering LK, ed. Red Book 2003: *Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2003.

Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. *Eur J Haematol*. Nov 2003;71(5):319-326.

Jockovich M, Mendenhall NP, Sombeck MD, Talbert JL, Copeland EM, 3rd, Bland KI. Long-term complications of laparotomy in Hodgkin's disease. *Ann Surg*. Jun 1994;219(6):615-621; discussion 621-614.

Kaiser CW. Complications from staging laparotomy for Hodgkin disease. *J Surg Oncol*. 1981;16(4):319-325.

SURGERY

THYROIDECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
132	**Thyroidectomy** **Info Link:** Total thyroidectomy is uncommon, but if done is associated with the risk of hypoparathyroidism. This complication generally occurs in the early postoperative period and may persist. Patients with a history of total thyroidectomy should be monitored for signs and symptoms of hypoparathyroidism (e.g., parasthesias, muscle cramping, altered mental status, hyperreflexia, tetany, hypocalcemia, and hyperphosphatemia)	**Hypothyroidism**			**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** (Yearly; Consider more frequent screening during periods of rapid growth) **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** (Yearly; Consider more frequent screening during periods of rapid growth) **SCREENING** **TSH** **Free T4** (Yearly; Consider more frequent screening during periods of rapid growth)	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 132 REFERENCES

La Quaglia MP, Telander RL. Differentiated and medullary thyroid cancer in childhood and adolescence. *Semin Pediatr Surg*. Feb 1997;6(1):42-49.

Lallier M, St-Vil D, Giroux M, et al. Prophylactic thyroidectomy for medullary thyroid carcinoma in gene carriers of MEN2 syndrome. *J Pediatr Surg*. Jun 1998;33(6):846-848.

Telander RL, Moir CR. Medullary thyroid carcinoma in children. *Semin Pediatr Surg*. Aug 1994;3(3):188-193.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
133	**Radioiodine therapy (I-131 thyroid ablation)**	**Lacrimal duct atrophy**			**HISTORY** **Excessive tearing** (Yearly)	**Considerations for Further Testing and Intervention** Ophthalmology consultation as clinically indicated. **SYSTEM = Ocular** **SCORE = 2A**

SECTION 133 REFERENCES

Burns JA, Morgenstern KE, Cahill KV, Foster JA, Jhiang SM, Kloos RT. Nasolacrimal obstruction secondary to I(131) therapy. *Ophthal Plast Reconstr Surg*. Mar 2004;20(2):126-129.

Morgenstern KE, Vadysirisack DD, Zhang Z, et al. Expression of sodium iodide symporter in the lacrimal drainage system: implication for the mechanism underlying nasolacrimal duct obstruction in I(131)-treated patients. *Ophthal Plast Reconstr Surg*. Sep 2005;21(5):337-344.

Zettinig G, Hanselmayer G, Fueger BJ, et al. Long-term impairment of the lacrimal glands after radioiodine therapy: a cross-sectional study. *Eur J Nucl Med Mol Imaging*. Nov 2002;29(11):1428-1432.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
134	**Radioiodine therapy (I-131 thyroid ablation)**	**Hypothyroidism**			**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** (Yearly; Consider more frequent screening during periods of rapid growth) **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** (Yearly; Consider more frequent screening during periods of rapid growth) **SCREENING** **TSH** **Free T4** (Yearly; Consider more frequent screening during periods of rapid growth)	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

SECTION 134 REFERENCES

Safa AM, Schumacher OP, Rodriguez-Antunez A. Long-term follow-up results in children and adolescents treated with radioactive iodine (131I) for hyperthyroidism. *N Engl J Med*. Jan 23 1975;292(4):167-171.

Safa AM, Skillern PG. Treatment of hyperthyroidism with a large initial dose of sodium iodide I 131. *Arch Intern Med*. May 1975;135(5):673-675.

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
135	**Systemic MIBG (in therapeutic doses)** **Info Link:** MIBG used for diagnostic purposes (i.e., MIBG scanning) does NOT put patients at risk for hypothyroidism.	**Hypothyroidism**			**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** (Yearly; Consider more frequent screening during periods of rapid growth) **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** (Yearly; Consider more frequent screening during periods of rapid growth) **SCREENING** **TSH** **Free T4** (Yearly; Consider more frequent screening during periods of rapid growth)	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

SECTION 135 REFERENCES

Brans B, Monsieurs M, Laureys G, Kaufman JM, Thierens H, Dierckx RA. Thyroidal uptake and radiation dose after repetitive I-131-MIBG treatments: influence of potassium iodide for thyroid blocking. *Med Pediatr Oncol*. Jan 2002;38(1):41-46.

