CureSearch

Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 1.2 – March 2004

CureSearch
Children's Oncology Group

Abstract – Version 1.2
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Release date: March 2004

Status: Updated from Version 1.1 (name change and other minor modifications)

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. The information provided in these guidelines is important for primary care 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 the lifespan.

Source: 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 at www.survivorshipguidelines.org.

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 from 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 health care provider.

> *To cancer patients (if children, their parents or legal guardians):* Please seek the advice of a physician or other qualified health 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 1.2 – March 2004

Contributors

- Task Force
- Panel of Experts
- Reviewers
- Health Link Authors

Long-Term Follow-Up Guidelines
Task Force

The Children's Oncology Group Nursing Discipline and Late Effects Committee developed 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
Pediatric Nurse Practitioner - 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

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
Director, Epidemiology and Outcomes Research
and Survivorship Clinic
Department of Pediatric Hematology, Oncology,
and Bone Marrow Transplant
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

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
Assistant Professor of Pediatrics
Director, Long-term Follow-Up
Children's Hospital and Regional Medical 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

Wendy Landier, RN, MSN, CPNP, CPON®
Pediatric Nurse Practitioner
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

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 Oeffinger, MD
Director, After the Cancer Experience
Young Adult Program
Professor, University of Texas
Southwestern Medical School
Dallas, TX

Leslie L. Robison, PhD
Professor of Pediatrics
University of Minnesota Cancer Center
Minneapolis, MN

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

Long-Term Follow-Up Guidelines
Reviewers

The following individuals participated in the review process during development 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 Internal Medicine
Northwestern University
Chicago, IL

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
Department of Pediatric Hematology/Oncology and
Bone Marrow Transplant
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
Children's Hospital and Regional Medical Center
Seattle, WA

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

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

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 Family Practice and Community Medicine
University of Texas Southwestern Medical School
Dallas, TX

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 Pediatrics
University of Minnesota Cancer Center
Minneapolis, MN

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 Oncology
Johns Hopkins Hospital
Baltimore, MD

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

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

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*:

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

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

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

Debra L. Friedman MD, MS
Pediatric Hematology-Oncology
Children's Hospital and Regional Medical 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 Pediatric Hematology/Oncology
City of Hope Comprehensive Cancer Center
Duarte, CA

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

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

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

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

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

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

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

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

CureSearch

Children's Oncology Group

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

Version 1.2 – March 2004

Introduction & Instructions for Use

CureSearch
Children's Oncology Group

Introduction – Version 1.2
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. The guidelines are therefore organized according to therapeutic agent, and cross-referenced to other topics with related toxicities. 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, 90 (88%) of the screening recommendations outlined for the 102 therapeutic exposures in the COG-LTFU Guidelines comprise assessments derived primarily from the H&P, with 48 (47%) relying solely on the H&P and 21 (21%) relying on the H&P plus a baseline diagnostic study (e.g., lab, imaging), whereas 31 (30%) include periodic laboratory, diagnostic imaging, or other testing. 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 indexed by section number and listed in the reference section. Patient education materials complementing the guidelines have been organized into *Health Links* that feature health protective counseling on 33 topics, enhancing patient follow-up visits and broadening application of the guidelines.

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.

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 clinician (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.

Developer: The COG-LTFU Guidelines were developed as a collaborative effort of the Children's Oncology Group Nursing Discipline and the 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 (as of September 2003) was retrieved and reviewed during the development 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" and "complications" combined with keywords for each therapeutic exposure. References from the bibliographies of selected articles were used to broaden the search.

Methods: 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 16-member panel of experts in the late effects of pediatric malignancies, comprised of multidisciplinary representatives from the COG Late Effects Committee.

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 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. The current 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.

Plan for Updates: Development of any clinical care guideline is a dynamic process, requiring continual review and revision in order to keep the document current and clinically meaningful. Task forces have therefore been organized within the COG Late Effects Committee to monitor the literature and recommend changes to these guidelines as new information becomes available. A total of 20 task forces have been organized to focus on specific clinical topics (e.g., cardiovascular, neurocognitive, fertility/reproductive, etc.). Responsibilities of these task forces include presentation of an annual report to the Late Effects Committee describing new literature, and preparation of recommendations for guideline revisions, such as addition of agents/therapeutic exposures, revision of risk groups, revision of screening recommendations, development and/or modification of patient education materials, and modification of the reference list. The guidelines will be updated at least annually to reflect changes recommended by these task forces.

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.

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:

These guidelines are 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.

Implementation Considerations:

Initial concerns regarding implementation of the COG-LTFU Guidelines 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.

CureSearch
Children's Oncology Group

Instructions for Use – Version 1.2
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Using the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

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

Therapeutic Agent: The therapeutic intervention for malignancy, including chemotherapy, radiation therapy, surgery, blood/blood products, or hematopoietic cell transplant.

Section Number: Corresponds with Reference List and Index.

Potential Late Effects: Lists the most common late treatment complications associated with the therapeutic intervention.

Risk Factors: Lists 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: Lists 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, clinical exams, laboratory evaluations, diagnostic imaging studies, psychosocial assessments, or other indicated evaluations.

Minimum Recommended Frequency: Recommended minimum frequency of periodic evaluations based on risk factors and magnitude of risk as supported by medical literature and/or the combined clinical experience of the reviewers and panel of experts.

Health Protective Counseling: Suggested patient counseling regarding measures to prevent/reduce risk or promote early detection of the potential treatment complication. *Health Links* listed in the document are health education materials produced specifically to accompany this document. These *Health Links* are included in the Appendix and are also available on the COG website at www.survivorshipguidelines.org.

Note: *Throughout the Health Links series, the term "childhood cancer" is used to designate pediatric cancers that may occur during childhood, adolescence, or young adulthood. Health Links are designed to provide health information for survivors of pediatric cancer, regardless of whether the cancer occurred during childhood, adolescence, or young adulthood.*

Considerations for Further Testing and Intervention: Includes 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.

Cancer Screening Recommendations are included at the end of the guidelines. This section is organized 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).

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 are provided immediately following the guidelines. The Reference section contains medical citations corresponding to each numbered section of the guidelines. Included are references 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.

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 is imperative** in order to determine the location of each potential late effect associated with each therapeutic agent within this document.*

Scoring - Each recommendation in the guidelines was scored by the panel of experts (see accompanying "Explanation of Scoring" following the Index.) A tabulation of the final scores is included in this packet.

Importance of Comprehensive Treatment Summary

The *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* are based on therapeutic exposures received during cancer treatment. Availability of a comprehensive treatment summary, including all therapeutic agents received by the survivor, is assumed. Patients who do not have a comprehensive treatment summary should be instructed to obtain one from the institution(s) where they received their treatment. The comprehensive treatment summary should include the following information:

- Diagnosis, including site/stage, date, and relapse(s) if any
- Pertinent secondary diagnoses (e.g., second malignancy, Down syndrome)
- All chemotherapy agents received during treatment (including route of administration for all agents, cumulative doses for alkylators, bleomycin, and anthracyclines, and designation of "high dose" versus "standard dose" for methotrexate and cytarabine). Cumulative doses for all other agents should be provided if available.
- Radiation therapy summary for all fields, including type, site/volume, dates, total dose (in cGy), dose per fraction, and number of fractions.
- Surgical procedures
- Hematopoietic cell transplant(s), including type(s), date(s), conditioning regimen(s), and GVHD prophylaxis and/or treatment
- Significant complications, including treatment required
- Adverse drug reactions/allergies

We are hopeful that these *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, CPNP
Chair – COG Nursing Clinical Practice 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

Version 1.2 – March 2004

Long-Term Follow-Up Guidelines
for Survivors of Childhood, Adolescent, and Young Adult Cancers
Version 1.2 – March 2004

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Any cancer experience								
Clinician Info Link The Children's Oncology Group Long-Term Follow-Up Guidelines apply to patients who are ≥ 2 years after completion of therapy. For all patients treated prior to 1993, please also see Sections 81-83 to review screening recommendations related to presumed blood/blood product exposures.	1	**Psychosocial Effects** Depression Anxiety Post-traumatic stress Social withdrawal Educational problems	**Host factors** Female gender Family history of depression, anxiety, or mental illness **Social factors** Lower household income Lower educational achievement	**Host factors** CNS cancer or CNS-directed therapy Premorbid learning or emotional difficulties **Social factors** Failure to graduate from high school	Clinical interview	Yearly	**Health Link** Introduction to Long-Term Follow-Up after Treatment for Childhood, Adolescent, or Young Adult Cancer Emotional Issues after Childhood Cancer Educational Issues Following Treatment for Childhood Cancer **Resources** "Childhood Cancer Survivors" by Nancy Keene, Wendy Hobbie & Kathy Ruccione Sebastopol, CA: O'Reilly & Assoc., 2000 "Educating the Child with Cancer" edited by Nancy Keene. Candlelighters Childhood Cancer Foundation, Bethesda, MD, 2003.	Psychological consultation in patients with emotional difficulties related to cancer experience including physical deformities or chronic disabilities following cancer treatment. Consider appropriate psychotropic medications. Social work consultation. Consider evaluation of parent for post-traumatic stress syndrome. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources.
	2	**Limitations in healthcare and insurance access**	**Social factors** Lower household income Lower educational achievement		Clinical history	Yearly	**Health Link** Finding Appropriate Healthcare after Childhood Cancer	Social work consultation.
Any Chemotherapy								
	3	**Dental abnormalities** Tooth/root agenesis Root thinning/ shortening Enamel dysplasia	**Host factors** Any patient who has not developed permanent dentition **Cancer treatment** Any radiation treatment including oral cavity or salivary glands.	**Host factors** Younger age at treatment, especially < 5 years old	Dental exam and cleaning	Every 6 months	**Health Link** Dental Health	Regular dental care including fluoride applications. Baseline panorex prior to dental procedures to evaluate root development.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Alkylating Agents								
Mechlorethamine **Cyclophosphamide** **Ifosfamide** **Melphalan** **Chlorambucil** **Lomustine (CCNU)** **Carmustine (BCNU)** **Busulfan** **Thiotepa** **Procarbazine** **Non-classical alkylators:** **Dacarbazine** **Temozolamide** **Heavy metals:** **Cisplatin** **Carboplatin** **Clinician Info Link** Doses that cause gonadal dysfunction show individual variation. Sertoli cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function. Females can typically maintain gonadal function at higher cumulative doses. Prepubertal status does not protect from gonadal injury in males.	4	**Hypogonadism** **Infertility** **Early menopause (females)** **See related topics:** **Radiation – TBI, head/brain, abdomen, pelvis, or testes.** **Orchiectomy** **Clinician Info Link** Extensive information regarding infertility for physicians and patients available at American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	**Treatment factors** Higher cumulative doses of alkylators or combinations of alkylators Combined with radiation to: - abdomen/pelvis - CNS - head/neck - testes - craniospinal axis in girls (from ovarian scatter)	**Host factors** Male gender **Treatment factors** MOPP > 3 cycles Busulfan ≥ 600 mg/m^2 Cyclophosphamide ≥ 7.5 g/ m^2 cumulative or ≥ 200 mg/kg for stem cell transplant Any alkylators combined with: - testicular radiation - pelvic radiation - TBI	**Females:** Pubertal history (onset, tempo) Menstrual and pregnancy history Physical exam including height, weight, Tanner stage	Yearly	**Health Link** Female Health Issues after Childhood Cancer **or** Male Health Issues after Childhood Cancer Counsel currently menstruating women at increased risk of early menopause to be cautious about delaying childbearing. Counsel regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology/ obstetrics 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.
					FSH, LH, estradiol	Baseline at about age 11 and as clinically indicated in patients with: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency For patients who received alkylating chemotherapy for stem cell transplant conditioning, obtain baseline at age 8 and then yearly until normal puberty is established.		
					Males: Pubertal history (onset, tempo) History of sexual function (erections, nocturnal emissions, libido) History of medication use Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					FSH, LH, testosterone	Baseline at about age 11 and as clinically indicated in patients with: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency For patients who received alkylating chemotherapy for stem cell transplant conditioning, obtain baseline at age 9 and then yearly until normal puberty is established		
					Semen analysis	As requested by patient and for evaluation of infertility		
	5	**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)		Physical exam CBC/differential	Yearly up to 15 years after exposure to agent	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Busulfan **Carmustine (BCNU)** **Lomustine (CCNU)**	6	**Pulmonary fibrosis** **See related topics:** **Bleomycin** **Chest/thorax radiation**	**Treatment factors** Higher cumulative doses Combined with other pulmonary toxic therapy: - bleomycin - chest/thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **Medical conditions** Atopic history **Health behaviors** Cigarette smoking	**Treatment factors** BCNU ≥ 600 mg/m^2 Busulfan ≥ 500 mg (transplant doses)	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up and prior to general anesthesia. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction	**Health Link** Pulmonary Health 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	Pulmonary consultation for symptomatic pulmonary dysfunction. Influenza and Pneumovax immunization.
Busulfan	7	**Cataracts** **See related topics:** **Prednisone** **Dexamethasone** **Head/brain radiation** **TBI**	**Treatment factors** Combined with: - total body irradiation - brain/head radiation - corticosteroids	**Treatment factors** TBI given in single daily fraction Radiation dose ≥ 10 Gy with potential scatter to eye(s) Longer interval since treatment	Eye exam including funduscopic exam and visual acuity	Yearly	**Health Link** Eye Problems after Childhood Cancer	Ophthalmology consultation if problem identified. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP).
Cyclophosphamide **Ifosfamide**	8	**Hemorrhagic cystitis** **Bladder fibrosis** **Dysfunctional voiding** **See related topics:** **Pelvic radiation**	**Treatment factors** Higher cumulative doses (decreased incidence with Mesna) Combined with pelvic radiation **Health behaviors** Alcohol use Tobacco use	**Treatment factors** Cyclophosphamide dose ≥ 3 gm/m^2	Voiding history Urinalysis	Yearly Yearly	Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture negative macroscopic hematura.
	9	**Bladder malignancy** **See related topics:** **Pelvic radiation**	**Treatment factors** Combined with pelvic radiation		Urinalysis	Yearly	**Health Link** Reducing the Risk of Second Cancers	Urology consultation for culture negative macroscopic hematuria.
Ifosfamide	10	**Renal toxicity:** Glomerular toxicity Tubular toxicity -Renal tubular acidosis -Fanconi's syndrome -Hypophosphatemic rickets **See related topics:** **Cisplatin/Carboplatin** **Methotrexate** **Abdominal/pelvic radiation** **Cystectomy** **Nephrectomy**	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Combined with other nephrotoxic agents, such as: - cisplatin/carboplatin - aminoglycosides - amphotericin - immunosuppressants - abdominal radiation **Medical conditions** Tumor infiltration of kidney(s) Pre-existing renal impairment Nephrectomy or mononephric	**Host factors** Age < 5 years at time of treatment **Treatment factors** Ifosfamide dose ≥ 60 grams/m^2	Blood pressure BUN, creatinine, U/A Na, K, Cl, CO_2, Ca, Mg, $P0_4$ Creatinine clearance or GFR	Yearly Yearly Baseline electrolytes at entry into long-term follow-up. If normal, repeat every 5 years. If abnormal, repeat as clinically indicated. Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated	**Health Link** Kidney Health See also: Single Kidney Precautions	Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Heavy Metals								
Cisplatin **Carboplatin**	11	**Ototoxicity:** - Sensorineural hearing loss - Tinnitus - Vertigo **See related topics:** **Ear radiation** **Clinician Info Link** Prospective studies are needed to define ototoxic dose/effect relationship for carboplatin.	**Host factors** Age <4 years at treatment **Treatment factors** Combined with: - head/neck/cranial radiation - other 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	History and physical exam	Yearly	**Health Link** Hearing Problems after Childhood Cancer	Audiology consultation for assistive devices 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 to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources, IEP for preferential classroom seating or specialized classroom placement, FM trainer or other assistive devices, and other educational assistance as indicated.
					Audiogram or brainstem auditory evoked response (ABR, BAER)	Baseline at entry into long-term follow-up. If abnormal, follow yearly until stable. If clinical evidence of progressive hearing loss, obtain more frequently as indicated until stable.		
	12	**Peripheral sensory neuropathy** **Clinician Info Link** Neuropathy presents as persistent effect after therapy and is typically not late in onset.	**Treatment factors** Combined with vincristine	**Treatment factors** Cisplatin cumulative dose ≥ 300 mg/m^2	Neurologic exam	Yearly, until 2 to 3 years after therapy. Monitor yearly if symptoms persist.	**Health Link** Peripheral Neuropathy	Physical therapy referral for patients with symptomatic neuropathy. Physical therapy and occupational therapy assessment of hand function. Consider treatment with agent effective for neuropathic pain (e.g., gabapentin or amitriptyline).
	13	**Renal toxicity:** - Glomerular injury - Tubular injury - Renal insufficiency **See related topics:** **Ifosfamide** **Methotrexate** **Abdominal/pelvic radiation** **Cystectomy** **Nephrectomy**	**Treatment factors** Combined with other nephrotoxic agents, such as: - ifosfamide - aminoglycosides - amphotericin - immunosuppressants - cyclosporine - abdominal radiation therapy **Medical conditions** Mononephric Diabetes mellitus Familial hypertension	**Treatment factors** Cisplatin dose ≥ 200 mg/m^2	Blood pressure	Yearly	**Health Link** Kidney Health See also: Single Kidney Precautions In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis.	Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Yearly		
					Na, K, Cl, CO_2, Ca, Mg, $P0_4$	Baseline electrolytes at entry into long-term follow-up. If normal, repeat every 5 years. If abnormal, repeat as clinically indicated.		
					Creatinine clearance or GFR	Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated		
	14	**Dyslipidemia**	**Host factors** Family history of dyslipidemia **Medical conditions** Overweight/Obesity		Fasting lipid profile	Baseline, at entry into long-term follow-up; then as per United States Preventive Task Force Recommendations http://www.ahrq.gov/clinic/prevenix.htm If abnormal, refer for management of dyslipidemia	**Health Link** Health Promotion through Diet and Physical Activity	Lipid lowering strategies including diet, exercise, weight loss, and pharmacologic therapy (e.g., statin therapy).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Antimetabolites								
Cytarabine (high-dose IV) Note: High-dose IV is defined as any single dose ≥1000 mg/m^2 **See related topics:** **Methotrexate** **Head/brain radiation** **Clinician 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.	15	**Neurocognitive deficits:** **Diminished IQ** (combined with high dose and/or intrathecal methotrexate and/or cranial radiation.) **Functional deficits in**: **Processing speed** **Memory** (particularly visual, sequencing, temporal memory) **Sustained attention** **Visual-motor integration** **Math** **Reading** (particularly reading comprehension) **Planning and organization** **Clinician Info Link** Acute toxicity predominates if administered systemically as single agent. May contribute to late neurotoxicity if combined with intrathecal methotrexate and/ or cranial radiation.	**Host factors** Younger age at treatment CNS leukemia/lymphoma **Treatment factors** High-dose systemic administration (≥ 1000 mg/m^2 dose) In combination with: - dexamethasone - cranial radiation - total body irradiation - intrathecal methotrexate	**Host factors** Age < 3 years old at time of treatment Female gender **Treatment factors** Combined with methotrexate and/or cranial radiation. Radiation ≥ 24 Gy TBI with daily fraction ≥ 2 Gy	Clinical interview including assessment of educational or vocational progress	Baseline at entry into long-term follow-up, then yearly	**Health Link** Educational Issues Following Treatment for Childhood Cancer	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. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Refer to community services for vocational rehabilitation or for services for developmentally disabled.
					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		
		Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - mineralizing micro-angiopathy **Clinician Info Link** 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.	**Treatment factors** Combined with: - intrathecal methotrexate - dexamethasone - cranial radiation	**Treatment factors** High-dose IV administration combined with cranial radiation Radiation dose ≥ 24 Gy TBI with daily fraction ≥ 2 Gy	Clinical evaluation	Yearly		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: microvascular injury CT: calcifications Neurology consultation and follow-up.
					Brain MRI	As clinically indicated		
					Brain CT plus MRI with MR angiography	As clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Mercaptopurine **Thioguanine** **Clinician 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.	16	**Hepatic dysfunction** **Veno-occlusive disease** Acute toxicities predominate from which the majority of patients recover without sequelae. **See related topics:** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Transfusion (chronic hepatitis B & C)** **Hematopoietic cell transplant (liver toxicity)**	**Medical conditions** Viral hepatitis	**Medical conditions** Chronic viral hepatitis	Physical exam ALT, AST, bilirubin	Yearly Baseline at entry into long-term follow-up.	**Health Link** Liver Health	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.
Methotrexate **(PO, IV, IM)** **Clinician Info Link** Osteopenia and osteoporosis occur more commonly after methotrexate than does osteonecrosis. **See related topics:** **Corticosteroids** **Hematopoietic cell transplant** **(continued on next page)**	17	**Osteopenia** Bone mineral density ≥ 1 and < 2.5 SD below mean **Osteoporosis** Bone mineral density ≥ 2.5 SD below mean **Clinician Info Link** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density of young adults at peak bone age and defined as a T-score. 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 bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Host factors** Both genders at risk **Treatment factors** Corticosteroids Cranial/spinal, head/neck, gonadal radiation Hematopoietic cell transplantation **Medical conditions** Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism		Bone density evaluation (DEXA or quantitative CT) **Clinician 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.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.	**Health Link** Keeping Your Bones Healthy After Childhood Cancer Resource: National Osteoporosis Foundation website www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. ** 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 bone density more than 2.5 SD below mean or patients with history of multiple fractures, for other pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Methotrexate (PO, IV, IM)	18	**Renal dysfunction** Acute toxicities predominate, from which the majority of patients recover without sequelae. **See related topics:** **Ifosfamide** **Cisplatin/Carboplatin** **Abdominal/pelvic radiation** **Cystectomy** **Nephrectomy**	**Host factors** Mononephric Combined with other nephrotoxic agents: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppresants - cyclosporine - abdominal radiation **Medical conditions** Diabetes mellitus Familial hypertension	**Treatment factors** Treatment before 1970.	Blood pressure	Yearly	**Health Link** Kidney Health See also: Single Kidney Precautions	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Baseline at entry into long-term follow-up.		
					Na, K, Cl, CO_2 Ca, Mg, PO_4 Creatinine clearance or GFR.	Obtain in patients with abnormal BP, urinalysis, BUN, or creatinine. If abnormal, repeat as clinically indicated.		
	19	**Hepatic dysfunction** Acute toxicities predominate from which the majority of patients recover without sequelae. **See related topics:** **Mercaptopurine** **Dactinomycin** **Hepatic radiation** **Transfusion (chronic hepatitis B &C)** **Hematopoietic cell transplant (liver toxicity)**	**Treatment factors** Abdominal radiation **Medical conditions** Viral hepatitis	**Treatment factors** Treatment before 1970 **Medical conditions** Chronic viral hepatitis	Physical exam	Yearly	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver function on 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.
					ALT, AST, bilirubin	Baseline at entry into long-term follow-up.		

