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Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent,
and Young Adult Cancers

Version 1.2 – March 2004



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.

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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.

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- **Panel of Experts**
- **Reviewers**
- **Health Link Authors**

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

Version 1.2 – March 2004

Introduction & Instructions for Use



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:	<p>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.</p> <p>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.</p> <p>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.</p> <p>In a parallel effort led by the Nursing Clinical Practice Subcommittee, complementary patient education materials (<i>Health Links</i>) 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).</p>

- 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.



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:

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

Version 1.2 – March 2004

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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								
<p>Clinician Info Link The Children's Oncology Group Long-Term Follow-Up Guidelines apply to patients who are ≥ 2 years after completion of therapy.</p> <p>For all patients treated prior to 1993, please also see Sections 81-83 to review screening recommendations related to presumed blood/blood product exposures.</p>	1	<p>Psychosocial Effects Depression Anxiety Post-traumatic stress Social withdrawal Educational problems</p>	<p>Host factors Female gender Family history of depression, anxiety, or mental illness</p> <p>Social factors Lower household income Lower educational achievement</p>	<p>Host factors CNS cancer or CNS-directed therapy Premorbid learning or emotional difficulties</p> <p>Social factors Failure to graduate from high school</p>	Clinical interview	Yearly	<p>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</p> <p>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.</p>	<p>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.</p>
	2	<p>Limitations in healthcare and insurance access</p>	<p>Social factors Lower household income Lower educational achievement</p>		Clinical history	Yearly	<p>Health Link Finding Appropriate Healthcare after Childhood Cancer</p>	<p>Social work consultation.</p>
Any Chemotherapy								
	3	<p>Dental abnormalities Tooth/root agenesis Root thinning/ shortening Enamel dysplasia</p>	<p>Host factors Any patient who has not developed permanent dentition</p> <p>Cancer treatment Any radiation treatment including oral cavity or salivary glands.</p>	<p>Host factors Younger age at treatment, especially < 5 years old</p>	Dental exam and cleaning	Every 6 months	<p>Health Link Dental Health</p>	<p>Regular dental care including fluoride applications. Baseline panorex prior to dental procedures to evaluate root development.</p>

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 <u>or</u> 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 orchimetry.	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	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 symptomatic pulmonary dysfunction. Influenza and Pneumovax immunization.
					PFTs (including DLCO and spirometry) and CXR	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		
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	Yearly	Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture negative macroscopic hematuria.
					Urinalysis	Yearly		
	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	Yearly	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.
					BUN, creatinine, U/A	Yearly		
					Na, K, Cl, CO ₂ , Ca, Mg, P ₀₄	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		

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 Audiogram or brainstem auditory evoked response (ABR, BAER)	Yearly 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.	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.	
	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 BUN, creatinine, U/A Na, K, Cl, CO ₂ , Ca, Mg, P ₀₄ 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	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.
	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 Referral for formal neuropsychological evaluation	Baseline at entry into long-term follow-up, then yearly Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	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.
		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 Brain MRI Brain CT plus MRI with MR angiography	Yearly As clinically indicated 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	Osteopenia	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	<p>Renal dysfunction</p> <p>Acute toxicities predominate, from which the majority of patients recover without sequelae.</p> <p>See related topics: Ifosfamide Cisplatin/Carboplatin Abdominal/pelvic radiation Cystectomy Nephrectomy</p>	<p>Host factors Mononephric Combined with other nephrotoxic agents: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppressants - cyclosporine - abdominal radiation</p> <p>Medical conditions Diabetes mellitus Familial hypertension</p>	<p>Treatment factors Treatment before 1970.</p>	<p>Blood pressure</p>	<p>Yearly</p>	<p>Health Link Kidney Health See also: Single Kidney Precautions</p>	<p>Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.</p>
	19	<p>Hepatic dysfunction</p> <p>Acute toxicities predominate from which the majority of patients recover without sequelae.</p> <p>See related topics: Mercaptopurine Dactinomycin Hepatic radiation Transfusion (chronic hepatitis B & C) Hematopoietic cell transplant (liver toxicity)</p>	<p>Treatment factors Abdominal radiation</p> <p>Medical conditions Viral hepatitis</p>	<p>Treatment factors Treatment before 1970</p> <p>Medical conditions Chronic viral hepatitis</p>	<p>Physical exam</p>	<p>Yearly</p>		

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 Referral for formal neuropsychological evaluation	Yearly Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	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.
		Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) with or without imaging abnormalities: - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - mineralizing microangiopathy 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 administration (≥ 1000 mg/m ² dose) 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 Brain MRI Brain CT plus MRI with MR angiography	Yearly As clinically indicated 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	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.	Detailed history of exertional tolerance. EKG for evaluation of QT interval ECHO or MUGA for evaluation of systolic function	Yearly Baseline at entry into long-term follow-up 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).	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).

