Late Effects Screening Guidelines

Version 1.0 - March 2003

DISCLAIMER

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The following guidelines were developed by the Children's Oncology Group - Late Effects and Nursing Committees. These guidelines provide recommendations for screening and management of late effects potentially arising as a result of therapeutic exposures used in the treatment of childhood malignancies, and are designed for use beginning two or more years following the completion of therapy. The guidelines are **not** intended to provide guidance for follow-up of the cancer survivor's primary disease.

Children's Oncology Group is a research organization, and these guidelines were developed within the context of clinical research involving long term follow-up of childhood cancer survivors. The guidelines are provided at no-cost to Children's Oncology Group members who have participated and/or continue to participate in the research that has made these guidelines possible.

These guidelines are provided as a courtesy. They are an informational and educational service and are derived from in-depth review and assessment of current scientific and clinical information. They are not intended as a sole source of guidance in the evaluation of childhood cancer survivors. Rather, they are designed to assist clinicians by providing a framework for comprehensive, focused evaluations of childhood cancer survivors based on specific risk factors.

The Children's Oncology Group assumes no liability for damage resulting from the use or review of this information. While the Children's Oncology Group intends for these guidelines to reflect state-of-the-art medical knowledge and, in this regard, diligently attempts to keep the information current, the Children's Oncology Group makes no representation or warranty about the accuracy, reliability, completeness, relevance, or timeliness of the information herein and disclaims any such representation or warranty to such effect. Further, the Children's Oncology Group makes no representation or warranty that conforming to these guidelines will ensure compliance with federal, State, and/or local law. Clinicians and others who review this information are advised to consult with legal counsel to ensure compliance with federal, State, and/or local law. Further, these guidelines are not intended to supplant the functions of an Institutional Review Board (IRB), Privacy Board, or similarly constituted body.

The guidelines are not intended to replace clinical judgment, medical advice, or to exclude other legitimate criteria for screening, health counseling, or intervention for specific complications of childhood cancer treatment. Neither are they intended to exclude other reasonable alternative follow-up procedures. 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. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

Table of Contents

The following documents are included in this packet:

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The COG Late Effects Screening Guidelines: Introduction and Instructions for Use

The Children's Oncology Group Late Effects Screening Guidelines were developed as a collaborative effort of the Nursing Discipline and the Late Effects Committee. The purpose of these Guidelines is to provide recommendations for screening and management of late effects that may potentially arise as a result of therapeutic exposures used during treatment for childhood cancer.

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

The recommendations in the Guidelines are based on a thorough review of the literature as well as the collective clinical experience of the Task Force Members, Panel of Experts, and Reviewers. These guidelines are not intended to replace clinical judgment or to exclude other reasonable alternative follow-up procedures.

This initial release of the Guidelines is limited to COG members only at this time. They may not be cited and may not be distributed to non-COG members. As new information becomes available, the Guidelines will be updated periodically to reflect those changes. These Guidelines, and any subsequent revisions, will be posted on the COG website at:

http://members.childrensoncologygroup.org/Disc/lateeffects/default.asp

We recommend that clinicians check the website periodically for the latest updates and revisions. We anticipate (and in fact will welcome) wide dissemination of the Guidelines in the future; however, at this time, we are releasing them in a limited fashion in anticipation that some revisions may be required before the document is released to the public.

The Guidelines are organized by column as follows:

Therapeutic Agent: The therapeutic intervention for malignancy, including chemotherapy, radiation therapy, surgery, or transfusion.

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: List 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: 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 evaluation, diagnostic imaging, 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. Some of these educational materials are currently under development. Health Links available as of the release date of this document are included in the Appendix. Health Links not yet completed will be added to future revisions of the document and posted on the COG website as they become available.

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 childhood cancer treatment, as well as other factors listed above (e.g., genetic susceptibility).

Periodic Evaluations:

Standard Risk: Guidelines provided under the "Standard Risk" category in this document are per 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 these 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.

Also included in the Cancer Screening section are recommendations for periodic evaluations (including minimum recommended frequency), health protective counseling, and considerations for further testing and intervention.

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 also included in this packet.

We are hopeful that these Late Effects Screening Guidelines will enhance the follow-up care provided to childhood cancer survivors. If you have any questions, suggestions, or concerns regarding use of these guidelines, please contact:

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Version 1.0

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Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Any cancer experience								
Clinician Info Link Off therapy guidelines apply to patients who are ≥ 2 years after completion of therapy.	1	**Psychosocial Effects** Depression Anxiety Post-traumatic stress Social withdrawal, isolation	**Host factors** Female gender Family hx of depression, anxiety, or mental illness **Social factors** Lower household income Lower educational achievement	**Host factors** CNS cancer or CNS-directed therapy Premorbid learning or emotional difficulties **Social factors** Failure to graduate from high school	Clinical interview	Yearly	**Health Link** Emotional issues after childhood cancer **Resource** "Childhood Cancer Survivors: A Practical Guide to Your Future" by Nancy Keene, Wendy Hobbie & Kathy Ruccione Sebastopol, CA: O'Reilly & Assoc., 2000	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.
	2	**Limitations in healthcare and insurance access**	**Social factors** Lower household income Lower educational achievement		Clinical history	Yearly	**Health Link** Finding appropriate medical care after childhood cancer	Social work consultation.
Any Chemotherapy								
	3	**Dental abnormalities** Tooth/root agenesis Root thinning/ shortening Enamel dysplasia	**Host factors** Any patient who has not developed permanent dentition **Cancer treatment** Any radiation treatment including oral cavity or salivary glands.	**Host factors** Younger age at treatment, especially < 5 years old	Dental exam and cleaning	Every 6 months	**Health Link** Dental Health	Regular dental care including fluoride applications. Baseline panorex prior to dental procedures to evaluate root development.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Alkylating Agents								
Mechlorethamine **Cyclophosphamide** **Ifosfamide** **Melphalan** **Chlorambucil** **Lomustine (CCNU)** **Carmustine (BCNU)** **Busulfan** **Thiotepa** **Procarbazine** **Non-classical alkylators:** **Dacarbazine** **Temozolamide** **Heavy metals:** **Cisplatin** **Carboplatin** **Clinician Info Link** Doses that cause gonadal dysfunction show individual variation. Sertoli cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function. Females can typically maintain gonadal function at higher cumulative doses. Prepubertal status does not protect from gonadal injury in males.	4	**Hypogonadism** **Infertility** **Early menopause** **See related topics: Radiation – TBI, head/brain, abdomen, pelvis, or testes.** **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	**For females** Pubertal history (onset, tempo) Menstrual and pregnancy history Physical exam: height, weight, Tanner stage FSH, LH, estradiol **For males** Pubertal history (onset, tempo) History of sexual function (erections, nocturnal emissions, libido) History of medication use Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry. LH, FSH, testosterone Semen analysis	Yearly Baseline at age 11 or older and for: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency Yearly Baseline, at age 11 or older and for: - Delayed puberty - Clinical symptoms of testosterone deficiency As requested by patient and for evaluation of infertility	**Health Link** Fertility and pregnancy outcomes 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 oteopenia/osteoporosis in hypogonadal patients. 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.
	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	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 - cyclophosphamide - doxorubicin - dactinomycin - chest/thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **Medical conditions** Atopic history **Health behaviors** Cigarette smoking	**Treatment factors** BCNU ≥ 600 mg/m^2 Busulfan ≥ 500 mg (transplant doses)	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline, upon entry into long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction	**Health Link** Pulmonary Health Avoid SCUBA diving due to history of treatment with pulmonary–toxic chemotherapy	Pulmonary consultation for symptomatic pulmonary dysfunction. Influenza and Pneumovax immunization.
Cyclophosphamide **Ifosfamide**	7	**Hemorrhagic cystitis** **Bladder fibrosis** **Dysfunctional voiding** **See related topics:** **Pelvic radiation**	**Treatment factors** Higher cumulative doses (decreased incidence w/ Mesna) Combined with pelvic radiation **Health behaviors** Alcohol use Tobacco use	**Treatment factors** Cyclophosphamide dose ≥ 3 gm/m^2	Urinalysis	Yearly	Counsel to promptly report dysuria or gross	Urology consultation for culture negative macroscopic hematura.
	8	**Bladder malignancy** **See related topics:** **Pelvic radiation**	**Treatment factors** Combined with pelvic radiation		Urinalysis	Yearly	Counsel to promptly report dysuria or gross hematuria.	Urology consultation for culture negative macroscopic hematuria.
Ifosfamide	9	**Renal toxicity:** Glomerular toxicity Tubular toxicity -Renal tubular acidosis -Fanconi's syndrome -Hypophosphatemic rickets	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Combined with other nephrotoxic agents, such as: - cisplatin/carboplatin - aminoglycosides - amphotericin - immunosuppressants - abdominal radiation **Medical conditions** Tumor infiltration of kidney(s) Pre-existing renal impairment. Nephrectomy or mononephric	**Host factors** Age < 5 years at time of treatment **Treatment factors** Ifosfamide dose ≥ 60 grams/m^2	Blood pressure BUN, creatinine Urinalysis Na, K, Cl, CO_2, Ca, Mg, $P0_4$ Creatinine clearance or GFR	Yearly Yearly Yearly Baseline electrolytes at entry into LTFU. If normal, repeat every 5 years. If abnormal, repeat as clinically indicated. Baseline at entry into LTFU. If abnormal, repeat as clinically indicated	**Health Link** Kidney Health See also: Single Kidney Precautions	Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Heavy Metals								
Cisplatin **Carboplatin**	10	**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 $\geq$ 360 mg/m^2	History and physical exam Audiogram or brainstem auditory evoked response (ABR, BAER)	Yearly 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.	**Health Link** Hearing Conservation	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.
	11	**Peripheral sensory neuropathy** **Clinician Info Link** Neuropathy presents as persistent effect after therapy and is not late in onset.	**Treatment factors** Combined with vincristine	**Treatment factors** Cisplatin cumulative dose $\geq$ 300 mg/m^2	Neurologic exam	Yearly, until 2 to 3 years after therapy. Continue to follow-up yearly if symptoms persist.		Physical therapy referral for patients with symptomatic neuropathy. Physical therapy and occupational therapy assessment of hand function. If significant pain, treatment with anticonvulsant effective for neuropathic pain (e.g., gabapentin, or amitriptyline).
	12	**Renal toxicity:** - Glomerular injury - Tubular injury - Renal insufficiency	**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 $\geq$ 200 mg/m^2	Blood pressure BUN, creatinine Urinalysis Na, K, Cl, CO_2, Ca, Mg, $P0_4$ Creatinine clearance or GFR	Yearly Yearly Yearly Baseline electrolytes at entry into LTFU. If normal, repeat every 5 years. If abnormal, repeat as clinically indicated. Baseline at entry into LTFU. 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.
	13	**Dyslipidemia** (reports are conflicting that cisplatin predisposes to 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		Lipid lowering strategies including diet, exercise, weight loss, 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) **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). New deficits may emerge over time; extent of deficit depends on age at treatment, intensity of treatment, time since treatment.	14	**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 ($\geq$ 1000 mg/m^2 dose) In combination with: - dexamethasone - cranial radiation $\geq$ 18 Gy - total body irradiation - intrathecal methotrexate **Medical conditions** CNS leukemia/lymphoma with poor CSF reabsorption	**Host factors** Age < 3 years old at time of treatment Female gender **Treatment factors** Combined with methotrexate and/or cranial radiation. Radiation $\geq$ 24 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical interview including assessment of educational or vocational progress Referral for formal neuropsychological evaluation	Baseline at entry into LTFU, then yearly Baseline at entry into LTFU, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**Health Link** School and learning issues after 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** 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.	**Treatment factors** Combined with: - intrathecal methotrexate - dexamethasone - cranial radiation $\geq$ 18 Gy	**Treatment factors** High-dose IV administration	Clinical evaluation MRI CT plus MRI with MR angiography	Yearly As clinically indicated As clinically indicated		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: micro vascular injury CT: calcifications Neurology consultation and 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
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.	15	**Hepatic dysfunction** **Veno-occlusive disease** Acute toxicities predominate from which the majority of patients recover without sequelae.	**Medical conditions** Viral hepatitis	**Medical conditions** Chronic viral hepatitis	Physical exam ALT, AST, bilirubin	Yearly Baseline, upon 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** **(continued on next page)**	16	**Osteopenia** Bone mineral density ≥ 1 and < 2.5 SD below mean **Osteoporosis** Bone mineral density ≥ 2.5 SD below mean **Clinician Info Link** 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. 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 stem cell transplant **Medical conditions** Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism		Bone density evaluation (DEXA or quantitative CT) **Clinician Info Link** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat prn as clinically indicated.	**Health Link** Bone Health 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 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)	17	**Osteonecrosis** (avascular necrosis) **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. **See related topics: Corticosteroids**	**Host factors** Both genders at risk **Treatment factors** Combined with: - corticosteroids (dexamethasone effect is more potent than prednisone) - high-dose radiation to any bone **Medical conditions** Sickle cell disease	**Host factors** Older age (≥10 years old) at treatment **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	History	Yearly	**Health Link** Avascular Necrosis	Diagnostic imaging (radiograph, MRI) in patients with history of chronic pain. Orthopedic consultation for history of chronic joint pain in predisposed patient.
	18	**Renal dysfunction** Acute toxicities predominate, from which the majority of patients recover without sequelae.	**Host factors** Mononephric Combined with other nephrotoxic agents: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppresants - cyclosporine - abdominal radiation **Medical conditions** Diabetes mellitus Familial hypertension	**Treatment factors** Treatment before 1970.	Blood pressure BUN, creatinine Urinalysis Na, K, Cl, CO_2 Creatinine clearance or GFR.	Yearly Baseline, upon entry into long-term follow-up. Obtain in patients with abnormal BP, urinalysis, BUN, or creatinine. If abnormal, repeat as clinically indicated.	**Health Link** Kidney Health See also: Single Kidney Precautions	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
	19	**Hepatic dysfunction** Acute toxicities predominate from which the majority of patients recover without sequelae.	**Treatment factors** Abdominal radiation **Medical conditions** Viral hepatitis	**Treatment factors** Treatment before 1970 **Medical conditions** Chronic viral hepatitis	Physical exam ALT, AST, bilirubin	Yearly Baseline, upon entry into long-term follow-up.	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver function on screening tests. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunization in patients lacking immunity.