Picco P, Garaventa A, Claudiani F, Gattorno M, De Bernardi B, Borrone C. Primary hypothyroidism as a consequence of 131-I-metaiodobenzylguanidine treatment for children with neuroblastoma. *Cancer*. Nov 1 1995;76(9):1662-1664.

van Santen HM, de Kraker J, van Eck BL, de Vijlder JJ, Vulsma T. High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during (131)I-meta-iodobenzylguanidine treatment in children with neuroblastoma. *Cancer*. Apr 1 2002;94(7):2081-2089.

van Santen HM, de Kraker J, van Eck BL, de Vijlder JJ, Vulsma T. 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*. Jul 15 2003;98(2):389-396.

BIOIMMUNOTHERAPY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
136	**Bioimmunotherapy** (e.g., G-CSF, IL-2, erythropoietin)	**Insufficient information currently available regarding late effects of biological agents**				**SYSTEM = N/A** **SCORE = N/A**

SECTION 136 REFERENCES

No information currently available regarding late effects.

BREAST CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
137 (Female)	**Breast**	Over age 40 Family history of breast cancer in first degree relative Early onset of menstruation Late onset of menopause (age 55 or older) Older than 30 at birth of first child Never pregnant Obesity Previous breast biopsy with atypical hyperplasia Hormone replacement therapy	Chest radiation with potential impact to the breast (see Section 68), including ≥ 20 Gy to the following fields: - Mantle - Mini-Mantle - Mediastinal - Chest (thorax) - Axilla BRACA1, BRACA2, ATM mutation	**PATIENTS AT STANDARD RISK (ACS Recommendation)** **PHYSICAL** **Clinical breast exam** (Every 3 years between ages 20-39, then yearly beginning at age 40) **SCREENING** **Mammogram** (Yearly, beginning at age 40) **PATIENTS AT HIGHEST RISK** **PHYSICAL** **Breast self exam** (Monthly, beginning at puberty) **Clinical breast exam** (Yearly, beginning at puberty until age 25, then every six months) **SCREENING** **Mammogram** (Yearly, beginning 8 years after radiation or at age 25, whichever occurs last) **Info Link:** There is currently a deficiency in the literature regarding whether or not TBI is a risk factor for the development of breast cancer. Monitoring of patients who received TBI should be determined on an individual basis. Mammography is currently limited in its ability to evaluate premenopausal breasts. The role of MRI is evolving for screening of other populations at high risk for breast cancer (e.g., premenopausal known or likely carriers of gene mutation of known penetrance).	**Health Links** **Breast Cancer** (for patients at highest risk only) **Counseling** For patients at highest risk, counsel to perform breast self-examination monthly, beginning at puberty. For standard risk patients, provide general guidance regarding routine screening beginning at age 40 per current ACS guidelines. **Considerations for Further Testing and Intervention** Surgery and/or oncology consultation as clinically indicated.

SECTION 137 REFERENCES

Breast Cancer Screening and Diagnosis Guidelines. *National Comprehensive Cancer Network Clinical Practice Guidelines*. July 13, 2004. Available at: www.nccn.org. Accessed January 5, 2006, 2005.

Diller L, Medeiros Nancarrow C, Shaffer K, et al. Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. *J Clin Oncol*. Apr 15 2002;20(8):2085-2091.

Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. Jul 29 2004;351(5):427-437.

Liberman L. Breast cancer screening with MRI--what are the data for patients at high risk? *N Engl J Med*. Jul 29 2004;351(5):497-500.

Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2005. *CA Cancer J Clin*. Jan-Feb 2005;55(1):31-44; quiz 55-36.

Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. *JAMA*. Mar 26 1997;277(12):997-1003.

Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol*. Mar 1 2002;20(5):1260-1268.

Shaw de Paredes E, Marsteller LP, Eden BV. Breast cancers in women 35 years of age and younger: mammographic findings. *Radiology*. Oct 1990;177(1):117-119.