Therapeutic Agent	Sec ##	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Methotrexate (IT, high-dose IV) Note: High-dose IV is defined as any single dose ≥1000 mg/m^2 **See related topics:** **Head/brain radiation** **Cytarabine (high-dose IV)** **Clinician 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.	20	**Neurocognitive deficits:** **Diminished IQ** (with high dose and/or intrathecal methotrexate and/or cranial radiation.) **Functional deficits in:** **Processing speed** **Memory** (particularly visual, sequencing, temporal memory) **Sustained attention** **Visual-motor integration** **Math** **Reading** (particularly reading comprehension) **Planning and organization**	**Host factors** Younger age at treatment CNS leukemia/lymphoma **Treatment factors** Intrathecal administration High-dose systemic administration (≥ 1000 mg/m^2 dose) In combination with: - dexamethasone - cranial radiation - total body irradiation - high-dose IV cytarabine **Medical conditions** CNS leukemia/lymphoma with poor CSF reabsorption	**Host factors** Age < 3 years old at time of treatment Female gender **Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose ≥ 24 Gy TBI with daily fraction ≥ 2 Gy	Clinical interview including assessment of educational or vocational progress	Yearly	**Health Link** Educational Issues Following Treatment for Childhood Cancer	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. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Refer to community services for vocational rehabilitation or for services for developmentally disabled.
					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		
		Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - mineralizing micro-angiopathy **Clinician Info Link** Neuro-imaging 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 **Treatment factors** Intrathecal administration High-dose systemic (≥ 1000 mg/m^2 dose) administration Triple intrathecal chemotherapy In combination with: - dexamethasone - cranial radiation - total body irradiation **Medical conditions** CNS leukemia/lymphoma with poor CSF reabsorption	**Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose ≥ 20 Gy TBI with daily fraction ≥ 2 Gy	Clinical evaluation	Yearly		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: microvascular injury CT: calcifications Neurology consultation and follow-up
					Brain MRI	As clinically indicated		
					Brain CT plus MRI with MR angiography	As clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Anthracycline antibiotics								
Doxorubicin **Daunorubicin** **Idarubicin** **Mitoxantrone** **Epirubicin** **See related topics:** **Chest/thorax radiation**	21	**Acute myeloid leukemia**	**Treatment factors** Less than 5 years since exposure to drug		Physical exam CBC/ differential	Yearly up to 10 years post exposure to anthracycline	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.
	22	**Cardiomyopathy** **Arrhythmias** **Clinician 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. Need for prospective studies 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/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: Mantle Mediastinal Total body irradiation Spinal ≥ 30 Gy Whole lung Whole abdomen Left hemiabdomen/flank Any left-sided upper abdominal field Combined with other cardiotoxic chemotherapy: - cyclophosphamide (100-200 mg/kg as conditioning for stem cell transplantation) - amsacrine **Medical conditions** Congenital heart disease Pregnancy Febrile illness Health behaviors Isometric exercise Drug use (e.g., cocaine, diet pills, ephedra, mahuang)	**Host factors** Female Black/ of African descent Younger than age 5 years at treatment **Treatment factors** Higher cumulative doses: ≥ 550 mg/m^2 in patients 18 years or older at time of treatment ≥ 300 mg/m^2 in patients younger than 18 years at time of treatment Any dose in infant Longer time elapsed since treatment	Detailed history of exertional tolerance. **Clinician Info Link** Note: exertional intolerance is uncommon in young patients (< 25 years). Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain.	Yearly	**Health Link** Heart Problems Following Treatment for Childhood Cancer Counsel patients with prolonged QT interval about use of medications that may further prolong QT interval (e.g., tricyclic anti- depressants, antifungals, macrolide antibiotics, metronidazole).	Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QT interval. Additional cardiology evaluation in patients who received ≥ 300 mg/m^2 or < 300 mg/m^2 plus chest radiation or TBI who are pregnant or planning pregnancy to include an EKG and echocardiogram before and periodically during pregnancy (especially during 3rd trimester) and monitoring during labor and delivery due to risk of cardiac failure. Consider excess risk of isometric exercise program in any high risk patient defined as needing screening every 1 or 2 years.
					EKG for evaluation of QT interval	Baseline at entry into long-term follow-up		
					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).		

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

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Anti-Tumor Antibiotics								
Bleomycin	23	**Interstitial pneumonitis** **Pulmonary fibrosis** **Acute respiratory distress syndrome (very rare)** **See related topics:** **Chest/thorax radiation** **Busulfan** **Carmustine** **Lomustine** **Clinician Info Link** Administration of high concentrations of oxygen may result in chronic progressive pulmonary fibrosis.	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Combined with other pulmonary toxic therapy: - busulfan - carmustine (BCNU) - lomustine (CCNU) - thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **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)	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up and prior to general anesthesia. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Bleomycin Alert 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.	Pulmonary consultation in patients with symptomatic or progressive pulmonary dysfunction. Influenza and Pneumococcal vaccines.
Dactinomycin	24	**No known late effects** (Dactinomycin has been associated with acute veno-occlusive disease, from which the majority of patients recover without sequelae) **See related topics:** **Mercaptopurine** **Methotrexate** **Hepatic radiation** **Transfusion (chronic hepatitis B &C)** **Hematopoietic cell transplant (liver toxicity)**	**Treatment factors** Hepatic radiation		Physical exam ALT, AST, bilirubin	Yearly Baseline at entry into long-term follow-up.	**Health Link** Liver Health	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.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Corticosteroids								
Prednisone **Dexamethasone**	25	**Osteopenia** (Bone mineral density 1-2.5 SD below mean) **Osteoporosis** (Bone mineral density ≥ 2.5 SD below mean) **Clinician Info Link** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density of young adults at peak bone age and defined as a T-score. 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 bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Host factors** Both genders at risk **Treatment factors** Combined with: - methotrexate - cranial or spinal radiation - other head/neck radiation - radiation to bones **Medical Conditions** Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism **See related topics:** **Methotrexate** **Hematopoietic cell transplant**	**Host factors** Older age at time of treatment **Treatment factors** Dexamethasone effect is more potent than prednisone.	Bone density evaluation (DEXA or quantitative CT) **Clinician 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.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.	**Health Link** Keeping Your Bones Healthy After Childhood Cancer National Osteoporosis Foundation website: www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. ** 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 bone density more than 2.5 SD below mean, or patients with history of multiple fractures, for other pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).
	26	**Avascular necrosis (AVN) (Osteonecrosis)** **Clinician Info Link** AVN typically occurs during the acute treatment phase, may progress over time or resolve. Multifocal AVN is significantly more common (3:1) than unifocal.	**Host factors** Both genders at risk **Treatment factors** Dexamethasone effect is more potent than prednisone. Combined with: - high-dose radiation to any bone **Medical conditions** Sickle cell disease	**Host factors** Older 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	Yearly	**Health Link** Avascular Necrosis	Diagnostic imaging (radiograph, MRI) in patients with history of chronic pain. Orthopedic consultation for history of chronic joint pain in predisposed patient.
	27	**Cataracts** **See related topics:** **Busulfan** **Head/brain radiation** **TBI**	**Treatment factors** Combined with: - total body irradiation - brain/head radiation - busulfan	**Treatment factors** TBI given in single daily fraction Radiation dose ≥ 10 Gy with potential scatter to eye(s) Longer interval since treatment	Eye exam including funduscopic exam and visual acuity	Yearly	**Health Link** Eye Problems after Childhood Cancer	Ophthalmology consultation if problem identified. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Enzymes								
Asparaginase	28	**No known late effects.** Acute toxicities predominate, from which the majority of patients recover without sequelae.						
Plant Alkaloids								
Vincristine **Vinblastine** **Clinician 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.	29	**Peripheral sensory or motor neuropathy:** - areflexia - weakness - foot drop - parasthesias	**Treatment factors** Combined with cisplatin **Medical conditions** Anorexia Severe weight loss	**Medical conditions** Charcot-Marie-Tooth disease	Neurologic exam	Yearly, until 2 to 3 years after therapy; continue to monitor yearly if symptoms persist.	**Health Link** Peripheral Neuropathy	Physical therapy referral for patients with symptomatic neuropathy. Physical therapy and occupational therapy assessment of hand function. Treatment with anticonvulsant effective for neuropathic pain (e.g., gabapentin and amitriptyline).
	30	**Vasospastic attacks** (Raynaud's phenomenon)	**Health behaviors** Tobacco use Illicit drug use		History Physical exam	Yearly	**Health Link** Raynaud's Phenomenon Counsel to wear appropriate protective clothing in cold environments and to not use tobacco or illicit drugs.	Vasodilating medications (calcium-channel blockers, alpha blockers) for patients with frequent, severe vasospastic attacks unresponsive to behavioral management.
Epipodophyllotoxins								
Etoposide (VP-16) **Teniposide (VM-26)** **Clinician Info Link** Administration schedules since ~1990 have been modified to reduce the risk of this complication.	31	**Acute myeloid leukemia**	**Medical conditions** Splenectomy (conflicting evidence)	**Treatment factors** Weekly or twice weekly administration Less than 5 years since exposure to drug.	Physical exam CBC/ differential	Yearly up to 10 years post exposure to agent	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Radiation								
All fields, including Total Body Irradiation **Clinician Info Link** General factors influencing radiation toxicity: - daily fraction size - cumulative dose - age of patient at irradiation - type of radiation used - toxicity may not be manifest until growth completed or patient ages	32	**Skin changes**: Fibrosis, telangiectasias, permanent hair loss, altered skin pigmentation	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose	**Host factors** Prepubertal at treatment **Treatment factors** Dose fraction ≥ 2 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly	**Health Link** Skin Health	
	33	**Secondary benign or malignant neoplasm** in or near radiation field	**Host factors** Cancer predisposing mutations: p53, RB1, NF1 **Treatment factors** High cumulative dose Large treatment volumes	**Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam with inspection and palpation of irradiated skin and soft tissues. Other evaluations based on treatment volumes	Yearly See recommendations for specific fields	**Health Link** Reducing the Risk of Second Cancers	Surgical and/or oncology consultation as clinically indicated.
	34	**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.	Physical exam	Yearly	**Health Link** Skin Health Reducing the Risk of Second Cancers	Dermatology consultation for evaluation and monitoring of atypical nevi. Oncology consultation as clinically indicated.
	35	**Bone malignancies**	**Host factors** Adolescent at treatment Cancer-predisposing mutation (e.g., p53, RB1, NF1) **Treatment factors** High 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.	Physical exam	Yearly	Counsel patient to report symptoms promptly (bone pain, bone mass, persistent fevers, etc.)	X-ray or other diagnostic imaging in patients with clinical symptoms. Oncology consultation as clinically indicated.
Total Body Irradiation (TBI)								

Potential complications related to total body irradiation (TBI) are addressed throughout this document.
In order to obtain a complete list of potential complications related to total body irradiation, with associated recommendations, refer to <u>all</u> of the following radiation sections in this document:

Radiation - All Fields, Head/Brain, Eye, Ear, Neck, Trunk, Chest/Thorax, Abdomen/Pelvis, Testicular

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Head/Brain Radiation								
Any field involving the head/brain, including: **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** **(continued on next page)**	36	**Neurocognitive deficits:** **Diminished IQ (< 85)** **Functional deficits in:** **Processing speed** **Memory** (particularly visual, sequencing, temporal memory) **Sustained attention** **Visual-motor integration** **Math** **Reading** (particularly reading comprehension) **Planning and organization** **Increased risk for social difficulties, psychological maladjustment.** **Clinician 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). The extent of deficit depends on age at treatment intensity of treatment and time since treatment. New deficits may emerge over time. **See related topics:** **Methotrexate** **Cytarabine** **Neurosurgery**	**Host factors** Younger age at treatment Primary CNS tumor ALL or relapsed ALL Head/neck tumors with brain in radiation field **Treatment factors** Combined with: - methotrexate (IT, high-dose IV) - dexamethasone - cytarabine (high-dose IV) - high dose chemotherapy with autologous or allogeneic hematopoietic cell transplantation.	**Host factors** Age < 3 years at time of treatment Female gender Tumor site in cerebral hemisphere **Treatment factors** Cranial irradiation **Social factors** Low SES Premorbid or family history of learning or attention problems.	Clinical interview including assessment of educational or vocational progress	Baseline and yearly	**Health Link** Educational Issues Following Treatment for Childhood Cancer	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. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Refer to community services for vocational rehabilitation or for services for developmentally disabled.
					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		
	37	**Clinical leukoencephalopathy** (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - cavernous hemangioma - mineralizing micro-angiopathy	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose Combined with: - high-dose methotrexate - intrathecal methotrexate or cytarabine **Medical conditions** Hydrocephalus requiring shunt Posterior fossa syndrome	**Host factors** Age < 2 years at time of treatment **Treatment factors** Dose ≥ 30 Gy Fraction dose ≥ 2 Gy	Clinical evaluation	Yearly		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadolinium-enhanced MRI: microvascular injury CT: calcifications Neurology consultation and follow-up.
					Brain MRI	As clinically indicated		
					Brain CT plus MRI with MR angiography	As clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Head/Brain Radiation (continued from previous page) **Any field involving the head/brain, including:** **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** (continued on next page)	38	**Stroke/Moyamoya Occlusive cerebral vasculopathy** **Clinician 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** Hypothalamic/chiasmatic glioma **Medical conditions** Sickle cell disease Neurofibromatosis	**Treatment factors** Dose ≥ 40 Gy	Clinical evaluation Brain MRI with diffusion-weighted imaging with MR angiography	Yearly As clinically indicated		Neurology consultation and follow-up. Physical and occupational therapy as clinically indicated.
	39	**Brain tumor:** High-grade astrocytoma Meningioma Sarcoma	**Host factors** Younger age at treatment Thiopurine methyl transferase (TPMT) genetic polymorphism Neurofibromatosis **Treatment factors** Higher radiation dose	**Host factors** Age < 6 years at time of treatment Ataxia telangiectasia	History & physical Neurologic exam Brain MRI	Yearly Baseline at maturity for all patients Every other year for patients with neurofibromatosis, beginning 2 years after radiation As clinically indicated for symptomatic patients		Neurosurgical consultation for tissue diagnosis and/or resection. Neuro-oncology consultation for medical management.
	40	**Growth hormone deficiency**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation doses Surgery in suprasellar region Pretransplant radiation Total body irradiation: ≥ 10 Gy single fraction ≥ 12 Gy fractionated	**Treatment factors** Radiation dose ≥ 18 Gy Pretransplant cranial radiation Single daily fraction TBI dose	Assess nutritional status. Monitor height, weight BMI percentiles Tanner staging Bone age	Every 6 months until growth is completed. Obtain in poorly growing children.	**Health Link** Growth Hormone Deficiency See also: Hypopituitarism www.magicfoundation.org	Endocrine consultation for: - drop in %ile on growth grid - growth velocity < 4-5 cm/year during childhood - growth below 3rd %ile - lack of pubertal growth spurt. Evaluate thyroid function in any poorly growing child.
	41	**Hyperprolactinemia**	**Treatment factors** Higher radiation dose Surgery or tumor in hypothalamic area	**Treatment factors** Radiation dose ≥ 50 Gy	Review of systems: Female: - galactorrhea - menstrual history Male: - decreased libido - galactorrhea Prolactin level	Yearly In all patients with galactorrhea; females with amenorrhea; males with decreased libido	**Health Link** Hyperprolactinemia www.magicfoundation.org	CT evaluation of sella turcica for pituitary adenoma in patients with hyperprolactinemia. Endocrine consultation for patients with hyperprolactinemia, amenorrhea, or galactorrhea.
	42	**Central hypothyroidism** (thyroid-releasing and thyroid-stimulating hormone deficiency)	**Treatment factors** Higher radiation dose Total body irradiation	**Treatment factors** Radiation dose ≥ 30 Gy	Free T4, TSH	Yearly	**Health Link** Thyroid Problems after Childhood Cancer. See also: Hypopituitarism	Consider TSH surge testing. Endocrine consultation for thyroid hormone replacement.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Head/Brain Radiation (continued from previous page) **Any field involving the head/brain, including:** **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** (continued on next page)	43	**Central adrenal insufficiency**	**Treatment factors** Higher radiation dose	**Treatment factors** Radiation dose ≥ 30 Gy	Review of systems: - failure to thrive - anorexia - dehydration - hypoglycemia - lethargy - unexplained hypotension	Yearly	**Health Link** Central Adrenal Insufficiency See also: Hypopituitarism Corticosteroid replacement therapy & stress dosing. Medic Alert bracelet. www.magicfoundation.org	Endocrine consultation for further evaluation and replacement steroids.
					8:00 AM serum cortisol in patients treated with ≥ 30 Gy radiation to hypothalamic-pituitary axis	Baseline at entry into long term follow-up and periodically as clinically indicated		
	44	**Precocious puberty**	**Host factors** Female gender Younger age at treatment **Treatment factors** Radiation doses ≥ 18 Gy		Physical exam including height, weight, Tanner stage	Yearly	**Health Link** Precocious Puberty www.magicfoundation.org	Endocrine consultation for accelerated puberty (puberty in girl < 8 years old and boy < 9 years old). Consider pelvic ultrasound in females to evaluate for ovarian tumor
					LH, FSH, estradiol or testosterone	As clinically indicated in patients with signs of accelerated pubertal progression and growth.		
					Bone age	Obtain in rapidly growing children.		
	45	**Gonadotropin deficiency (LH and FSH)**	**Treatment factors** Higher radiation dose	**Treatment factors** Radiation dose ≥ 30 Gy	**Females:** Pubertal history (onset, tempo) Menstrual and pregnancy history Physical exam including height, weight, Tanner stage	Yearly	**Health Link** Female Health Issues after Childhood Cancer **or** Male Health Issues after Childhood Cancer See also: Hypopituitarism Counsel currently menstruating women at increased risk of early menopause to be cautious about delaying childbearing. Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology/ obstetrics 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.
					FSH, LH, estradiol	Baseline at age 8, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency		
					Males: Pubertal history (onset, tempo) History of sexual function (erections, nocturnal emissions, libido) History of medication use Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					FSH, LH, testosterone	Baseline at age 9, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency		
					Semen analysis	As requested by patient and for evaluation of infertility		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Head/Brain Radiation (continued from previous page) **Any field involving the head/brain, including:** **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** **Mantle (sections 48 & 49 only)** **Cervical Spine (sections 48 & 49 only)**	46	**Overweight/Obesity** Definition by adult standards: body mass index (BMI) = wt (kg)/ht (M^2) Overweight: BMI ≥ 25-29.9 Obese: BMI ≥ 30 BMI calculator available on-line at: http://nhlbisupport.com/bmi/ Definition by pediatric standards for < 16 years old: Overweight is defined by sex-and age-specific 95%ile cutoff points of CDC/NCHS growth charts. Growth charts 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 gender **Treatment factors** Hypothalamic dose ≥ 20 Gy **Medical conditions** Inability to exercise	Blood pressure Growth percentile or Body mass index Fasting lipid profile Fasting insulin	Yearly Yearly Every 3-5 years in overweight or obese patients Obtain baseline for patients with acanthosis nigricans. Consider testing in overweight or obese patients with dyslipidemia.	**Health Link** Health Promotion through Diet and Physical Activity Obesity-related health risks.	Consider evaluation for other co-morbid conditions including: dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, insulin resistance. Nutritional counseling. Endocrine consultation for patients with dyslipidemia or hyperglycemia.
	47	**Chronic sinusitis**	**Treatment factors** Higher cumulative radiation doses to sinuses (≥ 30 Gy) Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical conditions** Atopic history Hypogammaglobulinemia		History Physical exam CT sinuses	Yearly As clinically indicated		Otolaryngology consultation as clinically indicated.
	48	**Xerostomia** Salivary gland dysfunction	**Treatment factors** Head and neck radiation involving the parotid gland Higher radiation doses Total body irradiation Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Salivary gland dose ≥ 30 Gy **Medical conditions** Chronic GVHD	History Physical exam	Yearly	**Health Link** Dental Health	Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine). Regular dental care including fluoride applications.
	49	**Dental abnormalities** Tooth/root agenesis Microdontia Root thinning/shortening Enamel dysplasia Periodontal disease Tooth decay Malocclusion Temporomandibular joint dysfunction	**Host factors** Younger age at treatment Gorlin's syndrome **Treatment factors** Higher radiation dose	**Host factors** Age < 5 years at time of treatment **Treatment factors** Dose ≥ 20 Gy (may occur in young children at 10 Gy)	Dental exam and cleaning	Every 6 months	**Health Link** Dental Health	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.
	50	**Craniofacial abnormalities**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose	**Host factors** Age < 5 years at time of treatment **Treatment factors** Dose ≥ 30 Gy	Physical exam Psychosocial assessment of adjustment	Yearly Yearly	Resource: FACES - The National Craniofacial Association www.faces-cranio.org/	Reconstructive craniofacial surgical consultation. Consultation with psychologist in patients with adjustment disorders related to facial asymmetry/deformity.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Eye radiation								
Any field involving the eye, including: **Total Body Irradiation** **Orbital/Eye** **Cranial (whole brain)** **Craniospinal** **Clinician Info Link**: Complications other than cataracts are generally associated only with orbital/eye radiation. Reduced visual acuity may be associated with cataracts, retinal damage, and optic nerve damage	51	**Cataracts**	**Treatment factors** Higher radiation dose Combined with: - corticosteroids - busulfan Longer interval since treatment	**Treatment factors** Dose ≥ 10 Gy TBI given in single daily fraction Fraction dose ≥ 2 Gy	Ophthalmology evaluation including funduscopic exam and visual acuity	Yearly for patients who received ≥ 30 Gy or TBI Every 3 years for patients who received < 30 Gy (these patients also need yearly funduscopic exams during yearly long-term follow-up visits)	**Health Link** Eye Problems after Childhood Cancer Resource: FACES - The National Craniofacial Association www.faces-cranio.org/	Ongoing ophthalmology follow-up for identified problems. Consider every 6 month ophthalmology evaluation for patients with corneal damage (usually associated with xerophthalmia) or complex ocular problems. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources.
		Orbital hypoplasia	**Treatment factors** Higher radiation dose Higher daily fraction dose	**Treatment factors** Dose ≥ 30 Gy Fraction dose ≥ 2 Gy				
		Lacrimal duct atrophy (resulting in excessive tearing)	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 40 Gy Fraction dose ≥ 2 Gy				
		Xerophthalmia (severe) (resulting from atrophy of lacrimal gland)	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 30 Gy Fraction dose ≥ 2 Gy				
		Keratitis	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 40 Gy Fraction dose ≥ 2 Gy				
		Keratoconjunctivitis sicca	**Treatment factors** Higher radiation dose Corticosteroids Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 40 Gy Fraction dose ≥ 2 Gy **Medical conditions** Chronic GVHD				
		Telangiectasias	**Treatment factors** Higher radiation dose	**Treatment factors** Dose ≥ 50 Gy Fraction dose ≥ 2 Gy				
		Retinopathy	**Treatment factors** Higher radiation dose **Medical conditions** Diabetes mellitus	**Treatment factors** Dose 45-65 Gy Fraction dose ≥ 2 Gy				
		Optic chiasm neuropathy	**Treatment factors** Higher radiation dose **Medical conditions** Diabetes mellitus Hypertension	**Treatment factors** Dose 50- 65 Gy Fraction dose ≥ 2 Gy				
		Enophthalmos **Chronic painful eye**	**Treatment factors** Higher radiation dose	Fraction dose ≥ 2 Gy				