Therapeutic Agent	Sec ##	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Methotrexate (IT, high-dose IV) **See related topics: 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). New deficits may emerge over time; extent of deficit depends on age at treatment, intensity of treatment, time since treatment.	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 ($\geq$ 1000 mg/m^2 dose) In combination with: - dexamethasone - cranial radiation $\geq$ 18 Gy - 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 $\geq$ 24 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical interview including assessment of educational or vocational progress Referral for formal neuropsychological evaluation	Yearly Baseline at entry into LTFU, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**Health Link** School and learning issues after 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** 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 ($\geq$ 1000 mg/m^2 dose) administration Triple intrathecal chemotherapy In combination with: - dexamethasone - cranial radiation - total body irradiation **Medical conditions** CNS leukemia/lymphoma with poor CSF reabsorption	**Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose $\geq$ 24 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical evaluation Brain MRI Brain CT plus MRI with MR angiography	Yearly As clinically indicated As clinically indicated		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: micro vascular injury CT: calcifications Neurology consultation and 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
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 15 years post exposure to anthracycline	Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.
	22	**Cardiomyopathy** **Arrhythmias** **Clinician Info Link** Dose levels 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 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/African American Younger than 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 from treatment **Age at Treatment*** < 1 year old < 1 year old < 1 year old 1-4 years old 1-4 years old 1-4 years old 1-4 years old ≥ 5 years old ≥ 5 years old ≥ 5 years old ≥ 5 years old ≥ 5 years old Any age with serial * Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)	Detailed history of exertional tolerance. **Clinician Info Link** Note: exertional intolerance is uncommon in young patients (< 25 years). Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain. EKG for evaluation of QT interval ECHO or MUGA for evaluation of systolic function **Chest Radiation** Yes No No Yes No No No Yes Yes No No No decrease in function	Yearly Baseline at entry to LTFU Baseline at entry to LTFU, then periodically, based on age at treatment, history of chest radiation and cumulative anthracycline dose (see table below). **Anthracycline Dose*** Any < 200 mg/m^2 ≥ 200 mg/m^2 Any < 100 mg/m^2 ≥ 100 to < 300 mg/m^2 ≥ 300 mg/m^2 < 300 mg/m^2 ≥ 300 mg/m^2 < 200 mg/m^2 ≥ 200 to < 300 mg/m^2 ≥ 300 mg/m^2 *based on equivalent mg of doxorubicin/ daunorubicin	**Health Link** The heart and anthracyclines 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). **Recommended Frequency** Every year Every 2 years Every year Every year Every 5 years Every 2 years Every year Every 2 years Every year Every 5 years Every 2 years Every year Every year	Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrrhythmia, or prolonged QT interval. Additional cardiology evaluation in patients who received ≥ 300 mg/m^2 or < 300 mg/m^2 plus chest radiation who are pregnant or planning pregnancy to include an EKG and echocardiogram before and periodically during pregnancy (especially during 3rd trimester) and monitoring during labor and delivery due to risk of cardiac failure. Consider excess risk of isometric exercise program in any high risk patient defined as needing screening every 1 or 2 years.

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** **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: - cyclophosphamide - doxorubicin - busulfan - dactinomycin - carmustine (BCNU) - lomustine (CCNU) - thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **Medical conditions** Renal dysfunction High dose oxygen support such as during general anesthesia **Health behaviors** Smoking	**Treatment factors** Bleomycin dose ≥ 400 U/m^2 (injury observed in doses 60-100 U/m^2 in children)	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline upon entry to long-term follow-up and prior to general anesthesia. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Bleomycin Alert Avoid SCUBA diving due to potential exacerbation of pulmonary fibrosis with high oxygen concentrations. Notify physicians of health history 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 Pneumovax immunization.
Dactinomycin	24	**No known late effects** (Dactinomycin has been associated with acute veno-occlusive disease, from which the majority of patients recover without sequelae)	**Treatment factors** Hepatic radiation		Physical exam ALT, AST, bilirubin	Yearly Baseline, upon entry into long-term follow-up.	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Corticosteroids								
Prednisone **Dexamethasone** **See related topics:** **Methotrexate**	25	**Osteopenia** (Bone mineral density 1-2.5 SD below mean) **Osteoporosis** (Bone mineral density ≥ 2.5 SD below mean) **Clinician Info Link** 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. Pediatric bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Host factors** Both genders at risk **Treatment factors** Combined with: - methotrexate - cranial or spinal radiation - other head/neck radiation - radiation to bones **Medical Conditions** Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism	**Host factors** Older age at time of treatment **Treatment factors** Dexamethasone effect is more potent than prednisone.	Bone density evaluation (DEXA or quantitative CT) **Clinician Info Link** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat prn as clinically indicated.	**Health Link** Bone Health 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 interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).
	26	**Osteonecrosis (avascular necrosis)** **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. **See related topics:** **Methotrexate**	**Host factors** Both genders at risk **Treatment factors** Dexamethasone effect is more potent than prednisone. Combined with: - high-dose radiation to any bone **Medical conditions** Sickle cell disease	**Host factors** Older age (≥10 years at time of treatment) **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	History	Yearly	**Health Link** Avascular Necrosis	Diagnostic imaging (radiograph, MRI) in patients with history of chronic pain. Orthopedic consultation for history of chronic joint pain in predisposed patient.
	27	**Cataracts**	**Treatment factors** Combined with: - total body irradiation - head and neck radiation - busulfan	**Treatment factors** TBI given in single daily fraction Radiation dose ≥ 10 Gy with potential scatter to eye(s) Longer interval since treatment	Eye exam including funduscopic exam and visual acuity	Yearly	**Health Link** Vision preservation	Ophthalmology consultation if problem identified. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Enzymes								
Asparaginase	28	**No known late effects.** Acute toxicities predominate, from which the majority of patients recover without sequelae.						
Plant Alkaloids								
Vincristine **Vinblastine** **Clinician Info Link** Acute toxicities most commonly occur and usually resolve prior to patients entering long-term follow-up. Neuropathy can persist after treatment and is 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	**Treatment factors** Doses ≥ 6-8 mg **Medical conditions** Charcot-Marie-Tooth disease	Neurologic exam	Yearly, until 2 to 3 years after therapy; continue to follow-up yearly if symptoms persist.		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) (rare)	**Health behaviors** Tobacco use Recreational drug use		History Physical exam	Yearly	Counsel to wear appropriate protective clothing in cold environments and to not use tobacco or recreational drugs.	Vasodilating medications (calcium-channel blockers, alpha blockers) for patients with frequent, severe vasospastic attacks unresponsive to behavioral management.
Epipodophyllotoxins								
Etoposide (VP-16) **Teniposide (VM-26)** **Clinician Info Link** Recent administration schedules 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 15 years post exposure to agent	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	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose	**Host factors** Prepubertal at treatment **Treatment factors** Dose fraction $\geq$ 200 cGy 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** Higher 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/ palpation of irradiated skin and soft tissues. Other evaluations based on treatment volumes (see recommendations for specific fields)	Yearly	**Health Link** Reducing the risk of second cancers	Surgical and/or oncology consultation as clinically indicated.
	34	**Dysplastic nevi** **Skin cancer:** Basal cell carcinoma Squamous cell carcinoma Melanoma	**Host factors** Gorlin's syndrome (nevoid basal cell carcinoma syndrome)	**Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly	**Health Link** Skin health Reducing the risk of second cancers	Dermatology consultation for evaluation and monitoring of atypical nevi. Oncology consultation as clinically indicated.
	35	**Bone malignancies**	**Host factors** Adolescent at treatment Cancer-predisposing mutation (e.g., p53, RB1, NF1) **Treatment factors** Higher radiation dose Combined with alkylating agents	**Treatment factors** Radiation dose $\geq$ 30 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly	Counsel patient to report symptoms promptly (bone pain, bone mass, persistent fevers, etc.)	X-ray or other diagnostic imaging in patients with clinical symptoms. Oncology consultation as clinically indicated.
Total Body Irradiation (TBI)								