Tardivon AA, Garnier ML, Beaudre A, Girinsky T. Breast carcinoma in women previously treated for Hodgkin's disease: clinical and mammographic findings. *Eur Radiol*. 1999;9(8):1666-1671.

Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. Sep 15 2004;292(11):1317-1325.

CERVICAL CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
138 (Female)	**Cervical**	Early age at first intercourse Multiple lifetime sex partners Smoking Sexually transmitted diseases	Personal history of cervical dysplasia Prenatal DES exposure HPV infection Immunosuppression Chronic steroid use HIV positive Chronic GVHD	**PATIENTS AT STANDARD RISK (ACS Recommendation)** **PHYSICAL** **Pelvic exam** (Every 1 to 2 years) **SCREENING** **Cervical PAP smear** (Yearly for regular PAP test. Every 2 years for liquid-based PAP test. After age 30, if patient has had 3 consecutive normal annual PAP tests, may screen every 2-3 years [with conventional or liquid-based cervical cytology] or every 3 years [with HPV DNA test plus cervical cytology]). **Info Link:** Begin screening (in patients with a cervix) 3 years after first vaginal intercourse, or at age 21, whichever occurs first.	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Gynecology and/or oncology consultation as clinically indicated.

SECTION 138 REFERENCES

Screening for Cervical Cancer. File Inventory, Systematic Evidence Review #25:http://www.ahrq.gov. Accessed July 11, 2005, 2005.
Cervical Screening. October 1, 2004; v 1.2005:www.nccn.org. Accessed July 11, 2005, 2005.
Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. *J Clin Oncol*. Jan 15 2001;19(2):464-471.
Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin*. Jan-Feb 2002;52(1):8-22.

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
139	**Colorectal**	High fat/low fiber diet Age ≥ 50 years Obesity	Radiation with potential impact to the colon/rectum (see Section 78), including ≥ 30 Gy to the following fields: - Whole abdomen - All upper abdominal fields - Pelvic - Spine (thoracic, lumbar, sacral) Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps in first degree relative	**PATIENTS AT STANDARD RISK (ACS Recommendation)** **SCREENING** **Option 1:** **Fecal occult blood (minimum of 3 cards)** (Yearly, beginning at age 50) AND/OR **Flexible sigmoidoscopy** (Every 5 years, beginning at age 50) *Note: The combination of yearly fecal occult blood testing and every 5 year flexible sigmoidoscopy is preferable to either test done alone.* **Option 2:** **Double contrast barium enema** (Every 5 years, beginning at age 50) **Option 3:** **Colonoscopy** (Every 10 years, beginning at age 50) **PATIENTS AT HIGHEST RISK** **SCREENING** **Colonoscopy** (Every 5 years [minimum]; more frequently if indicated based on colonoscopy results. Begin monitoring 10 years after radiation or at age 35, whichever occurs last. Monitor more frequently if clinically indicated. Per the ACS, begin screening earlier for the following high-risk groups: HNPCC [at puberty], FAP [at age 21 years], IBD [8 years after diagnosis of IBD]. Information from the first colonoscopy will inform frequency of follow up testing. **Info Link:** Reports of gastrointestinal malignancies in cohorts of long-term survivors suggest that radiation likely increases risk, but the median age of onset is not as well established as that of secondary breast cancer following chest radiation. The expert panel agreed that early onset of screening likely was beneficial, and that a prudent course would be to initiate screening for colorectal cancer for those at highest risk (abdominal, pelvic, and/or spinal radiation ≥ 30 Gy) at age 35, or 10 years post radiation, whichever occurs last. Surveillance should be done via colonoscopy as per recommendations for populations at highest risk, with information from the first colonoscopy informing the frequency of follow-up testing.	**Health Links** **Colorectal Cancer** **Considerations for Further Testing and Intervention** Gastroenterology, surgery and/or oncology consultation as clinically indicated.

SECTION 139 REFERENCES

Screening for Colorectal Cancer in Adults. July 2002; File Inventory, Systematic Evidence Review Number 7AHRQ Publication No. 02-S003:http://www.ahrq.gov/clinic/prev/colscinv.htm. Accessed July 11, 2005, 2005.

Colorectal Screening. March 24, 2005; v 1.2005:http://www.nccn.org. Accessed July 11, 2005, 2005.