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Ear radiation								
Any field involving the ear, including: **Total body irradiation** **Ear/Infratemporal** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal**	52	**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 Physical exam	Yearly	**Health Link** Hearing Problems after Childhood Cancer	Audiology consultation for assistive devices 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 to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources, IEP for preferential classroom seating or specialized classroom placement, FM trainer or other assistive devices, and other educational assistance as indicated.
					Audiogram or brainstem auditory evoked response (ABR, BAER)	For patients who received ≥ 30 Gy: Yearly after completion of therapy for 5 years (for patients < 10 yrs old continue yearly until age 10); then every 5 years. If abnormal, follow yearly until stable. Obtain more frequently if clinical evidence of progressive hearing loss. For patients who received < 30 Gy: Baseline at entry into long term follow-up, then as clinically indicated		
		Sensorineural hearing loss **Tinnitus** **See related topics:** **Cisplatin/Carboplatin**	**Host factors** Younger age at treatment CNS tumor CSF shunting **Treatment factors** Higher radiation dose Combined with other ototoxic agents, such as: - cisplatin - aminoglycosides	**Treatment factors** Doses ≥ 30-40 Gy				
Neck radiation								
Any radiation with potential impact to the neck/thyroid, including: **Total Body Irradiation** **Cervical** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Mantle** **Mediastinal** **Whole lung** **Spinal** **For Cervical Spine & Mantle see also:** **Section 48 (Xerostomia) and Section 49 (Dental Abnormalities)**	53	**Thyroid nodules**	**Host factors** Younger age at treatment Female gender **Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 25 Gy	Physical exam	Yearly	**Health Link** Thyroid Problems after Childhood Cancer.	Ultrasound for evaluation of palpable nodule(s). Endocrine and/or surgical consultation for diagnostic biopsy or thyroidectomy.
	54	**Thyroid cancer**	**Host factors** Younger age at treatment Female gender **Treatment factors** > 5-10 years after irradiation Cervical or total body irradiation		Physical exam	Yearly	**Health Link** Thyroid Problems after Childhood Cancer.	Ultrasound for evaluation of palpable nodule(s). Surgical consultation for resection. Nuclear medicine consultation for ablation of residual disease. Endocrine consultation for postoperative medical management.
	55	**Hypothyroidism**	**Host factors** Female gender **Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 20 Gy	History Physical exam TSH, free T4 Note: must be free T4 in females on OCP	Yearly; consider more frequent screening during periods of rapid growth	**Health Link** Thyroid Problems after Childhood Cancer.	Endocrine consultation for medical management.
	56	**Hyperthyroidism**	**Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 35 Gy	History Physical exam TSH, free T4	Yearly	**Health Link** Thyroid Problems after Childhood Cancer.	Endocrine consultation for medical management.
	57	**Carotid artery disease**		**Treatment factors** Dose ≥ 40 Gy	Clinical evaluation	Yearly		MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated.
					Doppler ultrasound of carotid vessels	As clinically indicated		
	58	**Esophageal stricture**	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin **Medical conditions** Gastroesophageal reflux	**Treatment factors** Dose ≥ 40 Gy	History	Yearly		Surgical and/or gastroenterology consultation for symptomatic patients.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Trunk radiation								
Any field from shoulders to pelvis including: **Total Body Irradiation** **Spinal (≥ 12 Gy)**	59	**Musculoskeletal growth problems:** - Hypoplasia - Fibrosis - Reduced or uneven growth - Shortened trunk height	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Larger treatment field Higher dose per fraction	**Host factors** Prepubertal at treatment **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones. Epiphysis in treatment field. Dose ≥ 20 Gy	Physical exam	Yearly		Orthopedic consultation if clinically significant or for any deficit noted in growing child. Plastic surgery consultation for reconstruction.
	60	**Scoliosis**	**Host factors** Younger age at irradiation Paraspinal malignancies Neurofibromatosis **Treatment factors** Hemithoracic or abdominal radiation Hemithoracic, abdominal or spinal surgery Radiation of only a portion of (rather than whole) vertebral body **Clinician 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 exam	Yearly until growth completed; may need more frequent assessment during puberty	**Health Link** Scoliosis and Kyphosis after Treatment for Childhood Cancer	Orthopedics consultation as indicated based on radiographic exam.
					Spine films	In patient with clinically apparent curve		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Chest/thorax radiation								
Any field involving the chest/thorax, including: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)** **Whole abdomen** **Any upper abdominal field**	61	**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 exam	Yearly until growth completed; may need more frequent assessment during puberty	**Health Link** Scoliosis and Kyphosis after Treatment for Childhood Cancer	Orthopedics consultation as indicated based on radiographic exam.
					Spine films	In patient with clinically apparent curve		
	62	**Esophageal stricture**	**Treatment factors** Higher radiation dose to esophagus Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin **Medical conditions** Gastroesophageal reflux	**Treatment factors** Dose ≥ 40 Gy	History	Yearly		Surgical and/or gastroenterology consultation for symptomatic patients.
Chest/thorax radiation with potential impact to the breast: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)**	63	**Breast cancer**	**Host factors** Family history of breast cancer **Treatment factors** Higher radiation dose Longer time from radiation (≥ 5-9 years since radiation)	**Host factors** Female gender	**For females only:** Breast self-examination	Monthly, beginning at puberty	**Health Link** Breast Cancer after Treatment for Childhood Cancer: Are You at Risk?	Surgical consultation for diagnostic procedure. Precautions about the use of HRT.
					Clinical breast exam	Yearly, beginning at puberty until age 25, then every 6 months.		
					Mammogram **Clinician Info Link** Mammography is currently limited in its ability to evaluate premenopausal breasts.	Yearly, beginning 8 years after radiation or at age 25 (whichever occurs last)		
	64	**Breast tissue hypoplasia**	**Host factors** Prepubertal at time of breast irradiation **Treatment factors** Higher radiation dose		Physical exam	Yearly		Surgical consultation for breast reconstruction after completion of growth.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Chest/thorax radiation with potential impact to the heart: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)** **Whole abdomen** **Left hemiabdomen/ flank** **Any left-sided upper abdominal field**	65	**Congestive heart failure** **Cardiomyopathy** **Pericarditis** **Pericardial fibrosis** **Valvular disease** **Myocardial infarction** **Arrhythmia** **Atherosclerotic heart disease** **See related topics:** **Anthracycline chemotherapy**	**Host factors** Younger age at irradiation Family history of dyslipidemia Coronary artery disease **Treatment factors** Radiation dose ≥20 Gy to chest/thorax Combined with radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Combined with other cardiotoxic chemotherapy: - anthracyclines - cyclophosphamide (100-200 mg/kg as conditioning for stem cell transplantation) - amsacrine Total body irradiation **Medical conditions** Hypertension Obesity Dyslipidemia Diabetes mellitus Premature ovarian failure (untreated) **Health behaviors** Smoking	**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	EKG	Baseline, at entry into long-term follow-up and as clinically indicated	**Health Link** Heart Problems Following Treatment for Childhood Cancer Health Promotion through Diet and Physical Activity	Cardiology consultation for patients with subclinical abnormalities on screening evaluations or with left ventricular dysfunction, dysrhythmia or prolonged QT interval. Additional cardiology evaluation for patients who are pregnant or planning pregnancy who: (1) received ≥ 30 Gy chest/thorax radiation, or (2) received TBI 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.
					ECHO	Baseline, at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose (see table).		
					Cardiology consultation for stress testing	For patients who received ≥ 40 Gy chest radiation alone or ≥ 30 Gy chest radiation plus anthracycline: obtain baseline 5-10 years after radiation		
					Fasting glucose and lipid profile	Every 3 to 5 years. If abnormal, refer for ongoing management		
					Detailed history of exertional tolerance **Clinician Info Link** Exertional intolerance is uncommon in patients younger than 25 years old. Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in young patients	Yearly		
Chest/thorax radiation with potential impact to the lungs: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)** **Whole abdomen** **Any upper abdominal field**	66	**Pulmonary fibrosis** **Delayed interstitial pneumonitis** **Restrictive/obstructive lung disease** **See related topics:** **Carmustine** **Lomustine** **Bleomycin** **Busulfan**	**Host factors** Younger age at irradiation **Treatment factors** Higher radiation dose to lungs Total body irradiation Combined with: - bleomycin - busulfan - carmustine (BCNU) - lomustine (CCNU) **Medical conditions** Atopic history **Health behaviors** Smoking	**Treatment factors** Whole lung radiation	Physical exam	Yearly	**Health Link** Pulmonary Health 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	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations.
					PFTs (including DLCO and spirometry) and CXR	Baseline at entry into long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.		

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/m^2	Every 2 years
		≥300 mg/m^2	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