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

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

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Head/Brain Radiation								
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). New deficits may emerge over time. The extent of deficit depends on age at treatment intensity of treatment, time since treatment. **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 stem 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 Predisposing or family history of learning or attention problems.	Clinical interview including assessment of educational or vocational progress Referral for formal neuropsychological evaluation	Baseline and yearly Baseline at entry into LTFU, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**Health Link** School and learning issues after 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.
	37	**Clinical leukoencephalopathy** (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - cavernous hemangioma - mineralizing micro-angiopathy	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose Combined with: - high-dose methotrexate - intrathecal methotrexate or cytarabine **Medical conditions** Hydrocephalus requiring shunt Posterior fossa syndrome	**Host factors** Age < 2 years at time of treatment **Treatment factors** Dose ≥ 55 Gy Fraction dose ≥ 2 Gy	Clinical evaluation Brain MRI Brain CT plus MRI with MR angiography	Yearly As clinically indicated As clinically indicated		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: micro vascular injury CT: calcifications Neurology consultation and 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
(continued from previous page) **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** **(continued on next page)**	38	**Stroke/moyamoya** **Occlusive cerebral vasculopathy** **Clinician Info Link** Moyamoya syndrome is the complete occlusion of one or more of the three major cerebral vessels with the development of small, immature collateral vessels which reflect an attempt to revascularize the ischemic portion of the brain.	**Host factors** Hypothalamic/chiasmatic glioma **Medical conditions** Sickle cell disease Neurofibromatosis	**Treatment factors** Dose ≥ 40 Gy	Clinical evaluation Brain MRI with diffusion-weighted imaging with MR angiography	Yearly As clinically indicated		Neurology consultation and follow-up. Physical and occupational therapy as clinically indicated.
	39	**Brain tumor:** High-grade astrocytoma Meningioma Sarcoma	**Host factors** Younger age at treatment Thiopurine methyl transferase (TPMT) genetic polymorphism Neurofibromatosis **Treatment factors** Higher radiation dose	**Host factors** Age < 6 years at time of treatment Ataxia telangiectasia	History & physical Neurologic exam Brain MRI	Yearly Baseline at maturity for all patients Every other year for patients with neuro-fibromatosis, beginning 2 years after radiation As clinically indicated for symptomatic patients		Neurosurgical consultation for tissue diagnosis and/or resection. Neuro-oncology consultation for medical management.
	40	**Growth hormone deficiency**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation doses Surgery in suprasellar region Pretransplant radiation Total body irradiation: ≥ 10 Gy single fraction ≥ 12 Gy fractionated	**Treatment factors** Radiation dose ≥ 18 Gy Pretransplant cranial radiation Single daily fraction TBI dose	Assess nutritional status. Monitor height, weight BMI percentiles Tanner staging Bone age	Every 6 months until growth is completed. Obtain in poorly growing children.		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	**Treatment factors** Radiation dose ≥ 50 Gy	Review of systems: - galactorrhea - menstrual history - pregnancy history Prolactin level	Yearly In patients with galactorrhea or amenorrhea		CT evaluation of sella turcica for pituitary adenoma in patients with hyperprolactinemia. Endocrine consultation for patients with hyperprolactinemia, amenorrhea, or galactorrhea.
	42	**Central hypothyroidism** (thyroid-releasing and thyroid-stimulating hormone deficiency)	**Treatment factors** Higher radiation dose Total body irradiation	**Treatment factors** Radiation dose ≥ 30 Gy	Free T4, TSH	Yearly		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
(continued from previous page) **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** **(continued on next page)**	43	**Central adrenal insufficiency**	**Treatment factors** Higher radiation dose	**Treatment factors** Radiation dose ≥ 30 Gy	Review of systems: - failure to thrive - anorexia - dehydration - hypoglycemia - lethargy - unexplained hypotension 8:00 AM serum cortisol in patients treated with ≥ 30 Gy radiation to hypothalamic-pituitary axis	Yearly Baseline on entry into long term follow-up and periodically as clinically indicated	Corticosteroid replacement and precautions about replacement therapy. Recommend wearing Medic Alert bracelet. Resource: Pediatric Endocrine Nurses (PENS) or Magic Foundation for hypopituitarism.	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 LH, FSH, estradiol testosterone Bone age	Yearly As clinically indicated in patients with signs of accelerated pubertal progression and growth. Obtain in rapidly growing children.		Endocrine consultation for accelerated puberty (puberty in girl < 8 years old and boy < 9 years old). Consider pelvic ultrasound.
	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 FSH, LH, estradiol	Yearly Baseline at age 11 or older and for: - Delayed puberty - Irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency	**Health Link** Fertility and pregnancy outcomes after childhood cancer 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. 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.
					Males: Pubertal history (onset, tempo) History of sexual function (erections, nocturnal emissions, libido). History of medication use. Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry. LH, FSH, testosterone Semen analysis	Yearly Baseline, at age 11 or older and for: - Delayed puberty - Clinical symptoms of testosterone deficiency. 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
(continued from previous page) **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** **(continued on next page)**	46	**Overweight/Obesity** Definition by adult standards: body mass index (BMI) = wt (kg)/ht (M2) 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. If abnormal, refer for management of dyslipidemia Obtain baseline for patients with acanthosis nigricans. Consider testing in overweight or obese patients with dyslipidemia. If abnormal, refer to endocrinologist	Obesity-related health risks. Health promotion through diet and physical activity	Consider evaluation for other co-morbid conditions including: dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, insulin resistance. Nutritional counseling. Endocrine consultation for patients with dyslipidemia or hyperglycemia.
	47	**Chronic sinusitis**	**Treatment factors** Higher cumulative radiation doses to sinuses (≥ 30 Gy) **Medical conditions** Atopic history Hypogammaglobulinemia		History Physical exam CT sinuses	Yearly As clinically indicated		Otolaryngology consultation as clinically indicated.
	48	**Xerostomia** Salivary gland dysfunction	**Medical conditions** Head and neck radiation involving the parotid gland Higher radiation doses Total body irradiation	**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 Temporo-mandibular 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 ≥ 30 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	Physical exam Psychosocial assessment of adjustment	Yearly Yearly	Resource: FACES - The National Craniofacial Association www.faces-cranio.org/	Plastic surgery/craniofacial surgery consultation for facial reconstruction. 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								
Total Body Irradiation **Orbital/Eye** **Cranial (whole brain)** **Craniospinal** **Clinician Info Link**: Complications other than cataracts are generally associated only with orbital/eye radiation.	51	**Cataracts**	**Treatment factors** Higher radiation dose Combined with: - corticosteroids - busulfan	**Treatment factors** Dose ≥ 10 Gy TBI given in single daily fraction	Ophthalmology evaluation including funduscopic exam and visual acuity	Yearly for patients who received ≥ 30 Gy or TBI Every 3 years for patients who received < 30 Gy (these patients also need yearly funduscopic exams during annual LTFU visits)	**Health Link** Vision preservation 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 sicca) or complex ocular problems. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources.
		Reduced visual acuity **Orbital hypoplasia**	**Treatment factors** Higher radiation dose Higher daily fraction dose	**Treatment factors** Fraction dose ≥ 2 Gy				
		Lacrimal duct atrophy	**Treatment factors** Higher radiation dose Combined with - doxorubicin - dactinomycin	**Treatment factors** Dose ≥ 40 Gy				
		Xerophthalmia (severe)	**Treatment factors** Higher radiation dose	**Treatment factors** Dose ≥ 30 Gy				
		Keratitis	**Treatment factors** Higher radiation dose	**Treatment factors** Dose ≥ 50 Gy				
		Keratoconjunctivitis sicca	**Treatment factors** Higher radiation dose Corticosteroids	**Treatment factors** Dose ≥ 50 Gy **Medical conditions** Chronic GVHD				
		Telangiectasias	**Treatment factors** Higher radiation dose	**Treatment factors** Dose ≥ 50 Gy				
		Retinopathy	**Treatment factors** Higher radiation dose **Medical conditions** Diabetes mellitus	**Treatment factors** Dose 45-65 Gy				
		Optic chiasm neuropathy	**Treatment factors** Higher radiation dose **Medical conditions** Diabetes mellitus Hypertension	**Treatment factors** Dose 50- 65 Gy				
		Endophthalmos **Chronic painful eye**	**Treatment factors** Higher radiation 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
Ear radiation								
Total body irradiation **Ear/Infratemporal** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal**	52	**Tympanosclerosis** **Otosclerosis** **Eustachian tube dysfunction** **Conductive hearing loss**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose **Medical conditions** Chronic otitis Chronic cerumen impaction	**Treatment factors** Dose ≥ 50 Gy	History and physical exam Audiogram or brainstem auditory evoked response (ABR, BAER)	Yearly For patients who received ≥ 30 Gy: Yearly after completion of therapy for 5 years (for patients < 10 yrs old continue yearly until age 10); then every 5 years. If abnormal, follow yearly until stable. Obtain more frequently if clinical evidence of progressive hearing loss. For patients who received < 30 Gy: Baseline at entry into long term follow-up, then as clinically indicated	**Health Link** Hearing conservation	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 ≥ 30-40 Gy				
Neck radiation								
Any radiation with potential impact to the neck/thyroid, including: **Total Body Irradiation** **Cervical** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oroparyngeal** **Mantle** **Mediastinal** **Whole lung** **Spinal**	53	**Thyroid nodules**	**Host factors** Younger age at treatment Female gender **Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 25 Gy	Physical exam	Yearly	**Health Link** Thyroid problems after childhood cancer.	Ultrasound for evaluation of palpable nodule(s). Endocrine and/or surgical consultation for diagnostic biopsy or thyroidectomy.
	54	**Thyroid cancer**	**Host factors** Younger age at treatment Female gender **Treatment factors** > 5-10 years after irradiation Cervical or total body irradiation		Physical exam	Yearly	**Health Link** Thyroid problems after childhood cancer.	Ultrasound for evaluation of palpable nodule(s). Surgical consultation for resection. Nuclear medicine consultation for ablation of residual disease. Endocrine consultation for postoperative medical management..
	55	**Hypothyroidism**	**Host factors** Female gender **Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 20 Gy	History Physical exam TSH, free T4 Note: must be free T4 in females on OCP	Yearly; consider more frequent screening during periods of rapid growth	**Health Link** Thyroid problems after childhood cancer.	Endocrine consultation for medical management.
	56	**Hyperthyroidism**	**Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 35 Gy	History Physical exam TSH, free T4	Yearly	**Health Link** Thyroid problems after childhood cancer.	Endocrine consultation for medical management.
	57	**Carotid artery disease**		**Treatment factors** Dose ≥ 40 Gy	Clinical evaluation 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: - dactinomycin - anthracyclines **Medical conditions** Gastroesophageal reflux	**Treatment factors** Dose ≥ 40 Gy	History	Yearly		Surgical and/or gastroenterology consultation for symptomatic patients.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Trunk radiation								
Any field from shoulders to pelvis including: **Total Body Irradiation** **Spinal (≥ 12 Gy)**	59	**Musculoskeletal growth problems:** - Hypoplasia - Fibrosis - Reduced or uneven growth - Shortened trunk height	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Larger treatment field Higher dose per fraction	**Host factors** Prepubertal at treatment **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones. Epiphysis in treatment field. Dose ≥ 20 Gy	Physical exam	Yearly		Orthopedic consultation if clinically significant or for any deficit noted in growing child. Plastic surgery consultation for reconstruction.
	60	**Scoliosis**	**Host factors** Younger age at irradiation Paraspinal malignancies Neurofibromatosis **Treatment factors** Hemithoracic or abdominal radiation Hemithoracic, abdominal or spinal surgery **Clinician Info Link**: Scoliosis is usually associated with radiation combined with 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/kyphosis	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/kyphosis	Orthopedics consultation as indicated based on radiographic exam.
	62	**Esophageal stricture**	**Treatment factors** Higher radiation dose to esophagus Radiomimetic chemotherapy: - dactinomycin - anthracyclines **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 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)	**Health Link** Reducing the risk of second cancers	Surgical consultation for diagnostic procedure. Precautions about the use of HRT.
	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**	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** Higher radiation dose to chest/thorax Combined with radiomimetic chemotherapy: - dactinomycin - anthracyclines Total body irradiation **Medical conditions** Hypertension Obesity Dyslipidemia Diabetes mellitus Premature ovarian failure (untreated) **Health behaviors** Smoking	**Treatment factors** Dose ≥ 40-45 Gy Anteriorly-weighted radiation fields Lack of subcarinal shielding	EKG ECHO Cardiology consultation for stress testing Fasting glucose and lipid profile **Age at Treatment*** < 1 year old < 1 year old 1-4 years old 1-4 years old ≥ 5 years old ≥ 5 years old ≥ 5 years old ≥ 5 years old Any age with serial * Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)	Baseline, at entry into long-term follow-up and as clinically indicated Baseline, at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose (see table below). For patients who received ≥ 40 Gy: obtain baseline 5-10 years after radiation Every 3 to 5 years. If abnormal, refer for ongoing management **Anthracycline Dose*** None Any None Any None, RT < 30 Gy None, RT ≥ 30 Gy < 300 mg/m^2 ≥ 300 mg/m^2 decrease in function * Based on equivalent mg of doxorubicin/ daunorubicin	**Health Link** The Heart and Radiation **Recommended Frequency** Every 2 years Every year Every 2 years Every year Every 5 years Every 2 years Every 2 years Every year Every year	Cardiology consultation in patients with subclinical abnormalities on screening evaluations or with left ventricular dysfunction, dysrhythmia or prolonged QT interval. Additional cardiology evaluation in patients who are pregnant or planning pregnancy who received TBI or ≥ 30 Gy chest/thorax radiation. 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.
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: - dactinomycin - bleomycin - busulfan - carmustine (BCNU) - lomustine (CCNU) - cyclophosphamide - doxorubicin **Medical conditions** Atopic history **Health behaviors** Smoking	**Treatment factors** Whole lung ≥ 20 Gy	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Avoid SCUBA diving due to history of treatment with pulmonary-toxic irradiation	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations.