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol*. Jun 2000;18(12):2435-2443.

Provenzale D, Gray RN. Colorectal cancer screening and treatment: review of outcomes research. *J Natl Cancer Inst Monogr*. 2004(33):45-55.

Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin*. Jan-Feb 2002;52(1):8-22.

van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol*. Feb 2000;18(3):487-497.

ENDOMETRIAL CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
140 (Female)	**Endometrial**	Obesity Older age Unopposed estrogen therapy Tamoxifen Diabetes Hypertension High fat diet Early menopause Late menopause Nulliparity Infertility Failure to ovulate	History of/at risk for hereditary nonpolyposis colon cancer (HNPCC)	**PATIENTS AT HIGHEST RISK (ACS Recommendation)** **SCREENING** **Endometrial biopsy** (Yearly, beginning at age 35 for patients at highest risk) **Info Link:** Women at highest risk should be informed that screening recommendation of endometrial biopsy beginning at age 35 is based on expert opinion in the absence of definitive scientific evidence and the potential benefits, risks, and limitations of testing for early endometrial cancer detection should be discussed.	**Health Links** **Reducing the Risk of Second Cancers**

SECTION 140 REFERENCES

Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2005. *CA Cancer J Clin.* Jan-Feb 2005;55(1):31-44..

LUNG CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
141	**Lung**	Smoking Workplace exposures to asbestos, arsenic, radiation Second hand smoke (in non-smokers)	Chest radiation with potential impact to the lung	**PATIENTS AT HIGHEST RISK** **HISTORY** **Cough** **Wheezing** **SOB** **DOE** (Yearly, and as clinically indicated) **PHYSICAL** **Pulmonary Exam** (Yearly, and as clinically indicated)	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Imaging and surgery and/or oncology consultation as clinically indicated.

SECTION 141 REFERENCES

Bauer T. Lung cancer screening. *Hematol Oncol Clin North Am*. Apr 2005;19(2):209-217.

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet*. Jul 10 1999;354(9173):99-105.

Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol*. Jun 2000;18(12):2435-2443.

ORAL CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
142	**Oral**	Tobacco use (smoking cigars, cigarettes, or pipes; dipping, chewing) Alcohol abuse Excessive sun exposure (increases risk of cancer of lower lip) HCT (allogeneic > autologous)	Head/brain radiation Neck radiation TBI Acute/chronic GVHD	**PATIENTS AT HIGHEST RISK** **PHYSICAL** **Oral cavity exam** (Yearly)	**Health Links** **Reducing Risk of Second Cancers** **Dental Health** **Considerations for Further Testing and Intervention** Head and neck/otolaryngology consultation as indicated.

SECTION 142 REFERENCES

Bhatia S, Yasui Y, Robison LL, et al. 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*. Dec 1 2003;21(23):4386-4394.

Joseph BK. Oral cancer: prevention and detection. *Med Princ Pract*. 2002;11 Suppl 1:32-35.

Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol*. Jun 2000;18(12):2435-2443.

PROSTATE CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
143 (Male)	**Prostate**	Older age, with steadily increasing risk after age 40 years.	African-American race Family history of prostate cancer in first degree relative	**ALL PATIENTS** **Clinicians should be prepared to discuss prostate cancer testing with patients** **Info Link:** The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cancers that may never have affected a patient's health. The USPSTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population. ACS concurs with this conclusion.	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Urology and/or oncology consultation as clinically indicated.

SECTION 143 REFERENCES

Prostate Cancer Early Detection. March 24, 2005; v 1.2005:http://www.nccn.org. Accessed July 11, 2005, 2005.
Screening for Prostate Cancer. December 2002; File Inventory, Systematic Evidence Review Number 16:http://www.ahrq.gov/clinic/prev/prostinv.htm. Accessed July 11, 2005, 2005.
Harris R, Lohr KN. Screening for prostate cancer: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. Dec 3 2002;137(11):917-929.
Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2005. *CA Cancer J Clin*. Jan-Feb 2005;55(1):31-44.