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Abdomen/Pelvis								
≥ 30 Gy to: **Whole abdomen** **Left upper quadrant** **Entire spleen**	67	**Functional asplenia** **Life-threatening infection** with encapsulated organisms (Haemophilus influenzae, Streptococcus pneumoniae, Meningococcus).	**Treatment factors** Higher radiation dose to entire spleen	**Treatment factors** Dose ≥ 30 Gy	Physical exam Blood culture	When febrile T ≥ 101°	**Health Link** Splenic Precautions Medical alert bracelet/card noting functional asplenia. Counsel to avoid malaria and tick bites if living in or visiting endemic areas.	In patients with T ≥ 101° (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. All patients should receive Pneumococcal booster 3 - 5 years after initial dose.
Total Body Irradiation **Renal** **Para-Aortic** **Whole abdominal** **Spinal (≥ 15 Gy)**	68	**Renal insufficiency** **Hypertension** **See related topics:** **Ifosfamide** **Methotrexate** **Cisplatin/Carboplatin** **Cystectomy** **Nephrectomy**	**Treatment factors** Higher radiation dose to kidneys Combined with: - doxorubicin, - dactinomycin Hyperfractionated radiation Total body irradiation Combined with other nephrotoxic agents such as: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppressants - cyclosporine **Medical conditions** Mononephric Diabetes mellitus Hypertension	**Treatment factors** Dose ≥ 15 Gy to whole kidney 14 Gy TBI without renal shielding	Blood pressure BUN, creatinine, U/A Na, K, Cl, CO_2 Ca, Mg, PO_4 Creatinine clearance or GFR	Yearly Yearly Obtain in patients with abnormal BP, urinalysis BUN, or creatinine. If abnormal, repeat as clinically indicated.	**Health Link** Kidney Health See also: Single Kidney Precautions	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
Total Body Irradiation **Whole abdomen** **Hepatic** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Transfusion (chronic hepatitis B &C)** **Hematopoietic cell transplant (liver toxicity)**	69	**Hepatic fibrosis** **Cirrhosis**	**Treatment factors** Higher radiation dose to liver **Medical conditions** Chronic hepatitis **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 exam ALT, AST, bilirubin	Yearly Baseline at entry into long-term follow-up.	**Health Link** Liver Health	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.
	70	**Hepatocellular carcinoma**	**Medical conditions** Chronic hepatitis B or C Cirrhosis **Treatment factors** Higher radiation dose to liver **Health behaviors** Alcohol use		AFP Liver ultrasound	Yearly in patients with chronic hepatitis Yearly in patients with cirrhosis	**Health Link** Reducing the Risk of Second Cancers Hepatitis after Childhood Cancer	Oncology consultation for medical management.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Total Body Irradiation **All abdominal and pelvic fields** **Spinal ≥ 20 Gy**	71	**Bowel obstruction**	**Treatment factors** Higher radiation dose to bowel Abdominal surgery **Clinician Info Link** Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery.	**Treatment factors** Dose ≥ 45 Gy (Obstruction may occur in people who received lower doses of abdominal radiation during childhood)	Physical exam KUB	With clinical symptoms of obstruction.		Surgical consultation in patients who fail medical management.
	72	**Chronic enterocolitis** **Fistula, Strictures**	**Treatment factors** Higher radiation dose to bowel Abdominal surgery	**Treatment factors** Dose ≥ 45 Gy	History	Yearly		Surgical and/or gastroenterology consultation for symptomatic patients.
					Serum protein, albumin	Yearly in patients with chronic diarrhea or fistula		
Total Body Irradiation **All abdominal and pelvic fields ≥ 25 Gy** **Spinal ≥ 25 Gy**	73	**Gastrointestinal malignancy**	**Host factors** Hepatoblastoma Familial polyposis **Treatment factors** Higher radiation dose to bowel Higher daily fraction dose Combined with chemotherapy (especially alkylators)	**Treatment factors** Radiation dose ≥ 25 Gy	*The following monitoring is to begin 15 years after radiation or at age 35 years (whichever occurs last). Monitor more frequently if clinically indicated.* **Choose one of the following three options:** Fecal occult blood (minimum 3 cards) — Yearly **AND** Flexible sigmoidoscopy — Every 5 years **OR** Double contrast barium enema — Every 5 years **OR** Colonoscopy — Every 10 years		**Health Link** Reducing the Risk of Second Cancers	Surgical and/or oncology consultation as needed.
Total body irradiation **Whole abdomen** **Pelvic** **Iliac/inguinal** **Para-aortic**	74	**Uterine vascular insufficiency** resulting in adverse outcomes such as spontaneous abortion, neonatal death, low-birth weight infant, fetal malposition, and premature labor	**Host factors** Females with Wilms tumor and associated müllerian anomalies **Clinician Info Link:** 10% of girls with Wilms tumor have congenital uterine anomalies **Treatment factors** Higher radiation dose to pelvis	**Host factors** Prepubertal at treatment **Treatment factors** Dose ≥ 20-30 Gy TBI	History	Yearly and as clinically indicated	**Health Link** Female Health Issues after Childhood Cancer Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	High-risk obstetrical care during pregnancy. High level ultrasound in women with Wilms tumor.
					Consider high-level ultrasound evaluation of genitourinary tract after pubertal development.	As clinically indicated in patient contemplating pregnancy.		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Total body irradiation **Whole abdomen** **Pelvic** **Iliac/inguinal** **Para-aortic** **Spinal ≥ 24 Gy**	75	**Ovarian dysfunction:** - Delayed/arrested puberty - Primary amenorrhea - Secondary amenorrhea - Premature ovarian failure - Early menopause - Infertility **See related topics:** **Alkylating agents** **Head/brain radiation**	**Host factors** Older age at irradiation **Treatment factors** Radiation dose to pelvis 6-10 Gy Combined with: - cranial radiation Combined with alkylating agent chemotherapy	**Treatment factors** Dose ≥ 10-20 Gy TBI Combined with cyclophosphamide dose ≥ 200 mg/kg (conditioning for stem cell transplant)	Pubertal history (onset, tempo) Symptoms of menopause (hot flashes, poor libido) Menstrual history Physical exam with height, weight, Tanner stage	Yearly	**Health Link** Female Health Issues after Childhood Cancer Risks and benefits of hormonal replacement therapy Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Gynecology or endocrinology consultation for hormonal replacement therapy. Consider evaluation for conditions exacerbated by hypogonadism (e.g., osteopenia/osteoporosis). Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies.
					LH, FSH, Estradiol	Baseline at age 8, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency		
Whole abdomen **Pelvic** **Iliac/inguinal** **Para-aortic** **Spinal ≥ 30 Gy**	76	**Hemorrhagic cystitis** **See related topics:** **Cyclophosphamide** **Ifosfamide**	**Treatment factors** Higher radiation dose	**Treatment factors** Combined with cyclophosphamide and/or ifosfamide	Urinalysis	Yearly	Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture-negative macroscopic hematuria.
	77	**Bladder fibrosis** **Dysfunctional voiding**	**Treatment factors** Higher cumulative radiation dose (≥ 45 Gy) Combined with: - cyclophosphamide - ifosfamide		Voiding history	Yearly		Urologic consultation for patients with incontinence or dysfunctional voiding.
	78	**Bladder malignancy** **See related topics:** **Cyclophosphamide** **Ifosfamide**	**Treatment factors** Radiation to pelvis Combined with: - cyclophosphamide - ifosfamide **Health behaviors** Alcohol use Tobacco use		Urinalysis	Yearly	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture-negative macroscopic hematuria.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Testicular radiation								
Total body irradiation **Testicular** **Pelvic** **Inguinal/femoral** **Spinal ≥ 24 Gy**	79	**Testicular dysfunction** **- Azoospermia** **- Infertility**	**Treatment factors** Radiation to testes 1 to 3 Gy: azoospermia may be reversible. 3 to 6 Gy: azoospermia possibly reversible (but unlikely)	**Treatment factors** Radiation to testes ≥ 6 Gy: azoospermia likely permanent	Semen analysis	As requested by patient and for evaluation of infertility. **Clinician Info Link** Late recovery of gonadal function has been reported.	**Health Link** Male Health Issues after Childhood Cancer Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Urology or endocrinology consultation for hormonal replacement therapy. Consider evaluation for conditions exacerbated by hypogonadism: e.g., osteopenia/osteoporosis. Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies.
		-Hypogonadism **-Delayed/arrested puberty** **See related topics:** **Alkylating agents** **Head/brain radiation**	Testicular irradiation combined with head/brain irradiation	Radiation to testes ≥ 20 Gy: Leydig cell damage (affecting testosterone production) Radiation combined with alkylating agents Combined with cyclophosphamide dose ≥ 200 mg/kg (conditioning for stem cell transplant) TBI	History of sexual function (erections, nocturnal emissions, libido).	Yearly		
					History of medication use.	Yearly		
					Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					LH, FSH, Testosterone	Baseline at age 9, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency		
Extremity radiation								
	80	**Musculoskeletal growth problems:** - Hypoplasia - Fibrosis - Reduced or uneven growth - Limb length discrepancy	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Larger treatment field Higher dose per fraction	**Host factors** Prepubertal at treatment **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones. Epiphysis in treatment field. Dose ≥ 20 Gy	Physical exam	Yearly	Counsel regarding increased risk of fractures in weight-bearing irradiated bones	Orthopedic consultation if clinically significant (limb length discrepancy, chronic pain) or for any deficit noted in growing child. Reconstructive surgical consultation.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Blood/blood products								
Clinician Info Link Consider exposure to any blood or serum product, including packed red cells, whole blood, white cells, platelets, fresh frozen plasma, cryoprecipitate, allogeneic marrow or stem cells, immunoglobulin preparations (e.g., IVIG, VZIG), and clotting factor concentrates. Since the vast majority of patients received some type of blood product during childhood cancer treatment, screening for Hepatitis and HIV (as indicated based on dates of treatment) is recommended unless there is absolute certainty that the survivor did not receive any blood or blood products. Screening of blood donors was initiated in the United States as follows (note - International screening policies may not include these measures): 1971 Hepatitis BsAg 1985 HIVAB HIV-1 EIA 1986 Surrogate ALT screening 1990 HCV EIA-I screening 1992 HCV EIA-II screening								
Blood or serum product prior to initiation of Hepatitis B screening of blood supply (prior to 1972 in the United States - date may differ in other countries).	81	**Chronic Hepatitis B** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Chronic hepatitis C** **Hematopoietic cell transplant (liver toxicity)**	**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 immuno-suppression	Hepatitis B surface antigen (HBsAg) AND Hepatitis B core antibody (anti HBc or HBcAb)	Once in patients who received treatment for cancer prior to 1972 (date may vary for international patients)	**Health Link** Hepatitis after Childhood Cancer	Gastroenterology or hepatology consultation for patients with chronic infection. Hepatitis A immunization in patients lacking immunity.
		Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	**Treatment factors** Stem cell transplantation **Medical conditions** Chronic hepatitis B, C **Health behaviors** Alcohol use	**Medical conditions** Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Physical exam ALT, AST, AFP, bilirubin, prothrombin time	Yearly in patients with chronic hepatitis		
					Liver ultrasound	Yearly in patients with cirrhosis		
Blood or serum product prior to initiation of Hepatitis C screening of blood supply (prior to 1993 in the United States - date may differ in other countries).	82	**Chronic Hepatitis C** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Chronic hepatitis B** **Hematopoietic cell transplant (liver toxicity)**	**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	**Treatment factors** Blood products prior to 1986 when surrogate screening of blood donors with ALT initiated and donors with self-reported high-risk behaviors deferred. Chronic immunosuppression	Hepatitis C antibody	Once in patients who received treatment for cancer prior to 1993 (date may vary for international patients)	**Health Link** Hepatitis after Childhood Cancer	Screen for viral hepatitis in patients with persistently abnormal liver function regardless of transfusion history. Consider HCV PCR screening in all transfused at risk patients (especially those with abnormal liver function) or in patients with persistent immunosuppression (stem cell transplant recipients). Gastroenterology or hepatology consultation for management of patients with chronic infection, progressive liver dysfunction, or other hepatitis-related sequelae. Hepatitis A and B immunization in patients lacking immunity.
					PCR to establish chronic infection	Once in patients with positive hepatitis C antibody		
		Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	**Treatment factors** Stem cell transplantation **Medical conditions** Chronic hepatitis B, C **Health behaviors** Alcohol use	**Medical conditions** Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Physical exam and ALT, AST, AFP, bilirubin, and prothrombin time	Yearly in patients with chronic hepatitis		
					Liver ultrasound	Yearly in patients with cirrhosis		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Blood or serum product after emergence of HIV in the blood supply and prior to initiation of HIV screening of blood supply (from 1977 through 1985 in the United States - dates may differ in other countries).	83	**HIV infection**	**Treatment factors** Blood products between 1977 and 1985 **Health behaviors** IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing **Medical conditions** HPV infection	**Health behaviors** High-risk behaviors	HIV 1 & 2 antibodies	Once in patients who received treatment for cancer between 1977 and 1985 (dates may vary for international patients).	Standard counseling regarding safe sex, universal precautions, exacerbating high-risk behaviors	Infectious diseases consultation for patients with chronic infection.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Surgery								
Amputation	84	**Cosmesis** **Functional and activity limitations** **Residual limb integrity problems** **Phantom pain**	**Host factors** Skeletally immature/ growing children		Physical exam Prosthetic evaluation	Yearly until completion of growth, or every 3 years if skeletally mature. Every 6 months until skeletally mature, then yearly thereafter.	Counsel regarding skin checks, signs of poor prosthetic fit, residual limb and prosthetic hygiene.	Psychological consultation in patients with emotional difficulties related to cosmesis and adaptation following amputation. Vocational rehabilitation referral.
Central venous catheter	85	**Thrombosis** **Vascular insufficiency** **Infection of retained cuff or line tract**			History Physical exam	Yearly, and as clinically indicated.		
Cystectomy	86	**Chronic urinary tract infection** **Renal dysfunction** **See related topics:** **Ifosfamide** **Cisplatin/Carboplatin** **Methotrexate** **Abdominal/pelvic radiation** **Nephrectomy**			Blood pressure BUN, creatinine, U/A Urine culture Urology evaluation Na, K, Cl, CO_2. Ca, Mg, PO_4 Creatinine clearance or GFR.	Yearly Yearly Yearly and as clinically indicated Yearly Obtain in patients with abnormal BP, U/A, BUN, or creatinine. If abnormal, repeat as clinically indicated	**Health Link** Kidney Health	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
Enucleation	87	**Cosmesis** **Poor prosthetic fit** **Orbital hypoplasia**	**Host factors** Younger age at enucleation **Treatment factors** Combined with radiation		Physical exam Ophthalmology Ocularist	Yearly		Psychological consultation in patients with emotional difficulties related to cosmesis and visual impairment. Vocational rehabilitation referral.
Laparotomy	88	**Adhesive/obstructive complications**	**Treatment factors** Combined with radiation		Physical exam	When symptomatic		Surgical consultation for patients unresponsive to medical management.
Limb sparing procedure	89	**Functional and activity limitations** **Contractures** **Loosening of endoprosthesis** **Chronic infection** **Chronic pain** **Limb length discrepancy**	**Host factors** Younger age at surgery Rapid growth spurt **Health behaviors** Higher risk of loosening in patients with high level of physical activity. Higher risk of contractures or functional limitations in patients with low level of physical activity.		Physical exam Radiograph Orthopedic follow-up	Yearly and as needed Yearly Every 6 months until skeletally mature, and yearly thereafter	**Health Link** Limb Salvage after Bone Cancer Counsel regarding need for antibiotic prophylaxis prior to dental and invasive procedures	Psychological consultation in patients with emotional difficulties related to cosmesis and adaptation following limb-sparing procedure. Vocational rehabilitation referral. Antibiotic prophylaxis prior to dental and invasive procedures
Nephrectomy	90	**Proteinuria** **Hyperfiltration** **Renal insufficiency** **Hydrocele** **See related topics:** **Ifosfamide** **Cisplatin/Carboplatin** **Methotrexate** **Abdominal/pelvic radiation** **Cystectomy**	**Treatment factors** Combined with other nephrotoxic therapy: - cisplatin, carboplatin - ifosfamide - kidney irradiation - abdominal irradiation - aminoglycosides - amphotericin - immunosuppresants - cyclosporine - methotrexate		Blood pressure BUN, creatinine, U/A Na, K, Cl, CO_2. Ca, Mg, PO_4 Creatinine clearance or GFR.	Yearly Yearly Obtain in patients with abnormal BP, U/A, BUN, or creatinine. If abnormal, repeat as clinically indicated	**Health Link** Single Kidney Precautions See also: Kidney Health	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Neurosurgery	91	**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. **Intracranial bleed/stroke** **Motor deficits** **Paralysis** **Movement disorders** **Ataxia** **Seizures** **Hydrocephalus** **Shunt malfunction** **Clinician Info Link** 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 diagnosis **Treatment factors** Combined with: - brain radiation - high-dose chemotherapy - intrathecal chemotherapy **Medical conditions** Hydrocephalus	**Host factors** Younger age at treatment (< 3 years) Supratentorial tumor **Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose ≥ 60 Gy **Medical conditions** Posterior fossa syndrome CNS infection **Social factors** Low SES Predisposing family history of learning or attention problems	Neurology evaluation	Yearly, until 2 to 3 years after surgery or stable; continue to monitor if symptoms persist. Every 6 months for patients with seizure disorder.	**Health Link** Educational Issues Following Treatment for Childhood Cancer	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. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Speech, physical, and occupational therapy in patients with persistent deficits. Consider nutrition, endocrine, and psychiatric (obsessive-compulsive behaviors) consultations in patients with hypothalamic pituitary axis tumors. Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadolinium-enhanced MRI: microvascular injury CT: calcifications
					Rehabilitation medicine/ physiatrist evaluation	Yearly, or more frequently as clinically indicated in patients with motor dysfunction		
					Neurosurgery evaluation	Yearly for patients with shunts.		
					Abdominal x-ray	At puberty growth spurt for patients with shunts to assure distal shunt tubing in peritoneum		
					Clinical assessment of educational or vocational progress	Baseline and yearly		
					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		
Orchiectomy	92	**Infertility** **Hypogonadism**	**Treatment factors** Bilateral orchiectomy Unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents		History of sexual function (erections, nocturnal emissions, libido).	Yearly	**Health Link** Male Health Issues after Childhood Cancer For patients with single testis - counsel to wear athletic supporter with protective cup during athletic activities.	Refer to endocrinologist for bilateral orchiectomy, delayed clinical signs of puberty, or persistently abnormal hormone levels Consider surgical placement of testicular prosthesis.
					History of medication use.	Yearly		
					Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					LH, FSH, Testosterone	For patients with bilateral orchiectomy, refer to endocrinology at about age 9. For patients with unilateral orchiectomy, obtain as clinically indicated for: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency		
					Semen analysis	As requested by patient and for evaluation of infertility		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Pelvic surgery	93	**Retrograde ejaculation** **Impotence** **Bowel incontinence** **Bladder incontinence** **Hydrocele**	**Treatment factors** Retroperitoneal node dissection		History	Yearly	**Health Link** For males: Male Health Issues after Childhood Cancer	Urologic consultation for patients with incontinence, dysfunctional voiding, or sexual dysfunction.
Pulmonary lobectomy, pulmonary wedge resection, pulmonary metastasectomy	94	**Pulmonary insufficiency**	**Treatment factors** Chest radiation Combined with pulmonary toxic therapy: - bleomycin - busulfan - carmustine (BCNU) - lomustine (CCNU) - chest/thoracic radiation - spinal radiation ≥30Gy - total body irradiation **Medical conditions** Atopic history **Health behaviors** Smoking		Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations.
Splenectomy	95	**Life-threatening infection** with encapsulated organisms (Haemophilus influenzae, Streptococcus pneumoniae, Meningococcus)			Physical exam Blood culture	When febrile T ≥ 101º	**Health Link** Splenic Precautions Medical alert bracelet/card noting asplenia. Counsel to avoid malaria and tick bites if living in or visiting endemic areas.	In patients with T ≥ 101º (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. All patients should receive Pneumococcal booster 3 - 5 years after initial dose.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Hematopoietic Cell Transplantation								
Clinician 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 **(continued on next page)**	**Immune system**							
	96	**Secretory IgA deficiency** **Hypogammaglobulinemia** **Chronic infections,** such as conjunctivitis, sinusitis, and bronchitis	**Medical conditions** Chronic GVHD	**Host factors** Low CD4 T-cell count	History	Yearly		Immunology or infectious diseases consultation for assistance with management of chronic infections.
	Liver							
	97	**Chronic hepatitis** **Cirrhosis** **Iron overload** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Transfusion (chronic hepatitis B & C)**	**Treatment factors** History of multiple transfusions Radiation to the liver **Medical conditions** Chronic GVHD Viral hepatitis **Health behaviors** Alcohol use		ALT, AST, bilirubin Ferritin	Baseline at entry into long term follow-up, Baseline at entry into long term follow-up	**Health Link** Liver Health	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. Hepatitis A and B immunizations in patients lacking immunity.
	Lungs							
	98	**Bronchiolitis obliterans** **Chronic bronchitis** **Bronchiectasis**	**Treatment factors** Allogeneic transplant Thoracic radiation Total body irradiation Pulmonary toxic chemotherapy **Medical conditions** Chronic GVHD	**Medical conditions** Prolonged immunosuppression related to GVHD prophylaxis	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction and prior to general anesthesia.	**Health Link** Pulmonary Health Patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumovax vaccination.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
	Muscles/Bones							
Hematopoietic cell transplantation (continued from previous page) **Clinician Info Link** Sources of donor stem cells for transplantation include: *Autologous* (patient's own marrow or stem cells are harvested prior to ablative therapy) *Allogeneic* (marrow or stem cells are harvested from a related or unrelated donor) *Cord blood* (stem cells harvested from umbilical cord blood) Donors are usually matched to the patient based on HLA (Human Leukocyte Antigen) typing (continued on next page)	99	**Joint contractures**	**Medical conditions** Chronic GVHD		Physical exam	Yearly		Consultation with rehabilitation medicine/physiatrist.
	100	**Osteopenia** Bone mineral density 1-2.5 SD below mean **Osteoporosis** Bone mineral density ≥2.5 SD below mean **Clinician Info Link** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density of young adults at peak bone age and defined as a T-score. 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 bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Treatment factors** Corticosteroids **Medical conditions** Hypogonadism **Behavioral factors** Physical inactivity	**Treatment factors** Prolonged corticosteroid therapy for chronic GVHD	Bone density evaluation (DEXA or quantitative CT) **Clinician 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.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.	**Health Link** Keeping Your Bones Healthy After Childhood Cancer National Osteoporosis Foundation website: www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D ** 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 bone density ≥ 2.5 SD below mean, or patients with history of multiple fractures, for other pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Hematopoietic cell transplantation (continued from previous page)	**Second Cancers**							
	101	**Myelodysplasia** **Acute myeloid leukemia**	**Treatment factors** Radiation therapy Stem cell priming with etoposide Alkylating agent chemotherapy Epipodophyllotoxins Anthracyclines Autologous transplant	**Host factors** Autologous transplant for non-Hodgkin's lymphoma and Hodgkin's disease	Physical exam CBC/differential	Yearly up to 15 years after exposure to agent.	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.
		Solid cancers most common are: - Basal/squamous cell - Melanoma - Oral cavity cancers - Liver cancer - CNS cancer - Thyroid cancer - Connective tissue - Cervical cancer	**Host factors** Younger age at transplant Fanconi's anemia **Treatment factors** Radiation therapy **Medical conditions** Hepatitis C infection Human papilloma virus infection Chronic GVHD of skin	**Treatment factors** Higher dose TBI	Physical exam	Yearly	**Health Link** Reducing the Risk of Second Cancers	Oncology consultation as clinically indicated.
		Lymphoma	**Treatment factors** Chemotherapy Stem cell transplant		Physical exam	Yearly		Oncology consultation as clinically indicated.
	Skin							
	102	**Alopecia** **Nail dysplasia** **Vitiligo** **Scleroderma**	**Treatment factors** Radiation therapy **Medical conditions** Chronic GVHD		Physical exam	Yearly	**Health Link** Skin Health	
General Health Screening								
	103	**Refer to United States Preventive Services Task Force recommendations at http://www.ahrq.gov/clinic/uspstfix.htm**						

Cancer Screening Guidelines

Note to Clinicians: "Highest Risk" guidelines below include suggested periodic evaluations for survivors of childhood, adolescent, or young adult cancers who are at increased risk of a specific cancer due to prior therapy, co-morbid conditions, family history, genetic susceptibility or other factors. "Standard Risk" guidelines below are per American Cancer Society recommendations for standard-risk populations and are provided 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). Specific decisions regarding cancer screening are the prerogative of the patient, family, and healthcare provider.

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Breast	104	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/thorax radiation with potential impact to the breast including : Total Body Irradiation Mantle Mediastinal Whole lung Spinal ≥30 Gy BRCA1, BRCA2, ATM mutation	**For females only:** **Standard Risk:** Breast self-examination Clinical breast exam Mammogram **Highest Risk:** Breast self-examination Clinical breast exam Mammogram **Clinician Info Link** Mammography is currently limited in its ability to evaluate premenopausal breasts.	 Monthly, beginning at age 20 Every 3 years between ages 20-39; then yearly beginning at age 40 Every year beginning at age 40 Monthly beginning at puberty. Yearly, beginning at puberty until age 25, then every 6 months Yearly, beginning 8 years after radiation or at age 25 (whichever occurs last)	**Health Link** Breast Cancer after Treatment for Childhood Cancer: Are You at Risk?	Surgery and/or oncology consultation as clinically indicated.
Cervical	105	Early age at first intercourse Multiple lifetime sex partners Cigarette smoking Sexually transmitted diseases	Personal history of cervical dysplasia. Prenatal DES exposure HPV infection Immunosuppression Chronic steroid use	*Begin screening (in patients with a cervix) 3 years after first vaginal intercourse, or at age 21, whichever occurs first* **Standard Risk:** Pelvic exam Cervical PAP smear **Highest Risk:** Pelvic exam Cervical PAP smear	 Every 1-2 years Yearly for regular PAP test; Every 2 years for liquid-based PAP test. After age 30: If patient has had 3 normal annual PAP tests in a row, may screen every 2-3 years. Yearly Yearly	**Health Link** Reducing the Risk of Second Cancers	Gynecology and/or oncology consultation as clinically indicated.