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 (Hemophilus 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	Prophylactic antibiotics at onset of febrile illness, if not taking daily. Counsel to seek immediate medical evaluation for temperature ≥ 101 for physical exam and blood culture. Counsel to advise all healthcare providers, including dentists, regarding functional asplenia. Immunize with Pneumococcal Meningococcal, HIB vaccines. Pneumococcal booster immunization after 5 years. Medical alert bracelet/card noting functional asplenia.
Total Body Irradiation **Renal** **Para-Aortic** **Whole abdominal** **Spinal (≥ 15 Gy)**	68	**Renal insufficiency** **Hypertension** **See related topics:** **Cisplatin** **Carboplatin** **Ifosfamide**	**Treatment factors** Higher radiation dose to kidneys Combined with: - doxorubicin, - dactinomycin Hyperfractionated radiation Total body irradiation Combined with other nephrotoxic agents such as: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppressants - cyclosporine **Medical conditions** Mononephric Diabetes mellitus Hypertension	**Treatment factors** Dose ≥ 15 Gy to whole kidney 14 Gy TBI without renal shielding	Blood pressure BUN, Creatinine Urinalysis Na, K, Cl, CO_2 Creatinine clearance or GFR	Yearly Yearly Obtain in patients with abnormal BP, urinalysis BUN or creatinine. If abnormal, repeat as clinically indicated.	**Health Link** Kidney Health See also: Single Kidney Precautions	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
Total Body Irradiation **Whole abdomen** **Hepatic**	69	**Hepatic fibrosis** **Cirrhosis**	**Treatment factors** Higher radiation dose to liver **Medical conditions** Chronic hepatitis **Health behaviors** Alcohol use	**Treatment factors** Dose ≥ 40 Gy to at least 1/3 of liver volume Dose 20-30 Gy to entire liver	Physical exam ALT, AST, bilirubin	Yearly Baseline, upon entry into long-term follow-up.	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity.
	70	**Hepatocellular carcinoma**	**Medical conditions** Chronic hepatitis B or C Cirrhosis **Treatment factors** Higher radiation dose to liver **Health behaviors** Alcohol use		AFP Liver ultrasound	Yearly in patients with chronic hepatitis Yearly in patients with cirrhosis		Oncology consultation for medical management.

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

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**	**Host factors** Older age at irradiation **Treatment factors** Higher radiation dose to pelvis 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 LH, FSH, Estradiol	Yearly Baseline at age 11 or older and for: - Delayed puberty - Irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency	**Health Link** Fertility and pregnancy outcomes 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	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.
Whole abdomen **Pelvic** **Iliac/inguinal** **Para-aortic** **Spinal ≥ 30 Gy**	76	**Hemorrhagic cystitis** **See related topics:** **Cyclophosphamide** **Ifosfamide**	**Treatment factors** Higher radiation dose **Health behaviors** Alcohol use Tobacco use	**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		Urinalysis	Yearly	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** **-Hypogonadism** **-Delayed/arrested puberty** **See related topics: Alkylating agents**	**Treatment factors** Radiation to testes 1 to 3 Gy: azoospermia may be reversible. 3 to 6 Gy: azoospermia possibly reversible (but unlikely) Testicular irradiation combined with head/brain irradiation	**Treatment factors** Radiation to testes ≥ 6 Gy: azoospermia likely permanent ≥ 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	Semen analysis History of sexual function (erections, nocturnal emissions, libido). History of medication use. Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry. LH, FSH, Testosterone	As requested by patient and for evaluation of infertility. **Clinician Info Link** Late recovery of gonadal function has been reported. Yearly Yearly Yearly Baseline, at age 11 or older and for: - Delayed puberty - Clinical symptoms of testosterone deficiency	**Health Link** Fertility and pregnancy outcomes after childhood cancer. Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	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.
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 radiated bones	Orthopedic consultation if clinically significant (limb length discrepancy, chronic pain) or for any deficit noted in growing child. Plastic surgery consultation for reconstruction.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Transfusion								
Clinician Info Link Consider any blood or serum product including: Packed red cells Whole blood White cells Platelets Fresh frozen plasma Cryoprecipitate Immunoglobulin preparations: IVIG, VZIG Note dates screening of blood donors initiated: 1971 Hepatitis BsAg 1985 HIVAB HIV-1 EIA 1986 Surrogate ALT screening 1990 HCV EIA-I screening 1992 HCV EIA-II screening Note: International screening policies may not include these measures.	81	**Chronic Hepatitis B**	**Host factors** Living in hyperendemic area **Treatment factors** Transfusion before 1972 **Health behaviors** IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing	**Host factors** Chronic immuno-suppression	Hepatitis B surface antigen (HBsAg) AND Hepatitis B core antibody (anti HBc, HBcAb)	Once in patients who received any blood or serum product prior to 1972	**Health Link** Liver Health	Gastroenterology or hepatology consultation for patients with chronic infection. Hepatitis A immunization in patients lacking immunity.
	82	**Chronic Hepatitis C**	**Host factors** Living in hyperendemic area **Treatment factors** Transfusion before 1993 **Health behaviors** IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing	**Treatment factors** Transfusion before 1986 when surrogate screening of blood donors with ALT initiated and donors with self-reported high-risk behaviors deferred. Chronic immunosuppression	Hepatitis C antibody PCR to establish chronic infection	Once in patients who received any blood or serum product prior to 1993 Once in patients with positive hepatitis C antibody	**Health Link** Liver Health	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.
		Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	**Treatment factors** Stem cell transplantation **Medical conditions** Chronic hepatitis C **Health behaviors** Alcohol use 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	Physical exam ALT, AST, bilirubin Prothrombin time AFP	Yearly in patients with chronic hepatitis B or C (PCR positive) Yearly in patients with chronic hepatitis		
	83	**HIV infection**	**Treatment factors** Transfusion before 1986 **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 any blood or serum product prior to 1986	Standard counseling regarding safe sex, universal precautions, exacerbating high-risk behaviors	Infectious diseases consultation for patients with chronic infection.

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

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Neurosurgery	91	**Neurocognitive deficits** vary with extent of surgery and postoperative complications. In general, mild delays occur in most areas of neuropsychological function compared to healthy children. **Intracranial bleed/stroke** **Motor deficits** **Paralysis** **Movement disorders** **Ataxia** **Seizures** **Hydrocephalus** **Shunt malfunction** **Clinician Info Link** New deficits may emerge over time. Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment.	**Host factors** Younger age at diagnosis **Treatment factors** Combined with: - brain radiation - high-dose chemotherapy - intrathecal chemotherapy **Medical conditions** Hydrocephalus	**Host factors** Younger age at treatment (< 3 years) Supratentorial tumor **Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose ≥ 60 Gy **Medical conditions** Posterior fossa syndrome CNS infection **Social factors** Low SES Predisposing family history of learning or attention problems	Neurology evaluation Rehabilitation medicine/ physiatrist evaluation Neurosurgery evaluation Abdominal x-ray Clinical assessment of educational or vocational progress Referral for formal neuropsychological 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. Yearly, or more frequently as clinically indicated in patients with motor dysfunction Yearly for patients with shunts. At puberty growth spurt for patients with shunts to assure distal shunt tubing in peritoneum Baseline and yearly Baseline at entry into LTFU, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**Health Link** School and learning issues after childhood cancer	Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual- motor integration, memory, comprehension of verbal instructions verbal fluency, executive function and planning. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Speech, physical, and occupational therapy in patients with persistent deficits. Consider nutrition, endocrine, and psychiatric (obsessive-compulsive behaviors) consultations in patients with hypothalamic pituitary axis tumors. Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: micro vascular injury CT: calcifications
Orchiectomy	92	**Infertility** **Hypogonadism**	**Treatment factors** Bilateral orchiectomy Unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents		History of sexual function (erections, nocturnal emissions, libido). History of medication use. Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry. LH, FSH, Testosterone Semen analysis	Yearly Baseline, at age 11 or older and for: - Delayed puberty - Clinical symptoms of testosterone deficiency. As requested by patient and for evaluation of infertility. **Clinician Info Link** Late recovery of gonadal function has been reported.	For patients with single testis: counsel to wear athletic supporter with protective cup during athletic activities.	Surgical placement of testicular prosthesis.

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		Urologic consultation for patients with incontinence, dysfunctional voiding, or sexual dysfunction.
Pulmonary lobectomy	94	**Pulmonary insufficiency**	**Treatment factors** Chest radiation Combined with pulmonary toxic therapy: - bleomycin - busulfan - carmustine (BCNU) - lomustine (CCNU) - cyclophosphamide - doxorubicin - dactinomycin - chest/thoracic radiation - spinal radiation $\geq$30Gy - total body irradiation **Medical conditions** Atopic history **Health behaviors** Smoking		Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline, upon entry to long-term follow-up. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Avoid SCUBA diving due to history of pulmonary lobectomy	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations.
Splenectomy	95	**Life-threatening infection** with encapsulated organisms (Hemophilus influenzae, Streptococcus pneumoniae, Meningococcus)			Physical exam Blood culture	When febrile T $\geq$ 101	**Health Link** Splenic precautions	Prophylactic antibiotics at onset of febrile illness, if not taking daily. Counsel to seek immediate medical evaluation for temperature $\geq$ 101 for physical exam, and blood culture. Counsel to advise all healthcare providers, including dentists, regarding functional asplenia. Immunize with Pneumococcal Meningococcal, HIB vaccines. Pneumococcal booster immunization after 5 years. Medical alert bracelet/card noting asplenia.