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	Yearly	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.
					PFTs (including DLCO and spirometry) and CXR	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.		
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	Yearly	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.
					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
Corticosteroids								
Prednisone Dexamethasone	25	<p>Osteopenia (Bone mineral density 1-2.5 SD below mean)</p> <p>Osteoporosis (Bone mineral density \geq 2.5 SD below mean)</p> <p>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 \geq 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.</p>	<p>Host factors Both genders at risk</p> <p>Treatment factors Combined with: - methotrexate - cranial or spinal radiation - other head/neck radiation - radiation to bones</p> <p>Medical Conditions Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism</p> <p>See related topics: Methotrexate Hematopoietic cell transplant</p>	<p>Host factors Older age at time of treatment</p> <p>Treatment factors Dexamethasone effect is more potent than prednisone.</p>	<p>Bone density evaluation (DEXA or quantitative CT)</p> <p>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.</p>	<p>Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.</p>	<p>Health Link Keeping Your Bones Healthy After Childhood Cancer</p> <p>National Osteoporosis Foundation website: www.nof.org</p>	<p>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).</p>
	26	<p>Avascular necrosis (AVN) (Osteonecrosis)</p> <p>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.</p>	<p>Host factors Both genders at risk</p> <p>Treatment factors Dexamethasone effect is more potent than prednisone. Combined with: - high-dose radiation to any bone</p> <p>Medical conditions Sickle cell disease</p>	<p>Host factors Older age (\geq10 years at time of treatment)</p> <p>Treatment factors Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.</p>	<p>History</p>	<p>Yearly</p>	<p>Health Link Avascular Necrosis</p>	<p>Diagnostic imaging (radiograph, MRI) in patients with history of chronic pain. Orthopedic consultation for history of chronic joint pain in predisposed patient.</p>
	27	<p>Cataracts</p> <p>See related topics: Busulfan Head/brain radiation TBI</p>	<p>Treatment factors Combined with: - total body irradiation - brain/head radiation - busulfan</p>	<p>Treatment factors TBI given in single daily fraction Radiation dose \geq 10 Gy with potential scatter to eye(s) Longer interval since treatment</p>	<p>Eye exam including funduscopic exam and visual acuity</p>	<p>Yearly</p>	<p>Health Link Eye Problems after Childhood Cancer</p>	<p>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).</p>

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.
Epidodophyllotoxins								
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 (nevroid 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 all 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 microangiopathy	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 \geq 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: \geq 10 Gy single fraction \geq 12 Gy fractionated	Treatment factors Radiation dose \geq 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 \geq 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 \geq 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	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.
	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.		
(continued on next page)	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 orchimetry.	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 comorbid 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 \geq 10 Gy TBI given in single daily fraction Fraction dose \geq 2 Gy	Ophthalmology evaluation including fundoscopic exam and visual acuity	Yearly for patients who received \geq 30 Gy or TBI Every 3 years for patients who received < 30 Gy (these patients also need yearly fundoscopic 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 \geq 30 Gy Fraction dose \geq 2 Gy				
		Lacrimal duct atrophy (resulting in excessive tearing)	Treatment factors Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	Treatment factors Dose \geq 40 Gy Fraction dose \geq 2 Gy				
		Xerophthalmia (severe) (resulting from atrophy of lacrimal gland)	Treatment factors Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	Treatment factors Dose \geq 30 Gy Fraction dose \geq 2 Gy				
		Keratitis	Treatment factors Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	Treatment factors Dose \geq 40 Gy Fraction dose \geq 2 Gy				
		Keratoconjunctivitis sicca	Treatment factors Higher radiation dose Corticosteroids Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	Treatment factors Dose \geq 40 Gy Fraction dose \geq 2 Gy Medical conditions Chronic GVHD				
		Telangiectasias	Treatment factors Higher radiation dose	Treatment factors Dose \geq 50 Gy Fraction dose \geq 2 Gy				
		Retinopathy	Treatment factors Higher radiation dose Medical conditions Diabetes mellitus	Treatment factors Dose 45-65 Gy Fraction dose \geq 2 Gy				
		Optic chiasm neuropathy	Treatment factors Higher radiation dose Medical conditions Diabetes mellitus Hypertension	Treatment factors Dose 50- 65 Gy Fraction dose \geq 2 Gy				
Enophthalmos Chronic painful eye	Treatment factors Higher radiation dose	Fraction dose \geq 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 \geq 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.
		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 \geq 30-40 Gy	Audiogram or brainstem auditory evoked response (ABR, BAER)	For patients who received \geq 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		
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 \geq 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 \geq 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 \geq 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 \geq 40 Gy	Clinical evaluation Doppler ultrasound of carotid vessels	Yearly As clinically indicated		MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated.
	58	Esophageal stricture	Treatment factors Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Medical conditions Gastroesophageal reflux	Treatment factors Dose \geq 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 Spine films	Yearly until growth completed; may need more frequent assessment during puberty In patient with clinically apparent curve	Health Link Scoliosis and Kyphosis after Treatment for Childhood Cancer	Orthopedics consultation as indicated based on radiographic exam.