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Colorectal	106	High fat/low fiber diet Age ≥50 years Obesity	Total body irradiation Abdominal or pelvic radiation ≥25 Gy Spinal radiation ≥25 Gy Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps in first degree relative	**Standard Risk:** Fecal occult blood (minimum of 3 cards) **AND/OR** Flexible sigmoidoscopy *Note: The combination of yearly fecal occult blood testing and every 5 year flexible sigmoidoscopy is preferable to either test done alone.* **OR** Double contrast barium enema **OR** Colonoscopy **Highest Risk:** Monitoring to begin 15 years after radiation or at age 35 years (whichever occurs last). Monitor more frequently if clinically indicated. **Choose from one of the following three options:** Fecal occult blood (minimum of 3 cards) **AND** Flexible sigmoidoscopy **OR** Double contrast barium enema **OR** Colonoscopy	 Yearly, beginning at age 50 Every 5 years beginning at age 50. Every 5 years beginning at age 50. Every 10 years beginning at age 50 Yearly, beginning 15 years after radiation or at age 35 (whichever occurs last). Every 5 years Every 5 years Every 10 years	**Health Link** Reducing the Risk of Second Cancers	Gastroenterology, surgery and/or oncology consultation as clinically indicated.
Endometrial	107	Obesity Older age Unopposed estrogen therapy	History of or at risk for hereditary nonpolyposis colon cancer (HNPCC)	**Highest Risk:** Endometrial biopsy	Yearly, beginning at age 35 for patients at highest risk.	**Health Link** Reducing the Risk of Second Cancers	

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Lung	108	Cigarette smoking Workplace exposures to asbestos, arsenic, radiation Second hand smoke (in non- smokers)	Chest/thorax radiation with potential impact to the lungs, including Total body irradiation Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Any upper abdominal field	**Highest Risk:** History and physical exam Imaging	 Yearly As clinically indicated	**Health Link** Reducing the Risk of Second Cancers	Surgery and/or oncology consultation as clinically indicated.
Oral	109	Tobacco use (smoking cigars cigarettes, or pipe; dipping, chewing), Alcohol abuse Excessive sun exposure increases risk of cancer of lower lip.	Head/brain radiation Neck radiation	**Highest Risk:** Oral cavity exam	 Yearly if tobacco use or history of head/neck radiation	**Health Link** Reducing the Risk of Second Cancers Dental Health	Head and neck/otolaryngology consultation as indicated.
Prostate	110	Older age, with steadily increasing risk after age 40.	African-American race Family history of prostate cancer in first degree relative	**Standard Risk:** Digital rectal exam Prostate specific antigen (PSA) **Highest Risk:** Digital rectal exam Prostate specific antigen (PSA)	 Yearly, beginning at age 50 Yearly, beginning at age 50 Yearly, beginning at age 45 Yearly, beginning at age 45	**Health Link** Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
Skin	111	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	**Standard Risk:** Clinical skin exam **Highest Risk:** Skin self exam Clinical skin exam with attention to pigmented nevi in radiation field.	 Every 3 years, from ages 20-39 Yearly, beginning at age 40. Monthly Yearly	**Health Link** Reducing the Risk of Second Cancers Skin Health	Surgery, dermatology, and/or oncology consultation as clinically indicated.
Testicular	112	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	**Standard Risk:** Testicular self-exam Clinical testicular exam **Highest Risk:** Testicular self-exam Clinical testicular exam	 Not indicated Every 3 years, ages 20-39, then yearly. Monthly, beginning at puberty Yearly	**Health Link** Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.

CureSearch

Children's Oncology Group

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

Version 1.2 – March 2004

References

Section	References
1	Deasy-Spinetta P. School issues and the child with cancer. Cancer 1993 May 15; 71(10Suppl): 3261-4.
	Elkin TD, Phipps S, Mulhern RK, et al. Psychological functioning of adolescent and young adult survivors of pediatric malignancy. Med Pediatr Oncol 1997 Dec; 29(6): 582-588.
	Hobbie WL, Stuber M, Meeske K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. J Clin Oncol 2000 Dec 15; 18(24): 4060-4066.
	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 2003 Feb 15;97(4): 1115-26.
	Rourke MT, Stuber ML, Hobbie WL, et al. Posttraumatic stress disorder: understanding the psychosocial impact of surviving childhood cancer into young adulthood. J Pediatr Oncol Nursing 1999 Jul; 16 (3): 126-135.
	Wissler KH, Proukou C. Navigating the educational system: a practical guide for nurse practitioners. J Pediatr Oncol Nurs. 1999 Jul; 16(3): 145-55.
	Zebrak 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 2002 Jul; 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 1997 Feb; 15(2): 547- 556.
2	Hays DM. Adult survivors of childhood cancer. Employment and insurance issues in different age groups. Cancer. 1993 May 15;71(10 Suppl):3306-9.
	Langeveld NE, Stam H, Grootenhuis MA, et al: Quality of life in young adult survivors of childhood cancer. Support Care Cancer 2002 Nov; 10(8): 579-600.
	Monaco GP, Fiduccia D, Smith G. Legal and societal issues facing survivors of childhood cancer. Pediatr Clin North Am. 1997 Aug;44(4):1043-58.
3	Goho C. Chemoradiation therapy: effect on dental development. Pediatric Dentistry 1993 Jan-Feb; 15 (1): 6-12.
	Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. Med Pediatr Oncol. 1995 Aug;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. 1997 Jun;11(6):792-6.
	Maguire A, Welbury RR. Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development. Dent Update. 1996 Jun;23(5):188-94. Erratum in: Dent Update 1996 Jul-Aug;23(6):238.
	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. Med Pediatr Oncol 1999 Oct; 33 (4): 362-371.
	Sonis AL, Tarbell N, Valachovic RW, et al. Dento- facial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. Cancer 1990 Dec 15; 66(12): 2645-2652.
4	Bath LE, Hamish W, Wallace B, et al. Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. Br J Obstet Gynecol 2002 Feb; 109(2):107-114.
	Bokemeyer C, Schmoll HJ, van Rhee J, et al. Long-term gonadal toxicity after therapy for Hodgkin's and non-Hodgkin's lymphoma. Ann Hematol 1994 Mar; 68(3): 105-110.
	Byrne J, Fears TR, Gail MH, et al. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 1992 Mar; 166(3): 788-793.
	DaCunha MF, Meistrich ML, Fuller LM, et al. Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. J Clin Oncol 1984 Jun; 2(6): 571-577.
	Howell SJ, Shalet SM. Testicular function following chemotherapy. Hum Reprod Update 2001 Jul-Aug; 7(4): 363-369.
	Kenney LB, Laufer MR, Grant FD, et al. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 2001 Feb; 91(3): 613-21.

Section	References
	Meistrich ML, Wilson G, Brown BW, et al. Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer 1992 Dec 1; 70(11): 2703-2712.
	Papadakis V, Vlachopapadopoulou E, Van Syckle K, et al. Gonadal function in young patients successfully treated for Hodgkin's disease. Med Pediatr Oncol 1999 May; 32(5): 366-372.
	Petersen PM, Hansen SW, Giwercman A, et al. Dose-dependent impairment of testicular function in patients treated with cisplatin-based chemotherapy for germ cell cancer. Ann Oncol 1994 Apr; 5(4):355-358.
	Relander T, Cavallin-Stahl E, Garwicz S, et al. Gonadal and sexual function in men treated for childhood cancer. Med Pediatr Oncol 2000 Jul: 35(1): 52-63.
	Teinturier C, Hartmann O, Valteau-Couanet D, et al. Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. BMT 1998 Nov; 22(10): 989-94.
	Sklar C. Reproductive physiology and treatment related loss of sex hormone production. Med Pediatr Oncol 1999 Jul; 33(1): 2-8.
5	Beaty O, Hudson MM, Greenwald C, et al. Subsequent malignancies in children and adolescents after treatment for Hodgkin's disease. J Clin Oncol 1995 Mar; 13(3): 603-609.
	Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 1996 Mar 21; 334(12):745-751.
	Cheruku R, Hussain M, Tyrkus M, et al. Myelodysplastic syndrome after cisplatin therapy. Cancer 1993 Jul 1; 72(1): 213-218.
	Greene MH, Harris EL, Gershenson DM, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. Ann Int Med1986 Sept; 105(3):360-367.
	Meadows AT, Obringer AC, Marrero O, et al. Second malignant neoplasms following childhood Hodgkin's disease: treatment and splenectomy as risk factors. Med Ped Oncol 1989; 17(6):477-484.
	Schellong G, Riepenhausen M, Creutzig U, et al. Low risk of secondary leukemias after chemotherapy without mechlorethamine in childhood Hodgkin's disease. J Clin Oncol 1997 Jun; 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 1999 Oct; 17(10): 3226-3233.
6	Ginsberg SJ, Comis RL. The pulmonary toxicity of antineoplastic agents. Semin Oncol 1982 Mar; 9(1): 34-51.
	Kreisman H, Wolkove N: Pulmonary toxicity of anti-neoplastic therapy. Semin Oncol 1992 Oct; 19(5): 508-20.
	O'Driscoll BR, Hasleton PS, Taylor PM, et al. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. N Engl J Med 1990 Aug 9; 323(6):378-382.
	Risks associated with SCUBA diving in childhood cancer survivors (personal communication with Brett Stolp MD, PhD, Duke University), 8-23-02
7	Dahlgren S, Holm G, Svanborg N, et al. Clinical and morphological side-effects of busulfan (Myleran) treatment. Acta Med Scand. 1972 Jul-Aug;192(1-2):129-35.
	Holmstrom G, Borgstrom B, Calissendorff B. Cataract in children after bone marrow transplantation: relation to conditioning regimen. Acta Ophthalmol Scand. 2002 Apr;80(2):211-5.
	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. 2001 Dec 15;98(13):3569-74.
8	Stillwell TJ, Benson RC. Cyclophosphamide-induced hemorrhagic cystitis: a review of 100 patients. Cancer 1988 Feb 1; 61(3):451-457.
	Stillwell TJ, Benson RC, Burgert EO. Cyclophosphamide-induced hemorrhagic cystitis in Ewing's sarcoma. J Clin Oncol 1988 Jan; 6(1):76-82.
9	Pederson-Bjergaardd 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 1988 Apr 21; 318(16):1028-1032.

Section	References
10	Burk CD, Restaino I, Kaplan BS, et al. Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. J Pediatr 1990 Aug; 117(2 Pt1): 331-335.
	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 1994 Nov; 16(4): 286-295.
	Skinner R, Sharkey IM, Pearson ADJ, et al. Ifosfamide, mesna, and nephrotoxicity in children. J Clin Oncol 1993 Jan; 11(1):173-190.
11	Macdonald MR, Harrison RV, Wake M, et al. Ototoxocity of carboplatin: comparing animal and clinical models at the Hospital for Sick Children. J Otolaryngol 1994 Jun; 23(3):151-59.
	Mahoney DH, Weaver T, et al. Ototoxicity with cisplatin therapy. J Pediatr 1983 Dec; 103(6): 1006-1007.
	McHaney VA, Kovnar E, Meyer WH, et al. Effects of radiation therapy and chemotherapy on hearing. In DM Green & GJ D'Angio (Eds), Late Effects of Treatment for Childhood Cancer. (pp 7-10). New York; Wiley-Liss, 1992.
	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 1989 Jun; 7(6):754-760.
12	Bosnjak S, Jelic S, Susnjar S, et al. Gabapentin for relief of neuropathic pain related to anticancer treatment: a preliminary study. J Chemother 2002 Apr; 14(2): 214-9.
	Cvitkovic E. Cumulative toxicities from cisplatin therapy and current cytoprotective measures. Cancer Treat Rev 1998 Aug; 24(4):265-281.
	Tuxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. Cancer Treat Rev 1994 Apr; 20(2): 191- 214.
13	Blanchetti MG, Kanaka C, Ridolfi-Luthy A, et al. Persisting renotubular sequelae after cisplatin in children and adolescents. Am J Nephrol 1991; 11(2):127-130.
	Ceremuzynski L, Gebalska J, Wolk R, et al. Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. J Int Med 2000 Jan; 247(1):78-86.
	Dentino M, Luft FC, Yum MN, et al. Long-term effect of cis-diamminedichloride platinum (CDDP) on renal function and structure in man. Cancer 1978 Apr; 41(4):1274-1281.
	Hutchison FN, Perez EA, Gandara DR, et al. Renal salt wasting in patients treated with cisplatin. Ann Intern Med 1988 Jan; 108(1):21-5.
	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 1998 Sep; 136(3): 480-490.
	Marina NM, Poquette CA, et al. Comparative renal toxicity of chemotherapy regimens including ifosfamide in patients with newly diagnosed sarcomas. J Pediatr Hematol 2000 Mar-Apr; 22(2):112-118.
14	Ellis PA, Fitzharris BM, George P, et al. Fasting plasma lipid measurements following cisplatin chemotherapy in patients with germ cell tumors. J Clin Oncol 1992 Oct;10 (10):1609-14.
	Gietema JA, Meinardi MT, Messerschmidt J et al. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. Lancet 2000 Mar 25;355(9209):1075-6.
	Meinardi MT, Gietema JA, van der Graaf WT et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol. 2000 Apr;18(8):1725-32.
	Raghavan D, Cox K, Childs A, et al. Hypercholesterolemia after chemotherapy for testis cancer. J Clin Oncol 1992 Sep; 10: 1386-1389.
15	Baker WJ, Royer GL, Weiss RB. Cytarabine and neurologic toxicity. J Clin Oncol 1991 Apr; 9(4): 679-683.
	Nand S, Messmore HL, Patel R, et al. Neurotoxicity associated with systemic high-dose cytosine arabinoside. J Clin Oncol 1986 Apr; 4(4):571-575.
	Truxen MK, Hansen SW. Neurotoxicity secondary to antineoplastic drugs. Cancer Treat Rev 1994 Apr; 20(2):191-214.
	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 1999 Sep; 17(9):2804-2810.

Section	References
16	Einhorn M, Davidsohn I. Hepatotoxicity of mercaptopurine. JAMA 1964; 188 (9): 802-806.
	Children's Oncology Group, Urgent Advisory for CCG-1952 (April 27, 2001).
17	Aisenberg J, Hsieh K, Kalaitzoglou G, et al. Bone mineral density in young adult survivors of childhood cancer. J Pediatr Hematol Oncol 1998 May-Jun; 20(3): 241-245.
	Arikoski P, Komulainen J, Voutilainen R, et al. Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 1998 May-Jun; 20 (3):234-240.
	Brennan B, Shalet SM. Reduced bone mineral density at completion of chemotherapy for a malignancy. Arch Dis Child 1999 Oct; 81 (4): 372.
	Gilsanz V, Carlson ME, Roe TF, et al. Osteoporosis after cranial radiation for acute lymphoblastic leukemia. J Pediatr 1990 Aug; 117(2 Pt 1): 238-244.
	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 2001 May; 15(5): 728-734.
	Leonard MB, Feldman HI, Zemel BS, et al. Evaluation of low density spine software for the assessment of bone mineral density in children. J Bone Miner Res 1998 Nov; 13(11):1687-1690.
	Leonard MB, Propert KJ, Zemel BS, et al. Discrepancies in pediatric bone mineral density reference data: potential for misdiagnosis of osteopenia. J Pediatr 1999 Aug; 135 (2 Pt 1):182-188.
	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 1998 Jan; 30(1):114-120.
	Nysom K, Holm K, Michaelsen KF, et al. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol 1998 Dec; 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, et al. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 2000 Oct; 35(4): 415-420.
18	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 1983 Mar; 1(3): 208-216.
	Christensen ML, Rivera GK, Crom WR, et al. Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. J Clin Oncol 1988 May; 6(5):797-801.
	Kreusser W, Herrmann R, Tschope W, et al. Nephrological complications of cancer therapy. Contrib Nephrol 1982; 33:223-238.
19	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 1992 Jan-Feb; 77(1): 49-53.
	McIntosh S, Davidson DL, O'Brien RT, et al. Hepatotoxicity in children with leukemia. J Pediatr 1977 Jun; 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.
20	Armstrong FD, Briery BG. Childhood cancer and the school. In RT Brown (Ed), *Handbook of Pediatric Psychology in School Settings*. New York: Lawrence, Erlbaum, Inc., 2003.
	Armstrong FD, Mulhern RK (1999). Acute lymphoblastic leukemia and brain tumors. In RT Brown (Ed), *Cognitive Aspects of Chronic Illness in Children.* (pp. 47-77). New York: Guilford Press.
	Bleyer WA, Fallavollita J, Robison L, et al. Influence of age, sex, and concurrent intrathecal methotrexate therapy on intellectual function after cranial irradiation during childhood: a report from the Children's Cancer Study Group. Pediatr Hematol Oncol 1990; 7(4):329-338.

Section	References
	Brown RT, Madan-Swain A, Pais R, et al. Chemotherapy for acute lymphocytic leukemia: cognitive and academic sequelae. J Pediatr 1992 Dec; 121(6): 885-889.
	Butler RW, Hill JM, Steinherz PG, et al. Neuro-psychological effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol 1994 Dec; 12(12): 2621-2629.
	Hertzberg H, Huk WJ, Ueberall MA, et al. CNS late effects after ALL therapy in childhood. Part 1: Neuroradiological findings in long-term survivors of childhood ALL - An evaluation of the interferences between morphology and neuropsychological performance. Med Pediatr Oncol 1997 Jun; 28(6):387-400.
	Kingma A, Mooyaart EL, Kamps WA, et al. Magnetic resonance imaging of the brain and neuro-psychological evaluation in children treated for acute lymphoblastic leukemia at a young age. Am J Pediatr Hematol Oncol 1993 May; 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 Radiation Oncol Biol Phys 1995 Jul 15; 32(4):913-918.
	Ochs I, Mulhern R, Fairclough D, et al. Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate: a prospective study. J Clin Oncol 1991 Jan; 9(1):145-151.
	Packer RJ, Mehta M. Neurocognitive sequelae of cancer treatment. Neurology 2002 Jul 9; 59(1):8-10.
	Packer RJ, Vezina G. Neurologic complications of chemotherapy and radiotherapy. In Berg BO, ed. Principles of Child Neurology. New York: McGraw- Hill, 1996.
	Riva D, Giorgi C, Nichelli F, et al. Intrathecal methotrexate affects cognitive function in children with medulloblastoma. Neurology 2002 Jul; 59(1):48-53.
	Waber D, Carpentieri SC, Klar N, et al. Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone. J Ped Hematol Oncol 2000 May-Jun; 22(3): 206-213.
	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 1995 Oct; 13(10):2490-2496.
21	Felix CA. Leukemias related to treatment with DNA topoisomerase II inhibitors. Med Pediatr Oncol 2001 May; 36(5):525-535.
22	Allen A. The cardiotoxicity of chemotherapeutic drugs. Semin Oncol 1992 Oct; 19 (5): 529-542.
	Ali MK, Ewer MS, Gibbs HR, et al. Late doxorubicin-associated cardiotoxicity in children. Cancer 1994 Jul; 74(1):182-188.
	Green DM, Hyland A, Chung CS, et al. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. J Clin Oncol 1999 Oct; 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 2001 Apr; 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 1993 Jul; 11 (7): 1208-1215.
	Jakacki RI, Goldwein JW, Larsen RL, et al. Cardiac dysfunction following spinal irradiation during childhood. J Clin Oncol 1993 Jun; 11 (6): 1033-1038.
	Keefe DL. Anthracycline-induced cardiomyopathy. Semin Oncol 2001 Aug; 28 (4 Suppl 12): 2-7.
	Kremer LCM, van Dalen EC, Offringa M, et al. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. J Clin Oncol 2001 Jan1; 19(1): 191-196.
	Krischer JP, Epstein S, Cuthbertson DD, et al. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: The Pediatric Oncology Group experience. J Clin Oncol 1997 Apr; 15(4):1544-52.
	Lipshultz SE, Colan SD, Gelber RD, et al. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 1991 Mar 21; 324(12):808-815.

Section	References
	Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995 Jun29; 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 1998 Feb; 16(2): 545-50. Sorensen K, Levitt G, Bull C, et al. Anthracycline dose in childhood acute lymphoblastic leukemia: issues of early survival versus late cardiotoxicity. J Clin Oncol 1997 Jan; 15(1):61-8. Tolba KA, Deliargyris EN. Cardiotoxicity of cancer therapy. Cancer Investigations 1999; 17(6):408-422.
23	Goldiner PL, Carlon GC, Cvitkovic E, et al. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. Br Med J 1978 Jun 24; 1(6128):1664-67. Kreisman H, Wolkove N. Pulmonary toxicity of antineoplastic therapy. Semin Oncol 1992 Oct; 19(5): 508-20. Marina N, 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 1995 Apr 1; 75(7):1706-11. Mefferd JM, Donaldson SS, Link MP. Pediatric Hodgkin's disease: pulmonary, cardiac, and thyroid function following combined modality therapy. Int J Radiation Oncology Biol Phys 1989 Mar; 16(3): 679-85. Risks associated with SCUBA diving in childhood cancer survivors (personal communication with Brett Stolp MD, PhD, Duke University), 8-23-02.
24	Green DM, Norkool P, Breslow NE, et al. 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 1990 Sep; 8(9): 1525-30.
25	Aisenberg J, Hsieh K, Kalaitzoglou G, et al. Bone mineral density in young adult survivors of childhood cancer. J Pediatr Hematol Oncol 1998 May-Jun; 20(3): 241-245. Halton JM, Wu B, Atkinson SA, et al. Comparative skeletal toxicity of dexamethasone and prednisone in childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2000 Jul-Aug; 22(4): 369. 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 2001 May; 15(5): 728-734. Nysom K, Holm K, Michaelsen KF, et al. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol 1998 Dec; 16 (12): 3752-3760.
26	Chan-Lam D, Prentice AG, Copplestone JA, et al. Avascular necrosis of bone following intensified therapy for acute lymphoblastic leukemia and high-grade malignant lymphoma. Br J Hematol 1994 Jan; 86(1): 227-230. Enrici RM, Anselmo AP, Donato V, et al. Avascular osteonecrosis in patients treated for Hodgkin's disease. Eur J Haematol 1998 Sep; 61(3):204-209. Mattano LA, Sather HN, Trigg ME, et al. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000 Sep 15; 18(18):3262-3272. Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001 Jun 15; 19 (12): 3066-3072.
27	Hoover DL, Smith LE, Turner SJ, et al. Opthalmic evaluation of survivors of acute lymphoblastic leukemia. Ophthalmology 1988 Feb; 95 (2): 151-155. Kaye LD, Kalenak JW, Price RL, et al. Ocular implications of long-term prednisone therapy in children. J Pediatr Ophthalmol Strabismus 1993 May-Jun; 30(3): 142-144. Nanda SK, Schachat AP. Ocular complications following radiation therapy to the orbit, In DM Green and GJ D'Angio (Eds). Late Effects of Treatment for Childhood Cancer. (pp 11-21). New York: Wiley-Liss, 1992.