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 Stem Cell Transplantation								
Clinician Info Link Complications after hematopoietic stem cell transplantation have multifactorial etiology: 1. prior therapy for primary malignancy 2. intensity of transplant conditioning 3. stem cell product (e.g., marrow, cord blood, peripheral stem cells) 4. donor (e.g., autologous, allogeneic, unrelated) 5. quality of donor to recipient match 6. complication of transplant process (immunosuppression and GVHD.) 7. complications in the post-transplant period. 8. underlying disease 9. host genetic factors 10. 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**	**Treatment factors** History of multiple transfusions Radiation to the liver **Medical conditions** Chronic GVHD Viral hepatitis **Health behaviors** Alcohol use		ALT, AST, bilirubin Ferritin	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 function on screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function. Note: PCR testing may be required in immunosuppressed patients who are negative for antibody. Gastroenterology or hepatology consultation if abnormal. Hepatitis A and B immunization in patients lacking immunity.
	Lungs							
	98	**Bronchiolitis obliterans** **Chronic bronchitis** **Bronchiectasis**	**Treatment factors** Allogeneic transplant Thoracic radiation Total body irradiation **Medical conditions** Chronic GVHD	**Medical conditions** Prolonged immunosuppression related to GVHD prophylaxis	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline, upon entry to long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Avoid SCUBA diving due to pulmonary compromise	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumovax vaccination.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
	Muscles/Bones							
Hematopoietic stem cell transplantation (continued from previous page)	99	**Joint contractures**	**Medical conditions** Chronic GVHD		Physical exam	Yearly		Consultation with rehabilitation medicine/physiatrist.
	100	**Osteopenia** Bone mineral density 1-2.5 SD below mean **Osteoporosis** Bone mineral density ≥2.5 SD below mean **Clinician Info Link** 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. 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 Radiation therapy **Medical conditions** Hypogonadism Chronic GVHD **Behavioral factors** Physical inactivity	**Treatment factors** Prolonged steroid therapy for 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 prn as clinically indicated.	**Health Link** Bone Health National Osteoporosis Foundation website: www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D ** Caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency; correction of chronic metabolic acidosis that could accelerate bone loss.). Endocrine consultation for patients with bone density ≥ 2.5 SD below mean, or patients with history of multiple fractures, for other interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).

(continued on next page)

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 stem 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.	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 Task Force recommendations at http://www.ahrq.gov/clinic/prevenix.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
Note to Clinicians: "Highest Risk" guidelines below include suggested periodic evaluations for childhood cancer survivors who are at increased risk of a specific cancer due to prior therapy, co-morbid conditions, family history, genetic susceptibility or other factors. "Standard Risk" guidelines below are per American Cancer Society recommendations for standard-risk populations and are provided here for reference. In addition, clinicians are encouraged to consult recommendations from other organizations, such as the U.S. Preventive Services Task Force (http://www.ahrq.gov/clinic/serfiles.htm). Specific decisions regarding cancer screening are the prerogative of the patient, family, and healthcare provider.							
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	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 Clinician breast exam Mammogram **Highest Risk:** Breast self-examination Clinician breast exam Mammogram **Clinician Info Link** Mammography is currently limited in its ability to evaluate premenopausal breasts..	 Monthly, beginning at age 20 Every 3 years between ages 20-40; then yearly beginning at age 40 Every year beginning age 40 Monthly beginning at puberty. Yearly, beginning at puberty until age 25, then every 6 months Yearly, beginning 8 years after radiation or at age 25 (whichever occurs last)	**Health Link** Reducing the risk of second cancers	Surgery and/or oncology consultation as clinically indicated.
Cervical	105	Early age at first intercourse Multiple lifetime sex partners Cigarette smoking Sexually transmitted diseases	Personal history of cervical dysplasia. Prenatal DES exposure HPV infection Immunosuppression Chronic steroid use	 **Standard Risk:** Pelvic exam Cervical PAP smear **Highest Risk:** Pelvic exam Cervical PAP smear	Begin screening 3 years after first vaginal intercourse, or at age 21, whichever comes first. 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 PAP tests in a row, may screen every 2-3 years. Yearly Yearly	**Health Link** Reducing the risk of second cancers	Gynecology and/or oncology consultation as clinically indicated.

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Colorectal	106	High fat/low fiber diet Age 50 to 75 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	**Standard Risk:** Fecal occult blood (minimum of 3 cards)	Yearly, beginning at age 50 **AND/OR**	**Health Link** Reducing the risk of second cancers	Gastroenterology, surgery and/or oncology consultation as clinically indicated.
				Flexibile sigmoidoscopy	Every 5 years beginning at age 50.		
				Note:The combination of yearly fecal occult blood testing and every 5 year flexible sigmoidoscopy is preferable to either test done alone.			
				OR			
				Double contrast barium enema	Every 5 years beginning at age 50.		
				OR			
				Colonoscopy	Every 10 years beginning at age 50		
				Highest Risk: Monitoring to begin 10 years after radiation or at age 25 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 10 years after radiation or at age 25 (whichever occurs last).		
				AND			
				Flexibile sigmoidoscopy	Every 5 years		
				OR			
				Double contrast barium enema	Every 5 years		
				OR			
				Colonoscopy	Every 10 years		
Endometrial	107		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 smoker or history of head/neck radiation	**Health Link** Reducing the risk of second cancers	Head and neck/otolaryngology consultation as indicated.
Prostate	110	Older age, with steadily increasing risk after age 40.	African-American race Family history of prostate cancer in first degree relative	**Standard Risk:** Digital rectal exam Prostate specific antigen (PSA)	 Yearly, beginning at age 50 Yearly, beginning at age 50	**Health Link** Reducing the risk of second cancers	Urology and/or oncology consultation as clinically indicated.
				Highest Risk: Digital rectal exam Prostate specific antigen (PSA)	 Yearly, beginning at age 45 Yearly, beginning at age 45		
Skin	111	Light skin color Chronic exposure to sun Atypical moles or > 50 moles	Any history of radiation Personal history of melanoma or skin cancer. Dysplastic nevi Family history of melanoma or skin cancer. History of severe sunburn at young age	**Standard Risk:** Clinical skin exam	 Every 3 years, from ages 20-39 Yearly, beginning at age 40.	**Health Link** Reducing the risk of second cancers	Surgery, dermatology, and/or oncology consultation as clinically indicated.
				Highest Risk: Skin self exam Clinical skin exam with attention to pigmented nevi in radiation field.	 Monthly Yearly		
Testicular	112		History of undescended testicle History of testicular cancer or carcinoma- in-situ in contralateral testis. History of gonadal dysgenesis Klinefelter's syndrome Family history of testicular cancer	**Standard Risk:** Testicular self-exam Clinical testicular exam	 Not indicated 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 Clinical testicular exam	 Monthly, beginning at puberty Yearly		

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Explanation of Scoring for the Late Effects 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 for childhood cancer. The recommendations are based on identified risk factors supported by the literature as well as by collective clinical experience.

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 the following categories:

> **Category 1**: There is uniform consensus that the recommendation is appropriate based on high-level evidence of an association between the therapeutic agent and the late effect.
>
> **Category 2A**: There is uniform consensus that the recommendation is appropriate based on lower-level evidence, including clinical experience, of an association between the therapeutic agent and late effect.
>
> **Category 2B**: There is nonuniform consensus that the recommendation is appropriate based on lower-level evidence, including clinical experience, of an association between the therapeutic agent and late effect.
>
> **Category 3**: There is major disagreement that the recommendation is appropriate.

"High-level evidence" was defined as evidence derived from high quality case control or cohort studies. "Lower-level evidence" was defined as 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 for the association/recommendation) or "2B" (there is nonuniform consensus among the reviewers regarding the strength of evidence for the association/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.

COG Late Effects Screening Guidelines - Scoring by Panel of Experts
Version 1.0 – March 2003

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	1
	AML/MDS	1
Non-classical alkylators: Dacarbazine Temozolamide Cisplatin Carboplatin	Hypogonadism Infertility Early menopause	2A
	AML/MDS	2A
Heavy Metals		
Cisplatin Carboplatin	Ototoxicity	1
	Peripheral Neuropathy	2A
	Renal toxicity	1
	Dyslipidemia	2B
Busulfan Carmustine (BCNU) Lomustine (CCNU)	Pulmonary fibrosis	1
Cyclophosphamide Ifosfamide	Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding	1
	Bladder malignancy	1
	Renal Toxicity	1
Antimetabolites		
Methotrexate (po, IV, IM)	Osteopenia, Osteoporosis	2B
	Osteonecrosis	2A
	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

THERAPY	LATE EFFECT	SCORE
Corticosteroids		
Prednisone Dexamethasone	Osteopenia, Osteoporosis	1
	Osteonecrosis	1
	Cataracts	1
Enzymes		
Asparaginase	No Known Late Effects	1
Plant alkaloids		
Vinca 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
	Xerostomia	1
	Dental abnormalities	1
	Craniofacial abnormalities	1

THERAPY	LATE EFFECT	SCORE
Eye radiation		
TBI Orbital/Eye Cranial (whole brain) Craniospinal	All adverse effects on eye: Cataracts Reduced visual acuity 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 Cervical Mantle Cranial (whole brain) Craniospinal Nasopharyngeal Oropharyngeal 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	1
	Scoliosis	1
Chest/thorax radiation		
Any field involving the chest/thorax: 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	Congestive heart failure Cardiomyopathy Pericarditis Pericardial fibrosis Valvular disease Myocardial infarction Arrhythmia Atherosclerotic heart disease	1

THERAPY	LATE EFFECT	SCORE
Chest/thorax radiation with potential impact to the lungs: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Any field involving the upper abdomen	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 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	1
Transfusion		
	Chronic Hepatitis B	1
	Chronic Hepatitis C	1
	Complications related to chronic hepatitis	1
	HIV infection	1

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

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

APPENDIX:
Patient Education Materials (Health Links)

The following Health Links are included in this packet:

- Bone Health after Childhood Cancer (Osteopenia/Osteoporosis)
- The Heart and Anthracyclines
- The Heart and Radiation
- School and Learning Issues after Childhood Cancer
- Thyroid Problems after Childhood Cancer
- Single Kidney Precautions

The following Health Links are planned for future release:

- Emotional Issues after Childhood Cancer
- Finding Appropriate Medical Care after Childhood Cancer
- Dental Health
- Avascular Necrosis
- Kidney Health
- Liver Health
- Hearing Conservation
- Fertility and Pregnancy Outcomes after Childhood Cancer
- Pulmonary Health
- Bleomycin Alert
- Vision Preservation
- Skin Health
- Reducing the Risk of Second Cancers
- Scoliosis/Kyphosis
- Splenic Precautions

Bone Health After Childhood Cancer

Strong bones are the foundation of a healthy body. They support our muscles and protect our internal organs. Treatment for childhood cancer sometimes damages the bones, causing an increased risk for developing osteoporosis (weak bones). Fortunately, there are several things you can do to strengthen your bones and avoid or minimize this problem.

Bone Mass (Strength) and Osteoporosis

Bones are made of calcium and other minerals. Throughout life, new bone tissue is continually being formed and old bone tissue is being removed, so calcium is always needed. During childhood and into young adulthood, bone formation usually occurs faster than bone loss, causing bones to grow and become heavier (more dense). In fact, nearly half of the bone in an adult's body is formed during the teen years. The average person reaches their peak bone density (bone strength) in the young adult years, usually between the ages of 25 and 30. As a person gets older, the process of bone removal gradually overtakes bone formation, and bones slowly lose strength as part of the normal aging process.

Osteoporosis: A Silent Disease

When not enough new bone tissue is formed, or when too much bone tissue is removed, the bones can become weak (brittle) and less dense (thin). If this happens, there is a much higher risk for breaking a bone of the hip, wrist, ribs, or other bones, from a simple fall. Also, the bones of the spine can collapse, which makes the person shorter and can lead to a curvature of the spine. This often causes many problems, including chronic pain. Weakening of the bones is called osteoporosis (osteo = bone; porosis = porous). Osteoporosis is sometimes called a "silent bone disease" because people often don't know that their bones have weakened until they break one or have back pain.