SKIN CANCER

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
144	**Skin**	Light skin color Chronic exposure to sun Atypical moles or ≥ 50 moles	Any history of radiation Personal history of melanoma or skin cancer Dysplastic nevi Family history of melanoma or skin cancer History of severe sunburn at young age	**PATIENTS AT STANDARD RISK** **Info Link:** The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for skin cancer using a total-body skin examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer. There are no randomized trials or case-control studies that directly examine whether screening by clinicians is associated with improved clinical outcomes such as reduced morbidity or mortality from skin cancer. No studies were found that evaluated whether screening improves the outcomes of these cancers. The American Cancer Society recommends skin examination as part of a cancer-related checkup, which should occur on the occasion of the patient's periodic health examination. Self-examination of skin is recommended once a month. **PATIENTS AT HIGHEST RISK** **PHYSICAL** **Skin self exam** (Monthly) **Dermatologic exam with attention to skin lesions and pigmented nevi in radiation field** (Yearly)	**Health Links** **Reducing the Risk of Second Cancers** **Skin Health** **Considerations for Further Testing and Intervention** Surgery, dermatology, and/or oncology consultation as clinically indicated.

SECTION 144 REFERENCES

Screening for Skin Cancer. File Inventory, Systematic Evidence Review Number 2:http://www.ahrq.gov/clinic/serfiles.htm. Accessed July 11, 2005, 2005.

Ferrini R. Screening for skin cancer. *Am Fam Physician*. Apr 1 2002;65(7):1401-1402.

Ferrini RL, Perlman M, Hill L. American College of Preventive Medicine practice policy statement: skin protection from ultraviolet light exposure. The American College of Preventive Medicine. *Am J Prev Med*. Jan 1998;14(1):83-86.

Ferrini RL, Perlman M, Hill L. American College of Preventive Medicine policy statement: screening for skin cancer. *Am J Prev Med*. Jan 1998;14(1):80-82.

Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst*. Apr 18 2001;93(8):618-629.

Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Jun 1 2005;23(16):3733-3741.

Wolden SL, Lamborn KR, Cleary SF, Tate DJ, Donaldson SS. Second cancers following pediatric Hodgkin's disease. *J Clin Oncol*. Feb 1998;16(2):536-544.

Sec #	Organ	At Risk Population	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
145 (Male)	**Testicular**	Young males	History of cryptorchidism History of testicular cancer or carcinoma in-situ in contralateral testis History of gonadal dysgenesis Klinefelter's syndrome Family history of testicular cancer	**Info Link:** For standard and high risk populations, the USPSTF recommends against routine screening for testicular cancer in asymptomatic adolescent and adult males. In 2004, the USPSTF found no new evidence that screening with clinical examination or testicular self-examination is effective in reducing mortality from testicular cancer. Even in the absence of screening, the current treatment interventions provide very favorable health outcomes. Given the low prevalence of testicular cancer, limited accuracy of screening tests, and no evidence for the incremental benefits of screening, the USPSTF concluded that the harms of screening exceed any potential benefits. ACS also no longer recommends clinical testicular cancer screening or testicular self-examination.	

SECTION 145 REFERENCES

Screening for Testicular Cancer PDQ. www.nci.nih.gov. Accessed 01/26/2003.

Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2005. *CA Cancer J Clin*. Jan-Feb 2005;55(1):31-44.

GENERAL HEALTH SCREENING

ANY CANCER EXPERIENCE

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling Further Considerations
146	**General Health Screening**				**SCREENING** **Refer to United States Preventive Services Task Force recommendations at** www.ahrq.gov/clinic/uspstfix.htm (Yearly)	**Considerations for Further Testing and Intervention** Childhood cancer survivors should receive general health maintenance per standard recommendations for age. Recommended preventive services per the USPSTF include screening for hypertension, obesity, depression, tobacco use, and alcohol misuse. In addition, certain subpopulations require screening for lipid disorders, sexually transmitted diseases, and diabetes mellitus. Others require counseling regarding the prevention of cardiovascular disease, osteoporosis, and other disorders. See www.ahrq.gov/clinic/uspstfix.htm for specific recommendations. Assess immunization status on all patients; reimmunize as indicated. See http://www.cdc.gov/nip/default.htm#schedules for current immunization schedules. For all HCT patients, reimmunization per CDC Guidelines (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm - see table 4) or EBMT Guidelines (http://www.nature.com/bmt/journal/v23/n7/pdf/1701641a.pdf).

SECTION 146 REFERENCES

Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000; 49:1-128 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm)

Ljungman P. Immunization of transplant recipients. *Bone Marrow Transplant*. 1999 Apr;23(7):635-6.