Section	References
	Zierhut D, Lohr F, Schraube P, et al. Cataract incidence after total-body irradiation. Int. J Radiation Oncol Biol Phys 2000 Jan 1; 46(1):131-135.
28	No late effects identified.
29	Graf WD, Chance PF, Lensch MW, et al. Severe vincristine neuropathy in Charcot-Marie-Tooth disease Type 1A. Cancer 1996 Apr 1; 77(7):1356-1362. Lehtinen SS, Huuskonen UE, Harila-Saari AH, et al. Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukemia. Cancer 2002 May 1; 94(9): 2466-73. Trobaugh-Lotrario AD, Smith AA, Odom LF. Vincristine neurotoxicity in the presence of hereditary neuropathy. Med Pediatr Oncol 2003 Jan; 40(1):39-43.
30	Bokemeyer C, Berger CC, Kuczyk MA, et al. Evaluation of long-term toxicity after chemotherapy for testicular cancer. J Clin Oncol 1996 Nov; 14(11): 2923-2932. Doll DC, Ringenberg QS, Yarbro JW. Vascular toxicity associated with antineoplastic agents. J Clin Oncol 1986 Sep; 4 (9): 1405-1417. Vogelzang NJ, Bosl GJ, Johnson K, et al. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Int Med 1981 Oct 31; 95(3): 288-292.
31	Pui CH, Relling MV, Behm FG, et al. L-asparaginase may potentiate the leukemogenic effect of the epipodophyllotoxins. Leukemia 1995 Oct; 9(10):1680-1684. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 1991 Dec 12; 325(24):1682-1687. Smith MA, Rubinstein L, Anderson JR, et al. Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. J Clin Oncol 1999 Feb; 17(2):569-77.
32	Marcus RB, McGrath B, O'Conner K, et al. Long-term effects on the musculoskeletal and integumentary systems and the breast. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (eds): Survivors of Childhood Cancer: Assessment and Management 1994; 14: 263-292., Mosby: St Louis.
33	Bhatia S, Ramsay NK, Steinbuch, M, et al. Malignant neoplasms following bone marrow transplant. Blood 1996 May 1; 87(9):3633-3639. Bhatia S, Robison LL, Oberlin O et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 1996 Mar 21; 334(12):745-751. Bhatia S, Sather HN, Pabustan OB, et al. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. Blood 2002 Jun 15; 99(12):4257-4264. Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Nat Cancer Inst 1998 Jul 15; 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 2001 Apr 18; 93(8): 618-629.
34	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2000, pp. 22-23. Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. J Natl Cancer Inst 1996 Dec 18; 88 (24): 1848-1853. Shore RE. Radiation-induced skin cancer in humans. Med Pediatr Oncol 2001 May; 36(5): 549-554.
35	Hawkins MM, Wilson LM, Burton HS, et al. Radiotherapy, alkylating agents and risk of bone cancer after childhood cancer. J Natl Cancer Inst 1996 Mar 6; 88(5):270-278. Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Nat Cancer Inst 1998 Jul 15; 90 (14): 1039-1071. Newton WA, Meadows AT, Shimada H, et al. Bone sarcomas as second malignant neoplasms following childhood cancer. Cancer 1991 Jan 1; 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 1987 Sep 3; 317(10):588-593.

Section	References
36	Armstrong FD, Briery BG. Childhood cancer and the school. In RT Brown (Ed), *Handbook of Pediatric Psychology in School Settings.* New York: Lawrence, Erlbaum, Inc., 2003.
	Armstrong FD, Mulhern RK (1999). Acute lymphoblastic leukemia and brain tumors. In RT Brown (Ed), *Cognitive Aspects of Chronic Illness in Children*. New York: Guilford Press.
	Bleyer WA, Fallavollita J, Robison L, et al. Influence of age, sex, and concurrent intrathecal methotrexate therapy on intellectual function after cranial irradiation during childhood: a report from the Children's Cancer Study Group. Pediatr Hematol Oncol 1990; 7(4): 329-338.
	Butler RW, Hill JM, Steinherz PG, et al. Neuro-psychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol 1994 Dec; 12(12): 2621-2629.
	Hoppe-Hirsch E, Brunet L, Laroussinie F, et al. Intellectual outcome in children with malignant tumors of the posterior fossa: influence of the field of irradiation and quality of surgery. Child Nerv Syst 1995 Jun; 11(6):340-345.
	Keene N, Hobbie W, Ruccione K. (ed) Childhood Cancer Survivors: A Practical Guide to Your Future. O Reilly, Sebastopol, 2002
	Kramer JH, Crittenden MR, De Santes K, et al. Cognitive and adaptive behavior 1 and 3 years following bone marrow transplantation. Bone Marrow Transplant 1997 Mar; 19(6):607-613.
	Mulhern RK, Kepner JL, Thomas PR, et al. Neuro-psychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol 1998 May; 16(5): 1723-1728.
	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 2001 Jan 15; 19(2):472-479.
	Phipps S, Dunavant M, Srivastava DK, et al. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. J Clin Oncol 2000 Mar; 18(5):1004-1011.
	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 2003 Jan; 40(1):26-34.
	Ris DM, Packer R, Goldwein J, et al. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group Study. J Clin Oncol 2001 Aug; 19(15): 3470-3476.
	Silber JH, Radcliffe J, Peckham V, et al. Whole-brain irradiation and decline in intelligence: the influence of dose and age on IQ score. J Clin Oncol 1992 Sep; 10(9): 1390-1396.
	Simms S, Kazak AE, Gannon T, et al. Neuropsychological outcome of children undergoing bone marrow transplantation. Bone Marrow Transplantation 1998 Jul; 22(2):181-184.
	Strother DR, Pollack AF, Fisher PG, et al. Tumors of the Central Nervous System. In Pizzo PA, Poplack DG (Eds). Principles and Practice of Pediatric Oncology, 4th Edition, Lippincott Williams & Wilkins, Philadelphia 2002; 805-808.
	Waber DP, Tarbell NJ, Fairclough D, et al. Cognitive sequelae of treatment of childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. J Clin Oncol 1995 Oct; 13(10):2490-2496.
	Walter AW, Mulhern RK, GajjarA, et al. Survival and neurodevelopmental outcome of young children with medulloblastoma at St. Jude Children's Research Hospital. J Clin Oncol 1999 Dec; 17(12):3720-3728.

Section	References
37	Heckl S, Aschoff A, Kunze S. Radiation-induced cavernous hemangiomas of the brain: a late effect predominantly in children. Cancer 2002 Jun 15; 94(12):3285-3291.
	Hertzberg H, Huk WJ, Ueberall MA, et al. CNS late effects after ALL therapy in childhood. Part 1: Neuroradiological findings in long-term survivors of childhood ALL - An evaluation of the interference between morphology and neuropsychological performance. Med Pediatr Oncol 1997 Jun; 28(6):387-400.
	Kingma A, Mooyaart EL, Kamps WA, et al. Magnetic resonance imaging of the brain and neuro-psychological evaluation in children treated for acute lymphoblastic leukemia at a young age. Am J Pediatr Hematol Oncol 1993 May; 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 Radiation Oncol Biol Phys 1995 Jul 15; 32(4):913-918.
38	Grenier Y, Tomita T, Marytmont MH, et al. Late postirradiation occlusive vasculopathy in childhood medulloblastoma: report of two cases. J Nerurosug 1998 Sep; 89(3):460-464.
	Kestle JR, Hoffman HJ, Mock AR. Moyamoya phemomenon after radiation for optic glioma. J Neurosurg 1993 Jul; 79(1):32-35.
	Rudoltz MS, Regine WF, Langston JW, et al. Multiple causes of cerebrovascular events in children with tumors of the parasellar region. J Neuro-Oncol 1998 May; 37(3): 251-261.
39	Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Nat Cancer Inst 1998 Jul 15; 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 2001 Apr 18; 93(8):618-629.
	Relling MV, Rubnitz JE, Rivera GK, et al. High incidence of secondary brain tumors after radiotherapy and antimetabolites. Lancet 1999 Jul 3; 354(9172): 34-9.
	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 1998 Dec; 16 (12): 3761-3767.
40	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 1999 Jun 15; 93 (12): 4109-4115.
	Costin G. Effects of low-dose cranial radiation on growth hormone secretory dynamics and hypothalamic-pituitary function. Am J Dis Child 1988 Aug; 142 (8): 847-852.
	Didcock E, Davies HA, Didi M, et al. Pubertal growth in young adult survivors of childhood leukemia. J Clin Oncol 1995 Oct; 13(10): 2503-2507.
	Donaldson SS. Pediatric patients: Tolerance levels and effects of treatment. In: Vaeth JM, Meyer JL (eds): Frontiers of Radiation Therapy and Oncology 1989; 23:390-407.
	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 1995 Jul 15; 86(2): 825-831.
	Gleeson HK, Shalet SM. Endocrine complications of neoplastic diseases in children and adolescents. Current Opin Pediatr 2001 Aug; 13(4):346-351.
	Huma Z, Boulad F, Black P, et al. Growth in children after bone marrow transplantation for acute leukemia. Blood 1995 Jul 15; 86(2): 819-824.
	Merchant TE, Williams T, Smith JM, et al. Pre- irradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. Int J Radiation Oncology Biol Phys 2002 Sep 1; 54(1): 45-50.
	Ogilvy-Stuart AL, Shalet SM. Growth and puberty after growth hormone treatment after irradiation for brain tumors. Arch Dis Child 1995 Aug; 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 2001 Jan 15; 19(2):480-487.
	Sanders JE, Pritchard S, Mahoney P, et al. Growth and development following marrow transplantation for leukemia. Blood 1986 Nov; 68 (5): 1129-1135.
	Schriock EA, Schell MJ, Carter M, et al. Abnormal growth patterns and adult short stature in 115 long-term survivors of childhood leukemia. J Clin Oncol 1991 Mar; 9(3):400-405.

Section	References
	Shalet SM, Crowne EC, Didi MA, et al. Irradiation-induced growth failure. Baillieres Clin Endocrinol Metab 1992 Jul; 6(3): 513-526.
	Shankar SM, Bunin NJ, Moshang T. Growth in children undergoing bone marrow transplantation after busulfan and cyclophosphamide conditioning. J Pediatr Hematol Oncol 1996 Nov; 18 (4): 362-366.
	Sklar C. Endocrine complications of the successful treatment of neoplastic diseases in childhood. Growth Genetics & Hormones 2001; 17: 37.
	Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug 1; 6: G17-22.Sklar CA. Growth following therapy for childhood cancer. Cancer Investigation 1995; 13(5): 511-516.
	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 radiation. J Pediatr 1993 Jul; 123(1):59-64.
	Sklar CA. Growth and neuroendocrine dysfunction following therapy for childhood cancer. Ped Clin N Amer 1997 Apr; 44(2):489-503.
	Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 1995 Mar 30; 31(5):1113-1121.
	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 1992 Feb 15; 79 (4): 1068-1073.
41	Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. New Engl J Med 1993 Jan 14; 328(2):87-94.
	Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Rad Oncol Biol Phys 1995 Mar 30; 31(5):1113-1121.
42	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 1990 May; 5(5):335-340.
	Lando A, Holm K, Nysom K, et al. Thyroid function in survivors of childhood acute lymphoblastic leukemia; the significance of prophylactic cranial irradiation. Clin Endocrinol 2001 Jul; 55(1):21-25.
	Livesey EA, Brook CG. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumors. Arch Dis Child 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 1999 Dec; 84(12): 4472-4479.
	Sanders JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. Bone Marrow Transplant 1991; 8 (suppl 1): 2-4.
	Sanders JE. Growth and Development After Hematopoietic Cell Transplantation. In Thomas ED, Blume KG, Forman SJ (Eds). Hematopoietic Cell Transplantation (2nd). (1999). Malden, MA: Blackwell Science, pp 764-775.
	Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug 1; 6: G17-22.
	Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Rad Oncol Biol Phys 1995 Mar 30; 31(5):1113-1121.
	Sklar CA, Kim TH, Ramsay NK. Thyroid dysfunction among long-term survivors of bone marrow transplantation. Am J Med 1982 Nov; 73(5):688-694.
43	Oberfield SE, Nirenberg A, Allen JC, et al. Hypothalamic-pituitary-adrenal function following cranial irradiation. Horm Research 1997; 47 (1): 9-16.
	Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Rad Oncol Biol Phys 1995 Mar 30; 31(5):1113-1121.
44	Mills JL, Fears TR, Robison LL, et al. Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia. J Pediatr 1997 Oct; 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 1996 Jun; 150(6):589-592.
	Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. J Clin Endocrinol Metab 1994 Jun; 78(6):1282-1286.

Section	References
	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 1989 Jul 20; 321(3): 143-51.
	Sklar CA. Growth and neuroendocrine dysfunction following therapy for childhood cancer. Pediatr Clin N Amer 1997 Apr; 44(2):489-503.
	Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Rad Oncol Biol Phys 1995 Mar 30; 31(5):1113-1121.
45	Mills JL, Fears TR, Robison LL, et al. Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia. J Pediatr 1997 Oct; 131(4):598-602
	Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. J Clin Endo Metab 1994 Jun; 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 1989 Jul 20; 321(3): 143-51.
	Schmiegelow M, Lassen S, Poulsen HS, et al. Gonadal status in male survivors following childhood brain tumors. J Clin Endocrinol Metab 2001 Jun; 86 (6): 2446-2452.
46	Brennan BM, Rahim A, Blum WF, et al. Hyperleptinaemia in young adults following cranial irradiation in childhood. Clin Endocrinol 1999 Feb; 50 (2): 163-169.
	Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. New Engl J Med 1993 Jan 14; 328(2):87-94.
	Didi M, Didcock ED, Davies HA, et al. High incidence of obesity in young adults after treatment of acute lymphoblastic leukemia in childhood. J Pediatr 1995 Jul; 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 1999 Aug; 135(2Pt1): 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 2003 Apr 1; 21(7):1359-1365.
	Reilly JJ, Ventham JC, Newell J, et al. Risk factors for excess weight gain in children treated for acute lymphoblastic leukemia. Int J Obes Relat Metab Disord 2000 Nov; 24(11):1537-41.
	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 2000 Aug; 35(2):91-95.
	Warner JT, Evans WD, Webb DKH, et al. Body composition of long-term survivors of acute lymphoblastic leukemia. Med Pediatr Oncol 2002 Mar; 38(3):165-172.
47	No manuscripts found to describe this late treatment effect in children.
48	Antin JH. Clinical Practice. Long-term care after hematopoietic-cell transplantation in adults. N Engl J Med 2002 Jul 4; 347 (1): 36-42.
	Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiation Oncol Biol Phys 1991 May 15; 21(1):109-122.
	Guchelaar HJ, Vermes A, Meerwaldt JH. Radiation- induced xerostomia: pathophysiology, clinical course and supportive treatment. Support Care Cancer. 1997 Jul; 5(4): 281-288.
49	Goho C. Chemoradiation therapy: effect on dental development. Pediatric Dentistry 1993 Jan-Feb; 15 (1): 6-12.
	Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. Med Pediatr Oncol. 1995 Aug;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. 1997 Jun;11(6):792-6.
	Maguire A, Welbury RR. Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development. Dent Update. 1996 Jun;23(5):188-94. Erratum in: Dent Update 1996 Jul-Aug;23(6):238.
	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. Med Pediatr Oncol 1999 Oct; 33 (4): 362-371.

Section	References
	Sonis AL, Tarbell N, Valachovic RW, et al. Dento- facial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. Cancer 1990 Dec 15; 66(12): 2645-2652.
50	Kaste SC, Chen G, Fontanesi J, et al. Orbital development in long-term survivors of retinoblastoma. J Clin Oncol 1997 Mar; 15(3):1183-1189. Paulino AC, Simon JH, Zhen W, et al. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiation Oncol Biol Phys 2000 Dec 1; 48 (5): 1489-1495. 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. Med Pediatr Oncol 1999 Oct; 33(4):362-371.
51	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. (pp 111-131). St. Louis: Mosby, 1994. Holmstrom G, Borgstrom B, Callissendorff B. Cataract in children after bone marrow transplantation: relation to conditioning regimen. Acta Ophthalmol Scand. 2002 Apr; 80(2):211-15. Kaste SC, Chen G, Fontanesi J, et al. Orbital development in long-term survivors of retinoblastoma. J Clin Oncol 1997 Mar; 15(3):1183-1189. Nanda SK, Schachat AP. Ocular complications following radiation therapy to the orbit in DM Green and GJ D'Angio (Eds). Late Effects of Treatment for Childhood Cancer. (pp 11-21). New York: Wiley-Liss, 1992. 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 2001 Jan 1; 19 (1): 197-204. Parsons JT, Bova FJ, Mendenhall WM. Response of the normal eye to high-dose radiotherapy. Oncology 1996 Jun; 10 (6): 837-852. Socie G, Salooja N, Cohen A, Rovelli A, Carreras E, Locasciulli A, Korthof E, Weis J, Levy V, Tichelli A; Late Effects Working Party of the European Study Group for Blood and Marrow Transplantation. Nonmalignant late effects after allogeneic stem cell transplantation. Blood. 2003 May 1;101(9):3373-85. van-Kempen-Harteveld ML, Belkacemi Y, Kal HB, et al. Dose-effect relationship for cataract induction after single-dose total body irradiation and bone marrow transplantation for acute leukemia. Int J Radiation Oncol Biol Phys 2002 Apr 1; 52(5): 1367-1374. Zierhut D, Lohr F, Schraube P, et al. Cataract incidence after total body irradiation. Int J Radiation Oncol Biol Phys 2000 Jan 1; 46 (1): 131-135.
52	Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiation Oncol Biol Phys 1991 May 15; 21(1):109-122. Fromm M, Littman P, Raney RB, et al. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. Cancer 1986 May 15; 57 (10): 2070-2076. Ho WK, Wei WI, Kwong DL, et al. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head Neck 1999 Sep; 21 (6): 547-553. Johannesen TB, Rasmussen K, Winther FO, et al. Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. Int J Radiat Oncol Biol Phys 2002 May 1; 53 (1): 86-90. Ondrey FG, Greig JR, Herscher L. Radiation dose to otologic structures during head and neck cancer radiation therapy. Laryngoscope 2000 Feb; 110(2Pt1):217-221. Paulino AC, Simon JH, Zhen W, et al. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiation Oncol Biol Phys 2000 Dec 1; 48 (5): 1489-1495. 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. Med Pediatr Oncol 1999 Oct; 33(4):362-371. 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 1989 Jun; 7(6):754-760.