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 Spine films	Yearly until growth completed; may need more frequent assessment during puberty In patient with clinically apparent curve	Health Link Scoliosis and Kyphosis after Treatment for Childhood Cancer	Orthopedics consultation as indicated based on radiographic exam.
	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	Yearly																																				
<table border="1"> <thead> <tr> <th colspan="4">RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM</th> </tr> <tr> <th>Age at Treatment*</th> <th>Radiation Dose</th> <th>Anthracycline Dose†</th> <th>Recommended Frequency</th> </tr> </thead> <tbody> <tr> <td rowspan="2"><5 years old</td> <td rowspan="2">Any</td> <td>None</td> <td>Every 2 years</td> </tr> <tr> <td>Any</td> <td>Every year</td> </tr> <tr> <td rowspan="3">≥5 years old</td> <td><30 Gy</td> <td>None</td> <td>Every 5 years</td> </tr> <tr> <td>≥30 Gy</td> <td>None</td> <td>Every 2 years</td> </tr> <tr> <td>Any</td> <td><300 mg/m²</td> <td>Every 2 years</td> </tr> <tr> <td colspan="3"></td> <td>≥300 mg/m²</td> <td>Every year</td> </tr> <tr> <td colspan="3">Any age with serial decrease in function</td> <td colspan="2">Every year</td> </tr> </tbody> </table> <p>*Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first) †Based on equivalent mg of doxorubicin/daunorubicin</p>									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	
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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	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.																																				