United States Preventive Services Task Force recommendations at http://www.ahrq.gov/clinic/uspstfix.htm

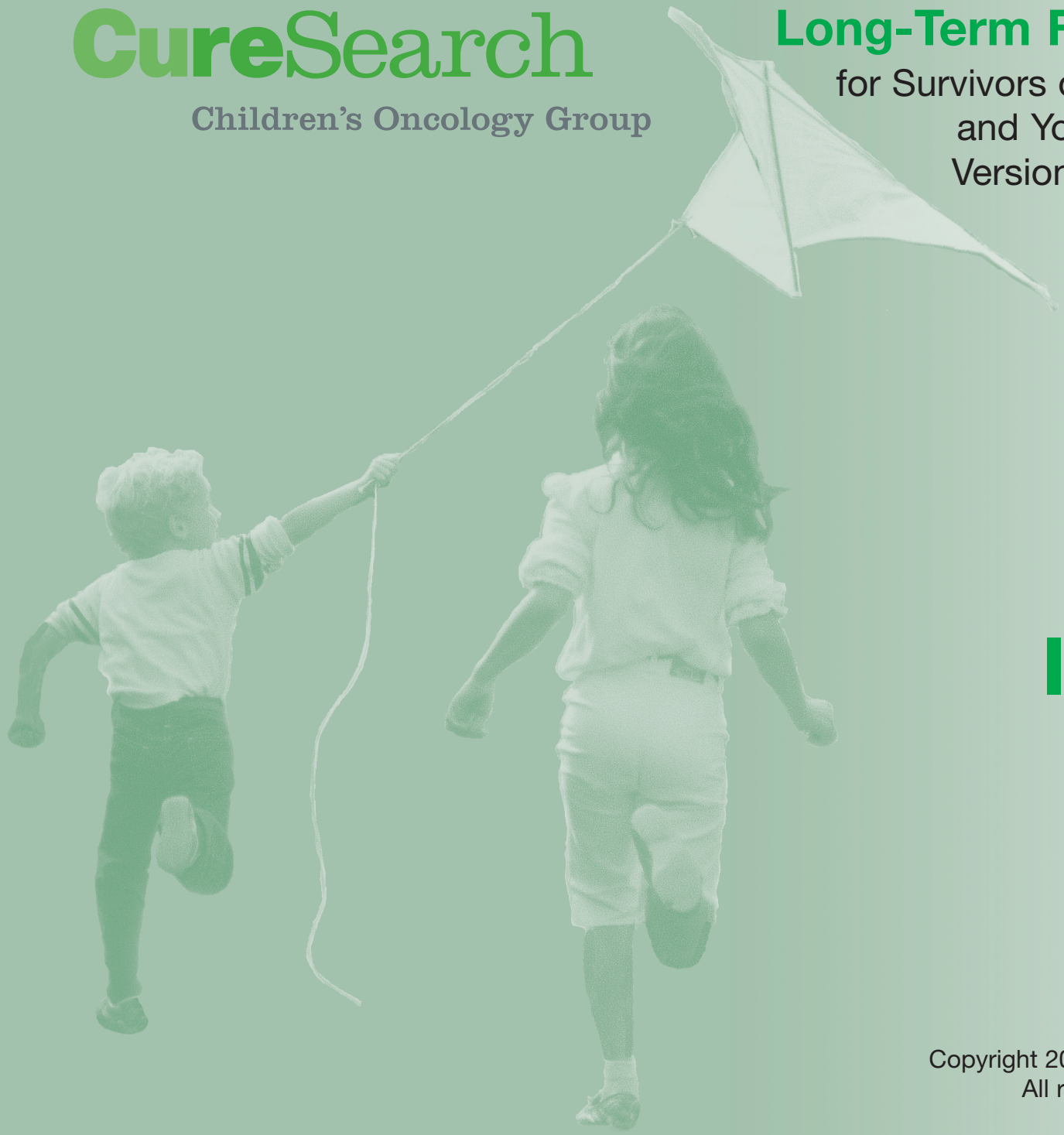
CureSearch

Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 2.0 – March 2006



Index

Index

Index (cont)

Index (cont)

Index (cont)

Index (cont)

Index (cont)

Index (cont)

Index (cont)

Index (cont)

Index (cont)