Section	References
53	Black P, Straaten A, Gutjahr P. Secondary thyroid carcinoma after treatment for childhood cancer. Med Pediatr Oncol 1998 Aug; 31 (2): 91-95. Constine LS, Donaldson SS, McDougall IR, et al. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer: 1984 Feb 15; 53(4):878-883. DeGroot LJ. Effects of irradiation on the thyroid gland. Endocrinol Metab Clinics North America 1993 Sep; 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 1986 Jul; 63(1): 107-112. 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 2000 Sep; 85(9):3227-3232.
54	Inskip PD. Thyroid cancer after radiotherapy for childhood cancer. Med Pediatr Oncol 2001 May; 36(5): 568-573. 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 1986 Jul; 63(1): 107-112. 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 2000 Sep; 85(9):3227-3232.
55	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 1997 Aug 15; 80 (4): 798-804. Constine LS, Donaldson SS, McDougall IR, et al. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer: 1984 Feb 15; 53(4):878-883. DeGroot LJ. Effects of irradiation on the thyroid gland. Endocrinol Metab Clinics North America 1993 Sep; 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 1990 May; 5(5): 335-340. Ogilvy-Stuart AL, Shalet SM, Gattamaneni HR. Thyroid function after treatment of brain tumors in children. J Pediatr 1991 Nov; 119 (5): 733-737. Sanders JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. Bone Marrow Transplant 1991; 8 (suppl 1): 2-4. Sanders JE. Growth and Development After Hematopoietic Cell Transplantation. In Thomas ED, Blume KG, Forman SJ (Eds). Hematopoietic Cell Transplantation (2nd). (1999). Malden, MA: Blackwell Science, pp 764-775. Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug 1; 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 2000 Sep; 85(9):3227-3232. Sklar CA, Kim TH, Ramsay NK. Thyroid dysfunction among long-term survivors of bone marrow transplantation. Am J Med 1982 Nov; 73(5):688-694.
56	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 1997 Aug 15; 80 (4): 798-804. Constine LS, Donaldson SS, McDougall IR, et al. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer: 1984 Feb 15; 53(4):878-883. DeGroot LJ. Effects of irradiation on the thyroid gland. Endocrinol Metab Clinics North America 1993 Sep; 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 1990 May; 5(5): 335-340. Ogilvy-Stuart AL, Shalet SM, Gattamaneni HR. Thyroid function after treatment of brain tumors in children. J Pediatr 1991 Nov; 119 (5): 733-737.

Section	References
	Sanders JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. Bone Marrow Transplant 1991; 8 (suppl 1): 2-4.
	Sanders JE. Growth and Development After Hematopoietic Cell Transplantation. In Thomas ED, Blume KG, Forman SJ (Eds). Hematopoietic Cell Transplantation (2nd). (1999). Malden, MA: Blackwell Science, pp 764-775.
	Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug 1; 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 2000 Sep; 85(9):3227-3232.
	Sklar CA, Kim TH, Ramsay NK. Thyroid dysfunction among long-term survivors of bone marrow transplantation. Am J Med 1982 Nov; 73(5):688-694.
57	Grenier Y, Tomita T, Marymont MH, et al. Late postirradiation occlusive vasculopathy in childhood medulloblastoma: report of two cases. J Nerurosug 1998 Sep; 89(3):460-464.
58	Mahboubi S, Silber JH. Radiation-induced esophageal strictures in children with cancer. Eur Radiol 1997; 7(1):119-122.
59	Donaldson SS. Pediatric patients: Tolerance levels and effects of treatment. In Vaeth JM, Meyer JL (eds): Frontiers of Radiation Therapy and Oncology 1989; 23:390-407.
	Fletcher BD. Effects of pediatric cancer therapy on the musculoskeletal system. Pediatr Radiol 1997 Aug; 27(8): 623-636.
	Katzman H, Waugh T, Berdon W. Skeletal changes following irradiation of childhood tumors. J Bone Joint Surgery Am 1969 Jul; 51(5): 825-842.
	Probert JC, Parker BR. The effects of radiation therapy on bone growth. Radiology 1975 Jan; 114(1):155-62.
	Probert JC, Parker BR, Kaplan HS. Growth retardation in children after megavoltage irradiation of the spine. Cancer 1973 Sep; 32(3):634-39.
60	Marcus RB, McGrath B, O'Conner K, et al. Long-term effects on the musculoskeletal and integumentary systems and the breast. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (eds): Survivors of Childhood Cancer: Assessment and Management 1994; 14: 263-292., Mosby: St Louis.
	Paulino A, Mayr NA, Simon JH, et al. Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. Int J Radiat Oncol Biol Phys 2002 Mar 15; 52(4):1025-1031.
	Paulino A, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms tumor. Int J Radiat Oncol Biol Phys 2000 Mar 15; 46(5): 1239-1246.
61	Marcus RB, McGrath B, O'Conner K, et al. Long-term effects on the musculoskeletal and integumentary systems and the breast. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (eds): Survivors of Childhood Cancer: Assessment and Management 1994; 14: 263-292., Mosby: St Louis.
	Paulino A, Mayr NA, Simon JH, et al. Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. Int J Radiat Oncol Biol Phys 2002 Mar 15; 52(4):1025-1031.
	Paulino A, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms tumor. Int J Radiat Oncol Biol Phys 2000 Mar 15; 46(5): 1239-1246.
62	Mahboubi S, Silber JH. Radiation-induced esophageal strictures in children with cancer. Eur Radiol 1997; 7(1):119-122.
63	Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 1996 Mar 21; 334(12): 745-751.
	Goss PE, Sierra S. Current perspectives on radiation-induced breast cancer. J Clin Oncol 1998 Jan; 16(1):338-347.
	Kaste SC, Hudson MM, Jones DJ, et al. Breast masses in women treated for childhood cancer. Incidence and screening guidelines. Cancer 1998 Feb 15; 82(4):784-792.
	National Comprehensive Cancer Network Practice Guidelines in Oncology - v.1.2002

Section	References
64	Furst CJ, Lundell M, Ahlback SO, et al. 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, et al. 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 Radiation Oncol Biol Phys 1991 Oct; 21(5):1187-93.
65	Adams MJ, Hardenbergh PH, Constine LS, et al: Radiation-associated cardiovascular disease. Critical Reviews in Oncology/Hematology 2003 Jan; 45(1):55-75.
	Eames GM, Crosson J, Steinberger J, et al. Cardiovascular function in children following bone marrow transplant: a cross-sectional study. Bone Marrow Transplant 1997 Jan; 19(1): 61-66.
	Glanzmann C, Kaufmann P, Jenni R, et al. Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiother Oncol 1998 Jan; 46 (1): 51-62.
	Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from National Wilms' Tumor Study Group. J Clin Oncol 2001 Apr 1; 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 1993 Jul; 11(7): 1208-15.
	Hertenstein B, Stefanic M, Schmeiser T, et al. Cardiac toxicity of bone marrow transplantation: predictive value of cardiologic evaluation before transplantation. J Clin Oncol 1994 May; 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 2000 Mar; 136(3):311-317.
	Jakacki RI, Goldwein JW, Larsen RL, et al. Cardiac dysfunction following spinal irradiation during childhood. J Clin Oncol 1993 Jun; 11 (6): 1033-1038.
	Lonnerholm G, Arvidson J, Andersson LG, et al. Myocardial function after autologous bone marrow transplantation in children: a prospective long-term study. Acta Pediatr 1999 Feb; 88(2):186-192.
	Pihkala J, Saarinen UM, Lundstrom U, et al. Effects of bone marrow transplantation on myocardial function in children. Bone Marrow Transplantation 1994 Feb; 13(2): 149-155.
66	Fanfulla F, Locatelli F, Zoia MC, et al. Pulmonary complications and respiratory function changes after bone marrow transplantation in children. Eur Respir J 1997 Oct; 10(10): 2301-2306.
	Frankovich J, Donaldson SS, Lee Y, et al. 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, et al. Pulmonary function changes in long-term survivors of bone marrow transplantation. Int J Radiat Oncol Biol Phys 1996 Aug 1; 36(1):67-75.
	Griese M, Rampf U, Hofmann D, et al. Pulmonary complications after bone marrow transplantation in children: twenty-four years of experience in a single pediatric center. Pediatr Pulmonol 2000 Nov; 30(5): 393-401.
	Kader HA, Khanna S, Hutchinson RM, et al. Pulmonary complications of bone marrow transplantation: the impact of variations in total body irradiation parameters. Clin Oncol 1994; 6(2): 96-101.
	McDonald S, Rubin P, Schwartz CL. Pulmonary effects of antineoplastic therapy. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (eds): Survivors of Childhood Cancer: Assessment and Management 1994; 14: 263-292. Mosby: St Louis.
	Nenadov Beck M, Meresse V, et al. Long-term pulmonary sequelae after autologous bone marrow transplantation in children without total body irradiation. Bone Marrow Transplant 1995 Dec; 16(6):771-775.
	Nysom K, Holm K, Hertz H, et al. Risk factors for reduced pulmonary function after malignant lymphoma in childhood. Med Pediatr Oncol 1998 Apr; 30(4):240-248.
	Nysom K, Holm K, Hesse B, et al. Lung function after allogeneic bone marrow transplantation for leukemia or lymphoma. Arch Dis Child 1996 May; 74(5): 432-436.

Section	References
	Palmas A, Tefferi A, Meyers JL, et al. Late onset noninfectious pulmonary complications after allogeneic bone marrow transplantation. Br J Haematol 1998 Mar; 100(4): 680-687.
	Risks associated with SCUBA diving in childhood cancer survivors (personal communication with Brett Stolp MD, PhD, Duke University), 8-23-02.
67	American Academy of Pediatrics. Immunization in special clinical circumstances. Report of the Committee on Infectious Diseases, 25th edition, American Academy of Pediatrics. 1997; 6-67.
	Coleman CN, McDougall IR, Dailey MO, et al. Functional hyposplenia after splenic irradiation for Hodgkin's disease. Ann Int Med 1982 Jan; 96(1):44-7.
	Stevens M, Brown E, Zipursky A. The effect of abdominal radiation on spleen function: a study in children with Wilms' tumor. Pediatr Hematol Oncol 1986; 3(1): 69-72.
	Weiner MA, Landmann RG, DeParedes L, et al. Vesiculated erythrocytes as a determination of splenic reticuloendothelial function in pediatric patients with Hodgkin's disease. J Ped Hematol Oncol 1995 Nov; 17(4): 1338-341.
68	Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiation Oncology Biol Phys 1991 May 15; 21(1):109-122.
	Keane WF, Crosson JT, Staley NA, et al. Radiation- induced renal disease: a clinicopathologic study. Am J Med 1976 Jan; 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 1996 Jul-Aug; 13(4): 375-379.
	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 1997 Dec; 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 1996 Feb; 14(2): 579-585.
	Mitus A, Tefft M, Feller FX. Long-term follow-up of renal functions of 108 children who underwent nephrectomy for malignant disease. Pediatrics 1969 Dec; 44(6): 912-921.
	Ritchey ML, Green DM, Thomas PRM, et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 1996 Feb; 26(2): 75-80.
	Tarbell NJ, Guinan EC, Niemeyer C, et al. Late onset of renal dysfunction in survivors of bone marrow transplantation. Int J Radiat Oncol Biol Phys 1988 Jul; 15(1): 99-104.
69	Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiation Oncology Biol Phys 1991 May 15; 21(1):109-122.
	Jirtle RL, Anscher MS, Alati T. Radiation sensitivity of the liver. Advances in Radiation Biol 1990; 14 269-311.
70	Strickland DK, Jenkins JJ, Hudson MM. Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. J Pediatr Hematol Oncol. 2001Nov; 23(8): 527-529
71	Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiation Oncology Biol Phys 1991 May 15; 21(1):109-122.
72	Mahboubi S, Silber JH. Radiation-induced esophageal strictures in children with cancer. Eur Radiol 1997; 7(1):119-122.
73	Bhatia S, Yasui Y, Robison LL, et al. High Risk of second malignant neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. J Clin Oncol. 2003 Dec 1;21(23):4386-94.
	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 2000 Jun; 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 2000 Feb; 18 (3): 498-509.
74	Blatt J. Pregnancy outcomes in long-term survivors of childhood cancer. Med Pediatr Oncol 1999 Jul; 33(1): 29-33.

Section	References
	Byrne J. Long term genetic and reproductive effects of ionizing radiation and chemotherapeutic agents on cancer patients and their offspring. Teratology 1999 Apr; 59(4): 210-215.
	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 2002 Apr; 38(4): 258-259.
	Critchley HO. Factors of importance for implantation and problems after treatment for childhood cancer. Med Pediatr Oncol 1999 Jul; 33(1): 9-14.
	Green DM, Peabody EM, Nan B, et al. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol 2002 May 15; 20(10): 2506-2513.
	Gulati SC, Van Poznak C. Pregnancy after bone marrow transplantation. J Clin Oncol 1998 May; 16(5): 1978-85.
	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 1996 Apr 1; 87 (7): 3045-3052.
	Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. Hosp Med 2000 Aug; 61(8): 550-557.
75	Bath LE, Hamish W, Wallace B, et al. Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. Br J Obstet Gynecol 2002 Feb; 109(2): 107-114.
	Bhatia S. Late effects of hematopoietic cell transplantation. In MC Perry (Ed): American Society of Clinical Oncology Educational Book, 37th Annual Meeting. 2001. Alexandria, VA. American Society of Clinical Oncology. Pp 375-385.
	Couto-Silva AC, Trivin C, Thibaud E, et al. Factors affecting gonadal function after bone marrow transplantation during childhood. Bone Marrow Transplant 2001 Jul; 28(1): 67-75.
	Grigg AP, McLachlan R, Zaja J, et al. Reproductive status in long-term bone marrow transplant survivors receiving busulfan-cyclophosphamide (120 mg/kg). Bone Marrow Transplant 2000 Nov; 26(10): 1089-1095.
	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 Children's Cancer Study Group. J Clin Oncol 1987 Nov; 5(11): 1759-1765.
	Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Amer 1998 Dec; 27(4): 927-43.
	Livesey EA, Brook CG. Gonadal dysfunction after treatment of intracranial tumours. Arch Dis Child 1988 May; 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 2000 Mar 15; 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 1999 May; 32(5): 366-372.
	Sanders JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. 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 1997 Feb; 130 (2): 210-216.
	Sklar C. Reproductive physiology and treatment related loss of sex hormone production. Med Pediatr Oncol 1999 Jul; 33(1): 2-8.
	Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug; 6: G17-22.
	Stillman RJ, Schinfeld JS, Schiff I, et al. Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol 1981 Jan; 139(1): 62-66.
	Thibaud E, Rodriguez-Macias K, Trivin C, et al. Ovarian function after bone marrow transplantation during childhood. Bone Marrow Transplant 1998 Feb; 21(3): 287-290.
	Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. Hosp Med 2000 Aug; 61(8): 550-557.
76	Hays DM, Raney RB, Wharam MD, et al. Children with vesical rhabdomyosarcoma (RMS) treated by partial cystectomy with neoadjuvant or adjuvant chemotherapy, with or without radiotherapy: a report from the Intergroup Rhabdomyosarcoma Study (IRS) Committee. J Pediatr Hematol Oncol 1995 Feb; 17(1): 46-52.

Section	References
	Raney B Jr , Heyn R, Hays DM, et al. Sequelae of treatment in 109 patients followed for 5-15 years after diagnosis of sarcoma of the bladder and prostate. Cancer 1993 Apr 1; 71(7): 2387-2394.
	Stillwell TJ, Benson RC. Cyclophosphamide-induced hemorrhagic cystitis: a review of 100 patients. Cancer 1988 Feb 1; 61(3): 451-457.
	Stillwell TJ, Benson RC, Burgert EO. Cyclophosphamide-induced hemorrhagic cystitis in Ewing's sarcoma. J Clin Oncol 1988 Jan; 6(1): 76-82.
77	Hays DM, Raney B, Wharam M, et al. Children with vesical rhabdomyosarcoma treated by partial cystectomy with neoadjuvant or adjuvant chemotherapy, with or without radiotherapy: a report from the Intergroup Rhabdomyosarcoma Study Committee. J Pediatr Hematol Oncol 1995 Feb; 17 (1): 46-52.
	Raney B Jr , Heyn R, Hays DM, et al. Sequelae of treatment in 109 patients followed for 5-15 years after diagnosis of sarcoma of the bladder and prostate. Cancer 1993 Apr 1; 71(7): 2387-2394.
78	Pederson-Bjergaardd 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 1988 Apr 21; 318(16): 1028-1032.
79	Bhatia S. Late effects of hematopoietic cell transplantation. In MC Perry (Ed): American Society of Clinical Oncology Educational Book, 37th Annual Meeting. 2001. Alexandria, VA. American Society of Clinical Oncology. pp 375-385.
	Couto-Silva AC, Trivin C, Thibaud E, et al. Factors affecting gonadal function after bone marrow transplantation during childhood. Bone Marrow Transplant 2001 Jul; 28(1): 67-75.
	Goldman S, Johnson FL. Effects of chemotherapy and irradiation on the gonads. Endocrinol Metab Clin North Amer 1993 Sep; 22(3): 617-629.
	Grigg AP, McLachlan R, Zaja J, et al. Reproductive status in long-term bone marrow transplant survivors receiving busulfan-cyclophosphamide (120 mg/kg). Bone Marrow Transplant 2000 Nov; 26(10): 1089-1095.
	Jacob A, Barker H, Goodman A, et al. Recovery of spermatogenesis following bone marrow transplantation. Bone Marrow Transplant 1998 Aug; 22 (3): 277-279.
	Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Amer 1998 Dec; 27(4):927-43.
	Kinsella TJ, Trivette G, Rowland J, et al. Long-term follow-up of testicular function following radiation therapy for early stage Hodgkin's disease. J Clin Oncol 1989 Jun; 7(6):718-724.
	Rowley MJ, Leach DR, Warner GA, et al. Effect of graded doses of ionizing radiation on the human testis. Radiation Research 1974 Sep; 59(3): 665-678.
	Sanders, JE. Endocrine problems in children after bone marrow transplant for hematologic malignancies. Boen Marrow Transplant 1991; 9 (suppl 1): 2-4.
	Sarafoglou K, Boulad F, Gillio A, et al. Gonadal function after bone marrow transplantation for acute leukemia during childhood. J Pediatr 1997 Feb; 130 (2): 210-216.
	Sklar C. Reproductive physiology and treatment related loss of sex hormone production. Med Pediatr Oncol 1999 Jul; 33(1): 2-8.
	Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug; 6: G17-22.
	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 1990 Dec; 8(12): 1981-7.
	Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. Hosp Med 2000 Aug; 61(8): 550-557.
80	Donaldson SS. Pediatric patients: tolerance levels and effects of treatment. In Vaeth JM, Meyer JL (eds): Frontiers of Radiation Therapy and Oncology 1989; 23:390-407.
	Fletcher BD. Effects of pediatric cancer therapy on the musculoskeletal system. Pediatr Radiol 1997 Aug; 27(8): 623-636.
	Katzman H, Waugh T, Berdon W. Skeletal changes following irradiation of childhood tumors. J Bone Joint Surgery Am 1969 Jul; 51(5): 825-842.
	Probert JC, Parker BR. The effects of radiation therapy on bone growth. Radiology 1975 Jan; 114(1): 155-62.

Section	References
	Probert JC, Parker BR, Kaplan HS. Growth retardation in children after megavoltage irradiation of the spine. Cancer 1973 Sep; 32(3): 634-39.
81	Dodd RY. The risk of transfusion-transmitted infection. N Engl J Med 1992 Aug 6; 327(6): 419-421.
82	Arico M, Maggiore G, Silini E, et al. Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. Blood 1994 Nov 1; 84(9): 2919-2922 Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV- related chronic disease. (Publication RR-19) 1998. Atlanta, GA: Author Cesaro S, Petris MG, Rossetti F, et al. Chronic hepatitis C virus infection after treatment for pediatric malignancy. Blood 1997 Aug 1; 90 (3): 1315-1320. Fink FM, Hocker-Schulz S, Mor W, et al. Association of hepatitis C virus infection with chronic liver disease in pediatric cancer patients. Eur J Pediatr 1993 Jun; 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 1997 Dec 1; 90 (11): 4628-4633. Paul IM, Sanders IM, Ruggiero F, et al. Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. Blood 1999 Jun 1; 93 (11): 3672-3677. Strasser SL, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. Blood 1999 May 15; 93 (10): 3259-3266. Strickland DK, Riely CA, Patrick CC, et al. Hepatitis C infection among survivors of childhood cancer. Blood 2000 May 15; 95(10): 3065-3070.
83	Busch MP, Young MJ, Samson SM et al. Risk of human immunodeficiency virus (HIV) transmission by blood transfusions before the implementation of HIV-1 antibody screening. The Transfusion Safety Study Group. Transfusion. 1991 Jan; 31(1): 4-11. Dodd RY. The risk of transfusion-transmitted infection. N Engl J Med 1992 Aug 6; 327(6): 419-421. Samson S, Busch M, Ward J. Identification of HIV-infected transfusion recipients: the utility of crossreferencing previous donor records with AIDS case reports. Transfusion. 1990 Mar-Apr; 30(3): 214-8.
84	Rougraff BT, Simon MA, Kneisl JS, et al. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. J Bone Joint Surg Am 1994 May; 76(5): 649-656.
85	Wilimas JA, Hudson M, Rao B, et al. Late vascular occlusion of central lines in pediatric malignancies. Pediatrics 1998 Feb; 101(2): E7.
86	Hautmann RE, de Petriconi R, Gottfried HW, et al. The ileal neobladder: complications and functional results in 363 patients after 11 years of followup. J Urol 1999 Feb; 161(2): 422-7. Jahnson S, Pedersen J. Cystectomy and urinary diversion during twenty years - complications and metabolic implications. Eur Urol 1993; 24(3): 343-9. Raney B Jr , Heyn R, Hays DM, et al. Sequelae of treatment in 109 patients followed for 5-15 years after diagnosis of sarcoma of the bladder and prostate. Cancer 1993 Apr 1; 71(7): 2387-2394. Sim HG, Lau WK, Cheng CW. A twelve-year review of radical cyctectomies in Singapore General Hospital. Ann Acad Med Singapore 2002 Sep; 31(5): 645-50.
87	Kaste SC, Chen G, Fontanesi J, et al. Orbital development in long-term survivors of retinoblastoma. J Clin Oncol 1997 Mar; 15(3); 1183-1189.
88	Kaiser CW. Complications from staging laparotomy for Hodgkin disease. J Surg Oncol 1981; 16(4): 319-325. Jockovich M, Mendenhall NP, Sombeck MD, et al. Long-term complications of laparotomy in Hodgkin's disease. Ann Surgery 1994 Jun; 219 (6): 615-624. 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 2000 Mar 15; 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 1996 Feb; 26(2): 75-80.