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	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			Yearly
						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.
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	Yearly	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.	
						ALT, AST, bilirubin			Baseline at entry into long-term follow-up.
	70	Hepatocellular carcinoma	Medical conditions Chronic hepatitis B or C Cirrhosis Treatment factors Higher radiation dose to liver Health behaviors Alcohol use		AFP	Yearly in patients with chronic hepatitis	Health Link Reducing the Risk of Second Cancers Hepatitis after Childhood Cancer	Oncology consultation for medical management.	
				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													
Total Body Irradiation All abdominal and pelvic fields Spinal \geq 20 Gy	71	Bowel obstruction	<p>Treatment factors Higher radiation dose to bowel Abdominal surgery</p> <p>Clinician Info Link Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery.</p>	<p>Treatment factors Dose \geq 45 Gy (Obstruction may occur in people who received lower doses of abdominal radiation during childhood)</p>	Physical exam KUB	With clinical symptoms of obstruction.		Surgical consultation in patients who fail medical management.													
	72	Chronic enterocolitis Fistula, Strictures	<p>Treatment factors Higher radiation dose to bowel Abdominal surgery</p>	<p>Treatment factors Dose \geq 45 Gy</p>	History Serum protein, albumin	Yearly Yearly in patients with chronic diarrhea or fistula		Surgical and/or gastroenterology consultation for symptomatic patients.													
Total Body Irradiation All abdominal and pelvic fields \geq 25 Gy Spinal \geq 25 Gy	73	Gastrointestinal malignancy	<p>Host factors Hepatoblastoma Familial polyposis</p> <p>Treatment factors Higher radiation dose to bowel Higher daily fraction dose Combined with chemotherapy (especially alkylators)</p>	<p>Treatment factors Radiation dose \geq 25 Gy</p>	<p><i>The following monitoring is to begin 15 years after radiation or at age 35 years (whichever occurs last). Monitor more frequently if clinically indicated.</i></p> <p>Choose one of the following three options:</p> <table border="0" style="width: 100%;"> <tr> <td style="border-right: 1px solid black;">Fecal occult blood (minimum 3 cards)</td> <td>Yearly</td> </tr> <tr> <td colspan="2" style="text-align: center;">AND</td> </tr> <tr> <td style="border-right: 1px solid black;">Flexible sigmoidoscopy</td> <td>Every 5 years</td> </tr> <tr> <td colspan="2" style="text-align: center;">OR</td> </tr> <tr> <td style="border-right: 1px solid black;">Double contrast barium enema</td> <td>Every 5 years</td> </tr> <tr> <td colspan="2" style="text-align: center;">OR</td> </tr> <tr> <td style="border-right: 1px solid black;">Colonoscopy</td> <td>Every 10 years</td> </tr> </table>	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	<p>Health Link Reducing the Risk of Second Cancers</p>	Surgical and/or oncology consultation as needed.
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																				
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	<p>Host factors Females with Wilms tumor and associated müllerian anomalies</p> <p>Clinician Info Link: 10% of girls with Wilms tumor have congenital uterine anomalies</p> <p>Treatment factors Higher radiation dose to pelvis</p>	<p>Host factors Prepubertal at treatment</p> <p>Treatment factors Dose \geq 20-30 Gy TBI</p>	History Consider high-level ultrasound evaluation of genitourinary tract after pubertal development.	Yearly and as clinically indicated As clinically indicated in patient contemplating pregnancy.	<p>Health Link Female Health Issues after Childhood Cancer</p> <p>Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org</p>	High-risk obstetrical care during pregnancy. High level ultrasound in women with Wilms tumor.													

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.	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). History of medication use.	Yearly	Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	
				Physical exam including height, weight, Tanner stage, testicular volume by Prader orchimetry.	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	Host factors Chronic immunosuppression	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.	
			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					
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)	Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	Treatment factors Stem cell transplantation	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	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.
			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	Medical conditions Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Hepatitis C antibody		
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 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.	
			Health behaviors IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing	Medical conditions Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	PCR to establish chronic infection	Once in patients with positive hepatitis C antibody			
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)	Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	Treatment factors Stem cell transplantation	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	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.
			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	Medical conditions Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Hepatitis C antibody		
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 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.	
			Health behaviors IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing	Medical conditions Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	PCR to establish chronic infection	Once in patients with positive hepatitis C antibody			
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)	Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	Treatment factors Stem cell transplantation	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	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.
			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	Medical conditions Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Hepatitis C antibody		