Risk Factors for Osteoporosis

There are certain factors that you cannot change that may affect your chances of developing osteoporosis. Genes are important—if you have someone in your family with osteoporosis, you are more likely to develop it. Women, especially those who have gone through menopause, are more likely to have this disease than men. People who are Caucasian or Asian, or people who are short or have small, thin frames, are also more likely to have osteoporosis. And the chances of developing osteoporosis increase for all people as they get older.

There are several things that can lead to osteoporosis at a young age. Smoking, a diet low in calcium, and lack of weight-bearing exercise can all increase the risk of osteoporosis. Consuming too much caffeine, drinking a lot of alcohol or carbonated beverages, and eating too much salt may also increase the risk.

Certain medications, when taken on a regular basis, can also increase the risk of osteoporosis. These include:

- Glucocorticoids (steroids such as prednisone and dexamethasone)
- High doses of thyroid hormone
- Certain anticonvulsants (phenytoin and barbiturates)
- Aluminum-containing antacids (such as Maalox® or Amphogel®)
- Gonadotropin-releasing hormone analogues (used for treatment of endometriosis)
- High doses of heparin (used to prevent blood clots)
- Cholestyramine (used to control blood cholesterol)

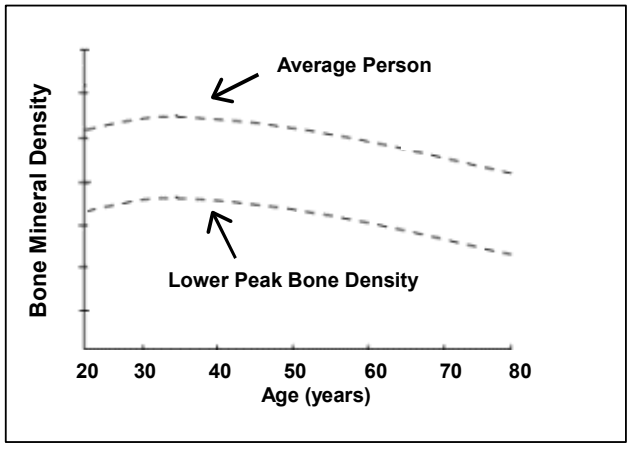
Many of these medications are essential treatments for certain medical conditions. If you are taking any of these medications, do not change your dosage or stop taking your medication without consulting with your healthcare provider.

Childhood Cancer Survivors and Their Bones

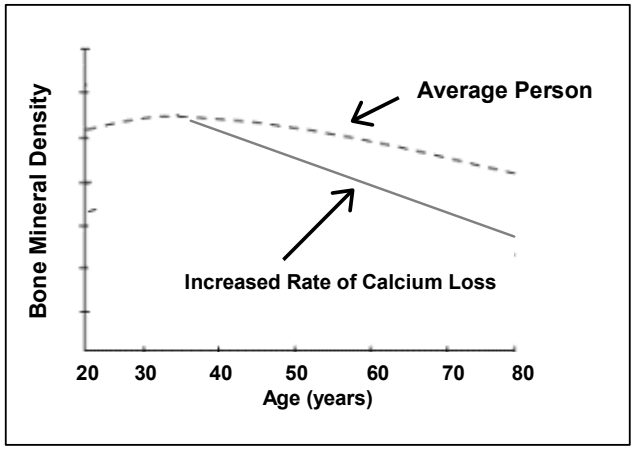
Some survivors of childhood cancer have an increased chance of getting osteoporosis. We know that treatment can affect the bones in two different ways. First, because of cancer treatment during childhood or adolescence, the survivor may never reach a normal peak bone density during the young adult years. This is shown in the figure below (Example 1), illustrating what happens to bone mineral density (bone strength) with aging. Note that in the average person, after reaching peak strength in young adulthood, the bone density gradually decreases with age. But the survivor may never reach normal peak bone density, and as a result, may develop osteoporosis at a younger age.

Another way that cancer treatment can affect the chances of getting osteoporosis is by causing the loss of bone at a faster rate than normal, as shown in the next figure (Example 2).

Some survivors may have both problems—a lower peak bone density and a faster rate of bone loss, which may lead to osteoporosis at a much younger age.



Example 1: Lower Peak Bone Density



Example 2: Increased Rate of Calcium Loss

Osteoporosis and Childhood Cancer Treatment

Survivors who received cancer treatment that included any of the following may be at increased risk for osteoporosis:

- Methotrexate.
- Steroids (glucocorticoids), such as prednisone and dexamethasone.
- Stem cell or bone marrow transplant, especially with associated chronic graft-versus-host disease.
- Treatments that result in premature (early) puberty.
- Treatments that result in ovarian or testicular failure, such as radiation therapy to the brain, radiation therapy to the testicles or ovaries, surgical removal of the testicles or ovaries, or high doses of alkylating chemotherapy (cyclophosphamide, ifosfamide, nitrogen mustard, melphalan, busulfan, BCNU, CCNU, and procarbazine).
- Treatments, such as radiation therapy to the brain, that result in growth hormone deficiency.
- Treatments, such as radiation therapy to the brain, neck, or chest that result in high levels of thyroid hormone (hyperthyroidism).
- Treatments that result in premature (early) menopause.
- Radiation to the bones.
- Prolonged periods of inactivity (bed rest).

What Lowers the Risk of Osteopososis?

Fortunately, there are many things you can do to reduce the risk of osteoporosis. If you could pick the one thing that would have the greatest impact on your life and lower your risk for a number of late effects and common adult health problems, it would be to make a lifetime habit of being physically active. Regular exercise, at least four times a week for about thirty minutes, makes a huge difference in the strength of bones.

Suggestions for exercise:

- Brisk walking is GREAT!
- Dancing, jazzercise and jogging are also excellent forms of exercise.
- If you are not active, begin slowly and build up each week.
- Exercise for short periods several times a day.
- Alternate the types of exercise to keep it fun.
- Find other ways to increase your activity level: Use the stairs rather than the elevator; When weather permits, park a few blocks from your destination and walk; Mow your own lawn; Take an exercise break at work or between classes.

Some people are limited to certain types of activity because of surgeries or other treatments for their cancer. If you have a problem with deciding how to best exercise or be active, discuss the options with your healthcare provider.

Most people do not have an adequate amount of calcium in their diet. The National Osteoporosis Foundation recommends that all adults have a daily dietary intake of 1000 to 1200 mg of calcium each day. Some healthcare providers recommend that survivors of childhood cancer get 1500 mg a day. The main sources of calcium in the diet are dairy products (milk, yogurt, cheese) and green, leafy vegetables.

Calcium in Foods

Food	Serving Size	Calcium
Milk	8 ounces	300 mg
Yogurt	8 ounces	400 mg
Cheese	1 ounce	200 mg
Broccoli	½ cup	47 mg
Pinto beans	½ cup	40 mg

If your diet is low in calcium and you are unable to consume 1200 to 1500 mg per day, then a calcium supplement pill is recommended. A wide variety of calcium supplements are available at the grocery or health food store.

Vitamin D is needed in order to absorb calcium. Skin makes this vitamin naturally when exposed to sunlight. Many dairy products also contain vitamin D. In general, you should not take more than 800 units of Vitamin D per day. Taking too much vitamin D can be harmful, so it's best to check with your healthcare provider before taking any vitamin D supplements.

Other important things that you can do to lower the risk for osteoporosis:

- Don't smoke, dip, or chew tobacco products (if you do now, quit!)
- Don't drink more than one alcoholic beverage per day (for example, 12 ounces of beer, 5 ounces of wine or 1.5 ounces of 80-proof distilled spirits)
- Avoid excessive intake of caffeinated products (such as coffee, cola, or tea)
- Avoid excessive consumption of carbonated soft drinks

What Follow-Up is Needed for Those at Risk?

Peak bone mass can be measured by a number of different methods. Dual energy x-ray absorptiometry (DEXA) is the most widely used technique. From this special x-ray of two or three sites (hip, wrist, low back), the bone density can be calculated. DEXA has a low radiation dose and is fairly precise and accurate. The bone mineral density is reported as a "T-score," which is a comparison to the peak bone mass of young adults in the general population. Osteopenia (low bone mass) is a T-score between –1.0 and –2.5 SD (standard deviations—a unit of variation), while osteoporosis is defined as a T-score of –2.5 SD or more.

A single test, such as a DEXA, evaluates bone mass only at one point in time and therefore does not tell you how rapidly bone loss is occurring. A follow-up DEXA, generally one or two years later, can show how the bone density is changing over time. After reviewing your treatment history and risk factors, your healthcare provider can advise you regarding the need for bone density testing. Generally, a baseline test is

done at age 18, but this can be done at an earlier age if needed, and the timing of the test is based on evaluation of each individual patient.

People who have osteopenia or osteoporosis should discuss treatment options with their healthcare provider. Medications, such as bisphosphonates and calcitonin, are available specifically for the treatment of low bone density. In addition, if you have low levels of male or female hormones, or low levels of growth hormone, you may also benefit from hormone replacement therapy.

Adapted by Wendy Landier, CPNP, March 2003, from: "Bone Health After Childhood Cancer" by Nancy Keene and Kevin Oeffinger MD, Candlelighters Quarterly, Spring 2002, with permission from Candlelighters Childhood Cancer Foundation (phone: 800-366-2223, internet: www.candlelighters.org), and "Strong Bones: A Foundation for Life", St. Jude Children's Research Hospital, After Completion of Therapy (ACT) Clinic, with permission.

Nancy Keene is co-author of *Childhood Cancer Survivors: A Practical Guide to Your Future* (O'Reilly & Associates, Sebastopol, CA, 2000)

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The Heart & Anthracyclines

Anthracyclines

Anthracyclines are a type of chemotherapy used to treat many childhood cancers. Included in the anthracycline group are doxorubicin (Adriamycin®), daunorubicin (daunomycin, Cerubidine®), idarubicin (Idamycin®), mitoxantrone (Novantrone®), and epirubicin. The use of anthracyclines has resulted in significant improvement in survival for children and adolescents with cancer, but it has also sometimes led to problems with the heart that may not become apparent until many years after treatment is completed. It is therefore important for each childhood cancer survivor who has received anthracyclines to continue to have regular medical check-ups so that if a problem with the heart develops, it can be detected and treated early.

The Heart

The heart is a large muscle that is divided into four chambers and is designed to pump blood throughout the body. The upper chambers are called “atria” and the lower chambers are called “ventricles.” The blood returning from the body enters the right atrium, is squeezed into the right ventricle, and then is pumped into the blood vessels in the lungs. It is here that the oxygen we breathe is transferred into the many small blood vessels in the lungs. The oxygen-rich blood returns to the left atrium and is then squeezed into the left ventricle, the largest and most powerful of the chambers. The left ventricle contracts to circulate the blood to the entire body.

The Problem

The cells of the heart muscle are called cardiomyocytes (cardio=heart, myo=muscle, cytes=cells). In ways that are not well understood, anthracyclines can damage the cardiomyocytes of the left ventricle. Over time, this can lead to thinning of the outside wall or muscle of the left ventricle, resulting in a stiff, noncompliant (loss of normal resiliency) left ventricle. The medical term for this condition is cardiomyopathy (cardio=heart, myo=muscle, pathy=abnormal, weakened).

Generally, this is not a problem while at rest, but when the heart needs to work harder, such as during exercise or strenuous physical activity, the stiff left ventricle may not be capable of increased pumping action. If this happens, the blood that is being pumped through the left side of the heart (atrium and ventricle) does not get pumped out fast enough and some of it “backlogs” in the small blood vessels of the lungs. Because the oxygen in the lungs is transferred to these small blood vessels, when the vessels become engorged with the backlogged blood, the oxygen cannot be transferred properly. Though this problem (called congestive heart failure) can be quite serious, there are medications that can help.