Section	References
89	Frieden RA, Ryniker D, Kenan S, et al. Assessment of patient function after limb-sparing surgery. Arch Phys Med Rehabil 1993 Jan; 74(1): 38-43. Nagarajan R, Neglia JP, Clohisy DR, et al. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? J Clin Oncol 2002 Nov 15; 20(22): 4493-4501. Rougraff BT, Simon MA, Kneisl JS, et al. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. J Bone Joint Surg Am 1994 May; 76(5): 649-656.
90	American Academy of Pediatrics: Committee on Sports Medicine and Fitness. Medical conditions affecting sports participation. Pediatrics 2001; 107:1205-09. Gerstenbluth RE, Spirnak JP, Elder JS**.** Sports participation and high grade renal injuries in children. J Urol. 2002 Dec;168(6):2575-8. McAleer IM, Kaplan GW, LoSasso BE. Renal and testis injuries in team sports. J Urol. 2002 Oct;168(4 Pt 2):1805-7. Mitus A, Tefft M, Feller FX. Long-term follow-up of renal functions of 108 children who underwent nephrectomy for malignant disease. Pediatrics 1969 Dec; 44(6): 912-921. 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 2000 Mar 15; 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 1996 Feb; 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. 2002 Oct;168(4 Pt 2):1811-4; discussion 1815.
91	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 2003 Jan; 40(1): 26-34.
92	Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 2002 Oct; 187(4): 1070-1080. Kenney LB, Laufer MR, Grant FD, et al. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 2001 Feb; 91(3): 613-21. Lin WW, Kim ED, Quesada ET, et al.. Unilateral testicular injury from external trauma: evaluation of semen quality and endocrine parameters. J Urology 1998 Mar; 159(3): 841-843.
93	Heyn R, Raney RB, Hays DM, et al. Late effects of therapy in patients with paratesticular rhabdomyo-sarcoma. J Clin Oncol 1992 Apr; 10 (4): 614-623.
94	Berend N, Woolcock AJ, Marlin GE. Effects of lobectomy on lung function. Thorax 1980 Feb; 35(2): 145-150. Bollinger CT, Jordan P, Soler M, et al. Pulmonary function and exercise capacity after lung resection. Eur Respir J 1996 Mar; 9(3): 415-421. Pelletier C, Lapointe L, LeBlanc P. Effects of lung resection on pulmonary function and exercise capacity. Thorax 1990 Jul; 45(7): 497-502. Risks associated with SCUBA diving in childhood cancer survivors (personal communication with Brett Stolp MD, PhD, Duke University), 8-23-02.
95	Immunization in special clinical circumstances. Report of the Committee on Infectious Diseases, 25th edition, American Academy of Pediatrics. 1997; 66-67. Jockovich M, Mendenhall NP, Sombeck MD, et al. Long-term complications of laparotomy in Hodgkin's disease. Ann Surgery 1994 Jun; 219 (6): 615-624. Kaiser CW. Complications from staging laparotomy for Hodgkin disease. J Surg Oncol 1981; 16(4): 319-325.
96	Nordoy T, Kolstad A, Endresen P, et al. Persistent changes in the immune system 4-10 years after ABMT. Bone Marrow Transplant 1999 Oct; 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 2001 Jun; 97(11): 3380-3389.

Section	References
	Storek J, Gooley T, Witherspoon RP, et al. Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. Am J Hematol 1997 Feb; 54(2): 131-138.
97	Paul IM, Sanders IM, Ruggiero F, et al. Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. Blood 1999 Jun 1;93 (11):3672-77.
	Strasser SL, Myerson D, Spurgeon CL, et al. Hepatitis C virus infection and bone marrow transplantation: a cohort study with 10-year follow-up. Hepatology 1999 Jun; 29(6): 1893-99.
	Strasser SL, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. Blood 1999 May 15; 93(10): 3259-3266.
98	Fanfulla F, Locatelli F, Zoia MC, et al. Pulmonary complications and respiratory function changes after bone marrow transplantation in children. Eur Respir J 1997 Oct;10(10): 2301-06.
	Gore EM, Lawton CA, Ash RC, et al. Pulmonary function changes in long-term survivors of bone marrow transplantation. Int J Radiat Oncol Biol Phys 1996 Aug 1; 36(1): 67-75.
	Griese M, Rampf U, Hofmann D, et al. Pulmonary complications after bone marrow transplantation in children: twenty-four years of experience in a single pediatric center. Pediatr Pulmonol 2000 Nov; 30(5): 393-401.
	Kader HA, Khanna S, Hutchinson RM, et al. Pulmonary complications of bone marrow transplantation: the impact of variations in total body irradiation parameters. Clin Oncol 1994; 6(2): 96-101.
	Nenadov Beck M, Meresse V, et al. Long-term pulmonary sequelae after autologous bone marrow transplantation in children without total body irradiation. Bone Marrow Transplant 1995 Dec; 16(6): 771-775.
	Nysom K, Holm K, Hesse B, et al. Lung function after allogeneic bone marrow transplantation for leukemia or lymphoma. Arch Dis Child 1996 May; 74(5): 432-436.
	Palmas A, Tefferi A, Meyers JL, et al. Late onset noninfectious pulmonary complications after allogeneic bone marrow transplantation. Br J Haematol 1998 Mar; 100(4): 680-687.
	Risks associated with SCUBA diving in childhood cancer survivors (personal communication with Brett Stolp MD, PhD, Duke University), 8-23-02.
99	Antin JH. Clinical Practice. Long-term care after hematopoietic-cell transplantation in adults. N Engl J Med 2002 Jul 4; 347 (1):36-42
100	Bhatia S, Ramsey NK, Weisdorf D, et al. Bone mineral density in patients undergoing bone marrow transplantation for myeloid malignancies. Bone Marrow Transpl 1998 Jul; 22(1): 87-90.
	Nysom K, Holm K Michaelson KF, et al. Bone mass after allogeneic BMT for childhood leukemia or lymphoma. Bone Marrow Transpl 2000 Jan; 25(2): 191-196.
	Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Frontiers in Bioscience 2001 Aug; 6: G17-22.
	Stern JM, Chesnut CH, Bruemmer B, et al. Bone density loss during treatment of chronic GVHD. Bone Marrow Transpl 1996 Mar; 17(3): 395-400.
101	Bhatia S, Louie AD, Bhatia R, et al. Solid cancers after bone marrow transplantation. J Clin Oncol 2001 Jan 15; 19(2): 464-71.
	Bhatia S, Ramsay NK, Steinbuch M, et al. Malignant neoplasms following bone marrow transplantation Blood 1996 May 1; 87(9): 3633-3639.
	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 2000 Mar 1; 95(5): 1588-1593.
	Lishner M, Patterson B, Kandel R, et al. Cutaneous and mucosal neoplasms in bone marrow transplant recipients. Cancer 1990 Feb 1; 65(3): 473-476.
	Socie G, Curtis RE, Deeg HJ, et al. New malignant diseases after allogeneic transplantation for childhood acute leukemia. J Clin Oncol 2000 Jan; 18(2): 348-357.
	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 1994 Dec; 12(12): 2535-2542.

Section	References
102	Antin JH. Clinical Practice. Long-term care after hematopoietic-cell transplantation in adults. N Engl J Med 2002 Jul 4; 347 (1): 36-42.
103	Refer to United States Preventive Task Force recommendations at http://www.ahrq.gov/clinic/uspstfix.htm
104	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 27. Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 1996 Mar 21; 334(12): 745-751. Goss PE, Sierra S. Current perspectives on radiation-induced breast cancer. J Clin Oncol 1998 Jan; 16(1): 338-347. Kaste SC, Hudson MM, Jones DJ, et al. Breast masses in women treated for childhood cancer: Incidence and screening guidelines. Cancer 1998 Feb 15; 82(4): 784-792. National Comprehensive Cancer Network Practice Guidelines in Oncology - v.1.2002 See also: http://www.ahrq.gov/clinic/serfiles.htm
105	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 27. See also: http://www.ahrq.gov/clinic/serfiles.htm
106	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 27. Bhatia S, Yasui Y, Robison LL, et al. High Risk of second malignant neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. J Clin Oncol. 2003 Dec 1;21(23):4386-94. See also: http://www.ahrq.gov/clinic/serfiles.htm
107	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 27.
108	Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999 Jul 10; 354(9173): 99-105.
109	Joseph BK. Oral cancer: prevention and detection. Med Princ Pract. 2002;11 Suppl 1:32-5.
110	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 27. See also: http://www.ahrq.gov/clinic/serfiles.htm
111	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 23-24. Ferrini RL, Perlman M, Hill L. American College of Preventive Medicine policy statement: screening for skin cancer. Am J Prev Med 1998 Jan; 14(1): 80-82. Ferrini RL, Perlman M, Hill L. American College of Preventive Medicine practice policy statement: Skin protection from ultraviolet light exposure. Am J Prev Med 1998 Jan; 14(1):83-6. See also: http://www.ahrq.gov/clinic/serfiles.htm
112	American Cancer Society Cancer Prevention and Early Detection: Facts and Figures 2003, p. 27 National Cancer Institute, Screening for Testicular Cancer PDQ. www.nci.nih.gov , accessed 01/26/03.

CureSearch

Children's Oncology Group

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

Version 1.2 – March 2004

Index

Index

Index

Index

Index

(continued next page)

Index

(continued next page)

Index

Index

(continued next page)

Index

Index

(continued next page)

Index

Index

Index

CureSearch

Children's Oncology Group

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

Version 1.2 – March 2004

Scoring

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 treatment for pediatric malignancies. 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

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.

Scoring

THERAPY	LATE EFFECT	SCORE
Any cancer experience	Psychosocial effects	2A
	Limitations in healthcare access	2A
Any chemotherapy	Dental abnormalities	1
Alkylating agents		
Classical alkylators: Mechlorethamine Cyclophosphamide Ifosfamide Melphalan Chlorambucil Lomustine (CCNU) Carmustine (BCNU) Busulfan Thiotepa Procarbazine	Hypogonadism Infertility Early menopause (females)	1
	AML/MDS	1
Non-classical alkylators: Dacarbazine Temozolamide Cisplatin Carboplatin	Hypogonadism Infertility Early menopause (females)	2A
	AML/MDS	2A
Cisplatin Carboplatin	Ototoxicity	1
	Peripheral neuropathy	2A
	Renal toxicity	1
	Dyslipidemia	2B
Busulfan Carmustine (BCNU) Lomustine (CCNU)	Pulmonary fibrosis	1
Busulfan	Cataracts	2B

THERAPY	LATE EFFECT	SCORE
Cyclophosphamide Ifosfamide	Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding	1
	Bladder malignancy	1
Ifosfamide	Renal toxicity	1
Antimetabolites		
Methotrexate (po, IV, IM)	Osteopenia, Osteoporosis	2B
	Renal dysfunction	2A
	Hepatic dysfunction	2A
Methotrexate (IT, high-dose IV)	Neurocognitive deficits Clinical leukoencephalopathy (with or without imaging abnormalities)	1
Cytarabine (high-dose IV)	Neurocognitive deficits Clinical leukoencephalopathy (with or without imaging abnormalities)	2A
Mercaptopurine Thioguanine	Hepatic dysfunction Veno-occlusive disease	2A
Anthracyclines		
Doxorubicin Daunorubicin Idarubicin Mitoxantrone Epirubicin	AML	1
	Cardiomyopathy Arrhythmia	1
Anti-tumor antibiotics		
Dactinomycin	No known late effects	1
Bleomycin	Interstitial pneumonitis Pulmonary fibrosis	1
	Acute respiratory distress syndrome	2B

Scoring

THERAPY	LATE EFFECT	SCORE
Corticosteroids		
Prednisone Dexamethasone	Osteopenia, Osteoporosis	1
	Avascular necrosis (AVN)	1
	Cataracts	1
Enzymes		
Asparaginase	No known late effects	1
Plant alkaloids		
Vincristine Vinblastine	Peripheral sensory or motor neuropathy	2A
	Vasospastic attacks (Raynaud's phenomenon)	2A
Epipodophyllotoxins		
Etoposide Teniposide	AML	1
Radiation		
All fields including TBI	Skin changes	1
	Secondary benign or malignant neoplasms	1
	Dysplastic nevi Skin cancer	1
	Bone malignancies	1
TBI	Complications scored under individual radiation fields	N/A

THERAPY	LATE EFFECT	SCORE
Head and brain radiation		
TBI Cranial (whole brain)	Neurocognitive deficits	1
	Clinical leukoencephalopathy (with or without neuro-imaging abnormalities)	1
	Stroke/moyamoya Occlusive cerebral vasculopathy	1
	Brain tumor	1
	Growth hormone deficiency	1
	Hyperprolactinemia	1
	Central hypothyroidism	1
	Central adrenal insufficiency	1
	Precocious puberty	1
	Gonadotropin deficiency	1
	Overweight/obesity	1
	Chronic sinusitis	1
	Craniofacial abnormalities	1
TBI Cranial (whole brain) Craniospinal Nasopharyngeal Oropharyngeal Orbital/Eye Ear/Infratemporal Mantle Cervical spine	Dental abnormalities	1
	Xerostomia	1

Scoring

THERAPY	LATE EFFECT	SCORE
Eye radiation		
TBI Orbital/Eye Cranial (whole brain) Craniospinal	All adverse effects on eye: Cataracts Orbital hypoplasia Lacrimal duct atrophy Xerophthalmia (severe) Keratitis Keratoconjunctivitis sicca Telangiectasias Retinopathy Optic chiasm neuropathy Endophthalmos Chronic painful eye	1
Ear radiation		
TBI Ear/Infratemporal Cranial (whole brain) Craniospinal Nasopharyngeal	Tympanosclerosis Otosclerosis Eustachian tube dysfunction Conductive hearing loss	1
	Sensorineural hearing loss Tinnitus	1
Neck radiation		
Any radiation to the neck, including: TBI Cranial (whole brain) Craniospinal Nasopharyngeal Oropharyngeal Cervical Mantle Mediastinal Whole lung Spinal	Thyroid nodules	1
	Thyroid cancer	1
	Hypothyroidism	1
	Hyperthyroidism	1
	Carotid artery disease	2A
	Esophageal stricture	1

THERAPY	LATE EFFECT	SCORE
Trunk radiation		
Any field from shoulders to pelvis including: TBI Spinal (≥12 Gy)	Musculoskeletal growth problems	1
	Scoliosis	1
Chest/thorax radiation		
Any field involving the chest/thorax, including: TBI Mantle Mediastinal Whole lung Spinal ≥ 30 Gy Whole abdomen Any upper abdominal field	Kyphosis	1
	Esophageal stricture	1
Chest/thorax radiation with potential impact to the breast: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy	Breast cancer	2A
	Breast tissue hypoplasia	1
Chest/thorax radiation with potential impact to the heart: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Left hemiabdomen/ Left flank Any left-sided upper abdominal field	Congestive heart failure Cardiomyopathy Pericarditis Pericardial fibrosis Valvular disease Myocardial infarction Arrhythmia Atherosclerotic heart disease	1

Scoring

THERAPY	LATE EFFECT	SCORE
Chest/thorax radiation with potential impact to the lungs: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Any upper abdominal field	Pulmonary fibrosis Delayed interstitial pneumonitis Restrictive/obstructive lung disease	1
Abdominal/Pelvic radiation		
≥30 Gy to: Whole abdomen Left upper quadrant Entire spleen	Functional asplenia Life-threatening infection	1
TBI Renal Para-aortic Whole abdomen Spinal (≥15 Gy)	Renal insufficiency Hypertension	1
TBI Whole abdomen Hepatic	Hepatic fibrosis Cirrhosis	1
	Hepatocellular carcinoma	2A
TBI All abdominal and pelvic fields Spinal (≥20 Gy)	Bowel obstruction	1
	Chronic enterocolitis Fistula, strictures	1
TBI ≥25 Gy to: All abdominal and pelvic fields Spine	Gastrointestinal malignancy	2A
TBI Whole abdomen Pelvic Iliac/Inguinal Para-aortic	Uterine vascular insufficiency	2B
TBI Whole abdomen Pelvic Iliac/Inguinal Para-aortic Spinal ≥24 Gy	Ovarian dysfunction	1
Whole abdomen Pelvic Iliac/Inguinal Para-aortic Spinal ≥30 Gy	Hemorrhagic cystitis	2A
	Bladder fibrosis Dysfunctional voiding	1
	Bladder malignancy	1
Testicular radiation		
TBI Testicular Pelvic Inguinal/femoral Spinal ≥24 Gy	Testicular dysfunction	1
Extremity radiation		
	Musculoskeletal growth problems	1
Blood/blood products		
	Chronic Hepatitis B	1
	Chronic Hepatitis C	1
	Complications related to chronic hepatitis	1
	HIV infection	1

Scoring

THERAPY	LATE EFFECT	SCORE
Surgery		
Amputation	Cosmesis Functional and activity limitations Residual limb integrity problems Phantom pain	1
Limb sparing procedure	Functional and activity limitations Contractures Loosening of endoprosthesis Chronic infection Chronic pain Limb length discrepancy	1
Enucleation	Cosmesis Poor prosthetic fit Orbital hypoplasia	1
Neurosurgery	Neurocognitive deficits Intracranial bleed/stroke Motor deficits Seizures Hydrocephalus Shunt malfunction	1
Laparotomy	Adhesive/obstructive complications	1
Orchiectomy	Infertility Hypogonadism	1
Pelvic surgery	Retrograde ejaculation Impotence Bowel incontinence Bladder incontinence Hydrocele	1
Splenectomy	Life-threatening infection	1
Nephrectomy	Proteinuria Hyperfiltration Renal insufficiency Hydrocele	1
Cystectomy	Chronic urinary tract infection Renal dysfunction	1
Placement of central venous catheter	Thrombosis Vascular insufficiency Infection of retained cuff or line tract	1
Hematopoietic cell transplantation		
Hematopoietic cell transplantation	Secretory IgA deficiency Hypogammaglobulinemia Chronic infection	1
	Alopecia Nail dysplasia Vitiligo Scleroderma	1
	Myelodysplasia AML	1
	Solid cancers	1
	Lymphoma	1
	Bronchiolitis obliterans Chronic bronchitis Bronchiectasis	1
	Chronic hepatitis Cirrhosis Iron overload	1
	Joint contractures	1
	Osteopenia Osteoporosis	1

Scoring

GENERAL HEALTH SCREENING	
General Health Screening	Not scored

CANCER SCREENING		
Organ	**Standard Risk**	**Highest Risk - Score**
Breast	Not scored (ACS recommendation)	2A
Cervical	Not scored (ACS recommendation)	2A
Endometrial	N/A	Not scored (ACS recommendation)
Colorectal	Not scored (ACS recommendation)	2A
Lung	N/A	1
Prostate	Not scored (ACS recommendation)	Not scored (ACS recommendation)
Testicular	Not scored (ACS recommendation)	2A
Skin	Not scored (ACS recommendation)	2A
Oral	N/A	1

CureSearch Children's Oncology Group

Health Links

Healthy living after treatment for childhood cancer

Version 1.2 – March 2004

All 33 Health Links can be downloaded
in a single PDF file ("Appendix")
or in individual PDF files
at www.survivorshipguidelines.org