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	Yearly until completion of growth, or every 3 years if skeletally mature.	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.
					Prosthetic evaluation	Every 6 months until skeletally mature, then yearly thereafter.		
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	Yearly	Health Link Kidney Health	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Yearly		
					Urine culture	Yearly and as clinically indicated		
					Urology evaluation	Yearly		
					Na, K, Cl, CO ₂ , Ca, Mg, PO ₄ Creatinine clearance or GFR.	Obtain in patients with abnormal BP, U/A, BUN, or creatinine. If abnormal, repeat as clinically indicated		
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	Yearly and as needed	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
					Radiograph	Yearly		
					Orthopedic follow-up	Every 6 months until skeletally mature, and yearly thereafter		
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 - immunosuppressants - cyclosporine - methotrexate		Blood pressure	Yearly	Health Link Single Kidney Precautions See also: Kidney Health	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Yearly		
					Na, K, Cl, CO ₂ , Ca, Mg, PO ₄ Creatinine clearance or GFR.	Obtain in patients with abnormal BP, U/A, BUN, or creatinine. If abnormal, repeat 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
Neurosurgery	91	<p>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.</p> <p>Intracranial bleed/stroke</p> <p>Motor deficits</p> <p>Paralysis</p> <p>Movement disorders</p> <p>Ataxia</p> <p>Seizures</p> <p>Hydrocephalus</p> <p>Shunt malfunction</p> <p>Clinician Info Link Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New deficits may emerge over time.</p>	<p>Host factors Younger age at diagnosis</p> <p>Treatment factors Combined with: - brain radiation - high-dose chemotherapy - intrathecal chemotherapy</p> <p>Medical conditions Hydrocephalus</p>	<p>Host factors Younger age at treatment (< 3 years) Supratentorial tumor</p> <p>Treatment factors High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose ≥ 60 Gy</p> <p>Medical conditions Posterior fossa syndrome CNS infection</p> <p>Social factors Low SES Predisposing family history of learning or attention problems</p>	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.	<p>Health Link Educational Issues Following Treatment for Childhood Cancer</p>	<p>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</p>
					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	<p>Infertility</p> <p>Hypogonadism</p>	<p>Treatment factors Bilateral orchiectomy Unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents</p>		History of sexual function (erections, nocturnal emissions, libido).	Yearly	<p>Health Link Male Health Issues after Childhood Cancer</p> <p>For patients with single testis - counsel to wear athletic supporter with protective cup during athletic activities.</p>	<p>Refer to endocrinologist for bilateral orchiectomy, delayed clinical signs of puberty, or persistently abnormal hormone levels Consider surgical placement of testicular prosthesis.</p>
					History of medication use.	Yearly		
					Physical exam including height, weight, Tanner stage, testicular volume by Prader orchimetry.	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 ≥ 30 Gy - total body irradiation Medical conditions Atopic history Health behaviors Smoking		Physical exam	Yearly	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.
					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.		
Splenectomy	95	Life-threatening infection with encapsulated organisms (Haemophilus influenzae, Streptococcus pneumoniae, Meningococcus)			Physical exam Blood culture	When febrile $T \geq 101^\circ$	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 $T \geq 101^\circ$ (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 $\geq 104^\circ$ 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
Hematopoietic cell transplantation (continued from previous page) Clinician Info Link Sources of donor stem cells for transplantation include: <i>Autologous</i> (patient's own marrow or stem cells are harvested prior to ablative therapy) <i>Allogeneic</i> (marrow or stem cells are harvested from a related or unrelated donor) <i>Cord blood</i> (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)		Muscles/Bones						
	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., 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							
Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
<p>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, comorbid 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.</p>							
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	Monthly, beginning at age 20 Every 3 years between ages 20-39; then yearly beginning at age 40 Every year beginning at age 40	Health Link Breast Cancer after Treatment for Childhood Cancer: Are You at Risk?	Surgery and/or oncology consultation as clinically indicated.
				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 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)		
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	<i>Begin screening (in patients with a cervix) 3 years after first vaginal intercourse, or at age 21, whichever occurs first</i>		Health Link Reducing the Risk of Second Cancers	Gynecology and/or oncology consultation as clinically indicated.
				Standard 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.		
				Highest Risk: Pelvic exam Cervical PAP smear	Yearly Yearly		

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:		Yearly, beginning at age 50 AND/OR Every 5 years beginning at age 50. <i>Note: The combination of yearly fecal occult blood testing and every 5 year flexible sigmoidoscopy is preferable to either test done alone.</i> OR Every 5 years beginning at age 50. OR Every 10 years beginning at age 50	Health Link Reducing the Risk of Second Cancers	Gastroenterology, surgery and/or oncology consultation as clinically indicated.
				Fecal occult blood (minimum of 3 cards)				
				Flexible sigmoidoscopy				
				OR				
				Double contrast barium enema				
				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)				Yearly, beginning 15 years after radiation or at age 35 (whichever occurs last).				
				AND				
Flexible sigmoidoscopy				Every 5 years				
				OR				
Double contrast barium enema				Every 5 years				
				OR				
Colonoscopy				Every 10 years				
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	Yearly, beginning at age 50	Health Link Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
				Prostate specific antigen (PSA)	Yearly, beginning at age 50		
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	Highest Risk: Digital rectal exam	Yearly, beginning at age 45	Health Link Reducing the Risk of Second Cancers Skin Health	Surgery, dermatology, and/or oncology consultation as clinically indicated.
				Prostate specific antigen (PSA)	Yearly, beginning at age 45		
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: Clinical skin exam	Every 3 years, from ages 20-39 Yearly, beginning at age 40.	Health Link Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
				Highest Risk: Skin self exam	Monthly		
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	Clinical skin exam with attention to pigmented nevi in radiation field.	Yearly	Health Link Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
				Standard Risk: Testicular self-exam	Not 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	Clinical testicular exam	Every 3 years, ages 20-39, then yearly.	Health Link Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
				Highest Risk: Testicular self-exam	Monthly, beginning at puberty		
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	Clinical testicular exam	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