Who is at Risk?

Many childhood cancer survivors who received anthracyclines have no heart damage at all. Others may have mild changes in heart functioning, but no progressive weakening of the heart muscle. However, some survivors experience progressive weakening of the

heart muscle (cardiomyopathy), and may also develop congestive heart failure. Survivors treated with a total anthracycline dose of 300 mg/m^2 (milligrams per square meter of body surface area) or more when younger than 18 years of age, or 550 mg/m^2 or more when 18 years or older, are at highest risk. Other risk factors are:

- Female gender.
- African American race.
- Young age when treated. Anyone treated before the age of 5 years, and especially those treated as infants, are at increased risk.
- Treatment with both anthracyclines and radiation to the heart. The types of radiation that can damage the heart are chest/thorax, mantle, mediastinal, lung, total body, whole or upper abdominal, left abdominal, left flank, or higher dose (≥30 Gy) spinal radiation.
- High doses of cyclophosphamide (Cytoxan) given as conditioning for stem cell transplant
- Treatment with Amsacrine.

In addition, a history of congenital heart disease (heart problems present at birth), or a family history of heart disease may also increase the risk of heart problems after treatment for childhood cancer.

What are the symptoms of anthracycline-related heart problems?

Possible symptoms of congestive heart failure include:

- Increasing shortness of breath or difficulty breathing during exercise
- Shortness of breath when lying flat, especially at night
- Chest pain (generally a smothering-type sensation)
- Increasing fatigue
- Poor appetite
- Swelling of the feet or ankles
- Persistent cough (which may produce white or pink-tinged phlegm)
- Wheezing
- Rapid heartbeat (feeling of heart racing or throbbing)

These symptoms may be caused by a variety of other medical conditions, so it is very important to see your healthcare provider if you have any of these symptoms.

Is there anything that could worsen the weakened heart muscle or cause symptoms to occur?

Yes, the following things can potentially worsen a weakened heart:

Pregnancy: During pregnancy, the increased volume of blood can stress the heart. Thus, the first time a female survivor may develop symptoms of heart problems may be during pregnancy or labor. It is therefore very important that a physician knowledgeable about this late effect evaluate a pregnant survivor who has been treated with an anthracycline.

High fevers: High fevers can cause the heart to pump faster and can place extra strain on a weakened heart.

Cocaine, diet pills, ephedra, mahuang: Use of these drugs can cause life-threatening heart rhythm disturbances in a person whose heart has been weakened by an anthracycline.

Weight lifting/exercise: Isometric exercises, such as weight lifting, can cause a sudden worsening of heart function. Heavy weight lifting, or any vigorous isometric exercise (especially if associated with breath holding) can be dangerous if a survivor already has some weakening of the heart muscle. Limited high repetition weight lifting (using low weights to perform an exercise no more than 15 to 20 times in a row with ease) is much less stressful to the heart and is more likely to be safe. Aerobic exercise (brisk walking, running) is generally safe and actually healthy for the heart. However, survivors with any symptoms of heart weakening should check with their healthcare provider before beginning any exercise program.

What monitoring is required for potential heart problems?

Anyone who has received anthracycline chemotherapy to treat childhood cancer should have a yearly medical evaluation, which should include specific evaluation of any symptoms relating to the heart. In addition, an electrocardiogram (ECG, EKG) should be done at the time the survivor enters long-term follow-up (usually about 5 years from diagnosis or 2 years from completion of therapy). An echocardiogram or MUGA scan is also recommended at the first long-term follow-up visit, then according to the following schedule (or as recommended by your healthcare provider):

Age at treatment*	Chest radiation	Total anthracycline dose**	Recommended frequency of ECHO or MUGA
< 1 year	Yes	Any	Every year
	No	<200 mg/m^2	Every 2 years
	No	≥200 mg/m^2	Every year
1 to 4 years old	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
	No	≥100 to <300 mg/m^2	Every 2 years
	No	≥300 mg/m^2	Every year
≥5 years old	Yes	<300 mg/m^2	Every 2 years
	Yes	≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
	No	≥200 to <300 mg/m^2	Every 2 years
	No	≥300 mg/m^2	Every year

* treatment with anthracycline or chest radiation (whichever was given first)

** based on total doses of doxorubicin/daunorubicin or the equivalent doses of other anthracyclines

In addition, female survivors who are pregnant or planning pregnancy may also require evaluation by a cardiologist. Cardiac monitoring during pregnancy/delivery may be necessary due to the extra strain on the heart that pregnancy (and especially labor) can produce.

How are these tests done?

An **electrocardiogram** (ECG, EKG) is a test used to evaluate heart rate and rhythm. Electrodes (small sticky patches) are placed on the chest, arms, and legs. Wires are attached to the electrodes and the electrical impulses of the heart are then recorded.

An **echocardiogram** is an ultrasound of the heart that measures the thickness of the muscle of the left ventricle (main pumping chamber) and evaluates the pumping ability of the heart. The two primary measures are the ejection fraction and the shortening fraction. The ejection fraction is a ratio, calculated by measuring the amount of blood that is pumped out with each beat and dividing it by the amount of blood that waits for the next cycle. The normal value for the ejection fraction depends on sex and age, but is generally 55% or higher. The shortening fraction is also a ratio, determined by the diameter change of the left ventricle between the relaxation and the contraction phases divided by the diameter of the left ventricle in the relaxation phase. Generally a value of 30% or higher is considered normal. A decrease in the shortening fraction is usually seen before a decrease in the ejection fraction.

A technician, nurse, or doctor administers the echocardiogram. The survivor lies on a table and has conductive jelly applied to the chest. Then the technician puts a transducer (which emits the ultrasound waves) on the jelly and moves the device around on the chest to obtain different views of the heart. Slight pressure is applied on the transducer and can sometimes cause discomfort. The test results are displayed on videotape and photographed for later interpretation.

A **MUGA** (multiple-gated acquisition) scan is another way of testing the motion of the heart and how well it pumps blood to the body. During this test, a small amount of radioactive isotope is injected into a vein. The survivor then lies on a table and a special camera moves above the table to obtain pictures of the heart in motion. Electrodes are also placed on the chest to monitor the heart's electrical impulses during the test.

What happens if a problem with the heart is detected?

Your healthcare provider will advise you about the follow-up care you need. Sometimes, a referral to a cardiologist (heart specialist) is needed for additional evaluation and/or treatment with medications

What can be done to prevent heart problems?

With increasing age, the risk of other types of heart disease (such as heart attacks and hardening of the arteries) also increases. Factors that can increase the risk of heart problems include smoking, being overweight, eating a high fat diet, and not exercising.

Medical conditions that increase the risk include diabetes, high blood pressure, and high blood cholesterol. You can reduce your risk of heart problems by:

- Not smoking (or quitting if you currently smoke).
- Maintaining a healthy body weight.
- Limiting the fat in your diet to no more than 30% of calories.
- Exercising moderately for at least 30 minutes most days of the week.

If you have diabetes, high blood pressure, or high blood cholesterol, keep these under good control with diet or medication as recommended by your healthcare provider. Be sure to promptly report any symptoms of heart problems to your healthcare provider.

Adapted by Wendy Landier, CPNP, March 2003, from "Anthracyclines and the Heart" by Nancy Keene and Kevin Oeffinger MD, Candlelighters Quarterly, Autumn 2000, with permission from Candlelighters Childhood Cancer Foundation (phone: 800-366-2223, internet: www.candlelighters.org); and "Staying Healthy: Know Your Risk" by Melissa Hudson MD, Childhood Cancer Survivor Study Newsletter, Summer 2001, used with permission.

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The Heart & Radiation

Radiation therapy is often an important part of the treatment for many childhood cancers. The use of radiation has made a tremendous difference in treating cancer in children and adolescents, leading to improved survival rates. Unfortunately, radiation given in childhood also has the potential to cause problems with the heart many years after treatment. Therefore it is important for each childhood cancer survivor who has received radiation to the heart to continue to have regular medical check-ups so that if a problem with the heart develops, it can be detected and treated early.

The Heart

The heart is a large muscle that is divided into four chambers and is designed to pump blood throughout the body. The upper chambers are called “atria” and the lower chambers are called “ventricles”. The blood returning from the body enters the right atrium, is squeezed into the right ventricle, and then is pumped into the blood vessels in the lungs. It is here that the oxygen we breathe is transferred into the many small blood vessels in the lungs. Then the oxygen-rich blood returns to the left atrium and is then squeezed into the left ventricle, the largest and most powerful of the chambers. The left ventricle contracts to circulate the blood to the entire body.

Blood flow between the heart chambers is controlled by four valves: aortic, mitral, pulmonary, and tricuspid. Each valve opens as blood flows into its respective chamber and then closes as the chamber contracts and squeezes the blood out. On the outside of the heart is a network of blood vessels (coronary arteries) that carry oxygen and nutrients to the hard-working heart muscle.

The Problem with Radiation

Most survivors who received radiation do not develop heart problems. But sometimes radiation can damage the heart in one of several ways, including damage to the heart muscle, the valves, or the coronary arteries. Each of these problems is quite different, so let’s discuss them one at a time.

Damage to the heart muscle is called cardiomyopathy (cardio = heart, myo = muscle, pathy = abnormal, weakened). This term is used when the muscle does not work as well as it should. It generally affects the left ventricle more than the other parts of the heart, causing it to be stiff and less responsive to changes. Usually when someone is at rest the heart does not have to work hard. But when the heart needs to work harder, such as during pregnancy or strenuous physical activity, the stiff left ventricle may not be able to increase its pumping action. If this happens, the blood that is being pumped through the left side of the heart (atrium and ventricle) does not get pumped out fast enough and some of it “backlogs” in the small blood vessels of the lungs. The oxygen in the lungs is transferred to these small blood vessels, and so when the vessels become engorged with the backlogged blood, the oxygen cannot be transferred properly. Though this problem—called congestive heart failure—can be quite serious, there are medications that can help.

Radiation can also damage the valves in the heart, especially the two valves on the left side of the heart (mitral and aortic). If a valve is damaged, it can either become “leaky” so that blood flows backwards into the chamber it came from, or it can become “stiff” and not open very well, slowing the flow of blood. Problems with valves can cause the heart to work too hard, and lead to congestive heart failure and other heart problems.

A third problem that can be caused by radiation is premature coronary artery disease. The network of small blood vessels on the outside of the heart feeds the heart muscle with oxygen and nutrition. The interior of normal, healthy blood vessels is smooth. Radiation can roughen the inside of blood vessels, and these rough spots are sites where fatty deposits (plaques) may develop. Calcium deposits can harden the plaques, resulting in atherosclerosis (hardening of the arteries). Coronary artery disease (coronary = heart; artery = blood vessel) is when one or more of the blood vessels becomes clogged with plaque. It is similar to a clogged pipe that does not allow much liquid to flow through it. If this happens, the heart muscle cannot get enough oxygen and nutrition for all of its work. So when the heart needs to work harder and it cannot get enough oxygen or nutrition, a person may experience chest pain (angina), which will last a few minutes until the oxygen gets through the partially clogged artery. If the blood vessel is fully blocked, the part of the muscle that was depending upon the oxygen from that vessel dies (a heart attack). If it is a small blood vessel supplying a small amount of heart muscle, then the person has a small or minor heart attack. But if it is a larger vessel feeding a larger amount of heart muscle, the heart attack is serious and can be life-threatening.

Occasionally, other radiation-related problems affecting the heart can occur, including pericarditis (an inflammation of the thin membrane that surrounds the heart), pericardial fibrosis (scarring of the thin membrane that surrounds the heart) and arrhythmias (abnormal heart rhythms).