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CureSearch

Children's Oncology Group

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

Version 1.2 – March 2004

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Scoliosis	60
Thyroid cancer	54
Thyroid nodules	53
Valvular disease (cardiac)	65
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Arrhythmia	65
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Breast tissue hypoplasia	64
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Carotid artery disease	57
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Kyphosis	61
Musculoskeletal growth problems	59
Myocardial infarction	65
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Thyroid nodules	53
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Delayed interstitial pneumonitis	66
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Hyperthyroidism	56
Hypothyroidism	55
Kyphosis	61
Musculoskeletal growth problems	59
Myocardial infarction	65
Pericardial fibrosis	65
Pericarditis	65

Therapy	Section
Whole lung (continued)	
Pulmonary fibrosis	66
Restrictive/obstructive lung disease	66
Scoliosis	60
Thyroid cancer	54
Thyroid nodules	53
Valvular disease (cardiac)	65

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Therapy	Section
Abdominal/Pelvic Radiation	

Note: *The following are potential late effects for all abdominal and pelvic fields:*

Any radiation dose to an abdominal or pelvic field:	
Bone malignancies	35
Bowel obstruction	71
Chronic enterocolitis	72
Dysplastic nevi, skin cancer	34
Fistula, strictures (bowel)	72
Musculoskeletal growth problems	59
Scoliosis	60
Secondary benign or malignant neoplasms	33
Skin changes (fibrosis, telangiectasias)	32
Dose ≥ 25 Gy to an abdominal or pelvic field:	
Gastrointestinal malignancy	73

Whole abdomen

Any dose:

Arrhythmia	65
Atherosclerotic heart disease	65
Bladder fibrosis/dysfunctional voiding	77
Bladder malignancy	78
Bowel obstruction	71
Cardiomyopathy	65
Cirrhosis	69
Congestive heart failure	65
Delayed interstitial pneumonitis	66
Esophageal stricture	62
Hemorrhagic cystitis	76
Hepatic fibrosis	69
Hepatocellular carcinoma	70
Hypertension	68
Kyphosis	61
Myocardial infarction	65
Ovarian dysfunction	75
Pericardial fibrosis	65
Pericarditis	65

Therapy	Section
Whole abdomen (continued)	

Pulmonary fibrosis	66
Renal insufficiency	68
Restrictive/obstructive lung disease	66
Uterine vascular insufficiency	74
Valvular disease (cardiac)	65
≥ 30 Gy:	
Functional asplenia	67
Life-threatening infection	67

Any upper abdominal field

Delayed interstitial pneumonitis	66
Esophageal stricture	62
Kyphosis	61
Pulmonary fibrosis	66
Restrictive/obstructive lung disease	66

Left Upper Quadrant

Arrhythmia	65
Atherosclerotic heart disease	65
Cardiomyopathy	65
Congestive heart failure	65
Delayed interstitial pneumonitis	66
Esophageal stricture	62
Functional asplenia (≥ 30 Gy)	67
Kyphosis	61
Life-threatening infection (≥ 30 Gy)	67
Myocardial infarction	65
Pericarditis, pericardial fibrosis	65
Pulmonary fibrosis	66
Restrictive/obstructive lung disease	66
Valvular disease (cardiac)	65

Entire spleen

Arrhythmia	65
Atherosclerotic heart disease	65
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Life-threatening infection (≥ 30 Gy)	67
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Therapy	Section
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Esophageal stricture	62
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Myocardial infarction	65
Pericarditis, pericardial fibrosis	65
Pulmonary fibrosis	66
Restrictive/obstructive lung disease	66
Valvular disease (cardiac)	65
Para-aortic	
Bladder fibrosis/dysfunctional voiding	77
Bladder malignancy	78
Hemorrhagic cystitis	76
Hypertension	68
Ovarian dysfunction	75
Renal insufficiency	68
Uterine vascular insufficiency	74
Pelvic	
Bladder fibrosis/dysfunctional voiding	77
Bladder malignancy	78
Hemorrhagic cystitis	76
Ovarian dysfunction	75
Testicular dysfunction	79
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Bladder malignancy	78
Hemorrhagic cystitis	76
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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

THERAPY	LATE EFFECT	SCORE
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

THERAPY	LATE EFFECT	SCORE
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

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