Who is at risk of radiation-related heart problems?

Children or teens who received radiation to the following areas (fields) may be at risk:

- Chest/thorax
- Mantle (from the chin to the upper abdomen)
- Mediastinal (central part of the chest)
- Lung
- Spine, if dose was 30 Gy (3000 cGy/rads) or higher
- Whole or upper abdomen
- Left abdomen or left flank
- Total body irradiation (TBI)

Whether the heart sustains injury after radiation treatment depends on several factors including:

- Total radiation dose — Survivors who received doses of 40 Gy (4000 cGy/rads) or more are highest risk.

- Amount and areas of the heart treated.
- Chemotherapy drugs used. Anthracyclines such as doxorubicin (Adriamycin), daunorubicin (daunomycin, Cerubidine), idarubicin (Idamycin), mitoxantrone (Novantrone), and epirubicin. Dactinomycin (Actinomycin-D) also can increase the risk

Modern radiation techniques using lower total doses and cardiac (subcarinal) shielding are less likely to cause damage.

Other factors that may also increase the risk of subsequent heart problems include:

- Young age when treated. Anyone treated before the age of 5 years, and especially those treated as infants are at increased risk.
- Family history of high blood cholesterol or coronary artery disease
- Smoking
- Obesity
- High blood pressure
- High blood cholesterol levels
- Diabetes
- Premature menopause (if not taking hormone replacement therapy)

What are the symptoms of a heart problem from radiation?

The signs and symptoms of radiation-induced heart damage vary widely. Possible symptoms of congestive heart failure (resulting from a weakened heart or valve problems) include:

- Increasing shortness of breath or difficulty breathing during exercise
- Shortness of breath when lying flat, especially at night
- Chest pain (generally a smothering-type sensation)
- Increasing fatigue
- Poor appetite
- Swelling of the feet or ankles
- Persistent cough (which may produce white or pink-tinged phlegm)
- Wheezing
- Rapid heartbeat (feeling of heart racing or throbbing)

These symptoms may be caused by a variety of other medical conditions, so it is very important to see your healthcare provider if you have any of these symptoms.

Possible symptoms of coronary artery disease (resulting from clogged blood vessels in the heart) include:

- Uncomfortable pressure, fullness, squeezing or pain in the center of the chest that lasts a few minutes, or goes away and comes back.

- Pain that spreads to the shoulders, neck or arms.
- Chest discomfort with lightheadedness, fainting, sweating, nausea or shortness of breath.

Possible symptoms of other heart problems (such as pericarditis or arrhythmia) include:

- Sharp piercing pain in the center or the left side of the chest (often worsens with a deep breath).
- Rapid heartbeat, palpitations, dizziness, fainting or near fainting.

These symptoms may indicate a serious heart problem and require immediate medical attention. It is important for the childhood cancer survivor to have regular check-ups, including tests of heart function, in order to catch problems early when they may be easier to correct.

Is there anything that could worsen weakened heart muscle or cause symptoms to occur?

Yes, the following things can potentially worsen a weakened heart:

Pregnancy: During pregnancy, the increased volume of blood can stress the heart. Thus, the first time a female survivor may develop symptoms of heart problems may be during pregnancy or labor. It is very important that a physician knowledgeable about this late effect evaluate any pregnant survivor who received:

- Total body irradiation (TBI).
- Chest radiation at a dose of 30 Gy (3000 rads/cGy) or higher.
- Any dose of chest radiation if the survivor also received anthracycline chemotherapy.

High fevers: High fevers can cause the heart to pump faster and can place extra strain on a weakened heart.

Cocaine, diet pills, ephedra, mahuang: Use of these drugs can cause life-threatening rhythm disturbances in a person whose heart has been weakened by chest radiation.

Weight lifting/exercise: Isometric exercises, such as weight lifting, can cause sudden worsening of heart function. Heavy weight lifting, or any vigorous isometric exercise (especially if associated with breath holding) may be dangerous if a survivor already has some weakening of the heart muscle. Limited high repetition weight lifting (using low weights to perform an exercise no more than 15 to 20 times in a row with ease) is less stressful to the heart and more likely to be safe. Aerobic exercise (brisk walking, running) is generally safe and actually healthy for the heart. However, survivors with any symptoms of heart weakening or heart disease should check with their healthcare provider before beginning any exercise program.

What monitoring is required for potential heart problems?

Anyone who has received radiation during treatment for childhood cancer should have a yearly medical evaluation (which should include specific evaluation of any symptoms relating to the heart). In addition, an electrocardiogram (ECG, EKG) should be done at the time of entry into long-term follow-up (usually about 5 years from diagnosis or 2 years after completion of therapy), and then as recommended by your healthcare provider. A blood test to check for diabetes and high cholesterol levels (fasting glucose and lipid profile) should be done every 3 to 5 years. An echocardiogram or MUGA scan is also recommended at the first long-term follow-up visit, then according to the following schedule (or as recommended by your healthcare provider):

Age at treatment*	**Chest radiation dose**	**Total anthracycline dose****	**Recommended frequency of ECHO or MUGA**
<1 to 4 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
	Any	≥300 mg/m^2	Every year

* treatment with anthracycline or chest radiation (whichever was given first)

** based on total doses of doxorubicin/daunorubicin or the equivalent doses of other anthracyclines

Childhood cancer survivors who received a radiation dose of 40 Gy (4000 cGy/rads) or higher to fields involving the heart (as listed above) should also see a cardiologist (heart specialist) for baseline cardiac stress testing 5 to 10 years after the radiation was given.

In addition, female survivors who are pregnant or planning pregnancy may also require evaluation by a cardiologist. Cardiac monitoring during pregnancy/delivery may be necessary due to the extra strain on the heart that pregnancy (and especially labor) can produce.

How are these tests done?

An **electrocardiogram** (ECG, EKG) is a test used to evaluate heart rate and rhythm. Electrodes (small sticky patches) are placed on the chest, arms, and legs. Wires are attached to the electrodes and the electrical impulses of the heart are then recorded.

An **echocardiogram** is an ultrasound of the heart that measures the thickness of the muscle of the left ventricle (main pumping chamber) and evaluates the pumping ability of the heart. The two primary measures are the ejection fraction and the shortening fraction. The ejection fraction is a ratio, calculated by measuring the amount of blood that is pumped out with each beat and dividing it by the amount of blood that waits for the next cycle. The normal value for the ejection fraction depends on sex and age, but is

generally 55% or higher. The shortening fraction is also a ratio, determined by the diameter change of the left ventricle between the relaxation and the contraction phases divided by the diameter of the left ventricle in the relaxation phase. Generally a value of 30% or higher is considered normal. A decrease in the shortening fraction is usually seen before a decrease in the ejection fraction.

A technician, nurse, or doctor administers the echocardiogram. The survivor lies on a table and has conductive jelly applied to the chest. Then the technician puts a transducer (which emits the ultrasound waves) on the jelly and moves the device around on the chest to obtain different views of the heart. Slight pressure is applied on the transducer and can sometimes cause discomfort. The test results are displayed on videotape and photographed for later interpretation.

A **MUGA** (multiple-gated acquisition) scan is another way of testing the motion of the heart and how well it pumps blood to the body. During this test, a small amount of radioactive isotope is injected into a vein. The survivor then lies on a table and a special camera moves above the table to obtain pictures of the heart in motion. Electrodes are also placed on the chest to monitor the heart's electrical impulses during the test.

What happens if a problem with the heart is detected?

Your healthcare provider will advise you about the follow-up care you need. Sometimes, a referral to a cardiologist is needed for additional evaluation and/or treatment with medications

What can be done to prevent heart problems?

With increasing age, the risk of other types of heart disease (such as heart attacks and hardening of the arteries) also increases. Factors that can increase the risk of heart problems include smoking, being overweight, eating a high fat diet, and not exercising. Medical conditions that increase the risk include diabetes, high blood pressure, and high blood cholesterol. You can reduce your risk of heart problems by:

- Not smoking or quitting if you currently smoke.
- Maintaining a healthy body weight.
- Limiting the fat in your diet to no more than 30% of calories.
- Exercising moderately for at least 30 minutes most days of the week.

If you have diabetes, high blood pressure, or high blood cholesterol, keep these under good control with diet or medication as recommended by your healthcare provider. Be sure to promptly report any symptoms of heart problems to your healthcare provider.

Adapted by Wendy Landier, CPNP, March 2003, from "Radiation and the Heart" by Nancy Keene and Kevin Oeffinger MD, Candlelighters Quarterly, Winter 2000, with permission from Candlelighters Childhood Cancer Foundation (phone: 800-366-2223, internet: www.candlelighters.org); and "Staying Healthy: Know Your Risk" by Melissa Hudson MD, Childhood Cancer Survivor Study Newsletter, Summer 2001, used with permission.

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School and Learning Issues After Childhood Cancer: Information for Parents and Teachers

As treatment for childhood cancer has improved, more and more children are becoming long-term survivors. Often, treatment received for childhood cancer includes therapy to control or prevent spread of the disease to the brain and/or spinal cord (central nervous system). Although very effective for treatment of cancer, chemotherapy, radiation, or surgery to the brain sometimes causes problems with thinking, remembering, and learning. These types of problems are called "cognitive late effects." Very young children (less than 5 and particularly less than 2 years old at the time of treatment), whose brains are growing and developing, are more at risk than older children or teens. Each child is unique, and many will not have any cognitive late effects. However, it is wise for parents and teachers to be aware of the potential for these problems, so that children and teens at risk can be monitored closely and provided with extra help if the need arises.

What learning problems are associated with childhood cancer treatment?

The brain is a very complex structure that continues to grow and develop throughout childhood and adolescence. Although problems are occasionally evident right away (such as after brain surgery or high doses of brain radiation), many problems do not become apparent until years after therapy is completed.

Signs of common learning problems include trouble with:

- Handwriting (ability to write quickly and accurately).
- Spelling.
- Reading (particularly reading comprehension).
- Understanding math concepts, remembering math facts, comprehending math symbols, sequencing, and working with columns and graphs
- Difficulty in using calculators or computers.
- Auditory or visual language processing (trouble with vocabulary, blending sounds, and syntax).
- Concentration or attention span ("spacing out"). Some children become either inattentive or hyperactive or both.
- Slow processing speed (taking longer to comprehend and respond to new information), including trouble keeping pace with new material and trouble completing tasks within allotted time.
- Memory, especially problems with short-term memory, storage of new information, and information retrieval (such as trouble following multi-part instructions).
- Planning and organizational skills (sequencing).
- Coordination of visual and motor abilities (such as problems remembering and copying shapes).
- Social maturity and social skills (such as problems detecting social cues).
- Problem-solving (particularly when the problem has not been previously encountered).

These late effects can cause changes in learning style as well as social behavior. Some children and teens will have an overall decline in intellectual ability (IQ) over time, but many survivors do not. Significant declines in IQ scores are usually associated with high radiation doses, such as those given for brain tumors, especially when given to a very young child.

For children with brain tumors, the tumor location also influences the type and severity of learning disabilities that may develop. For example, children with temporal lobe tumors may have problems with memory. Surgery to the brain can also cause many late effects, and can vary in severity depending on the part of the brain that was operated on, the amount of healthy tissue removed, and complications occurring after surgery. Learning may also be affected by hydrocephalus, vision problems, hearing problems, and by medications used to treat seizures.

Cognitive late effects can affect survivors' education, social life, relationships, and job performance. The effect on individual children is quite variable. Some children have no late effects, and some develop very subtle disabilities, while others develop life-altering problems.

What testing is recommended?

Any child who has had any of the following treatment(s) for childhood cancer should undergo a formal neuropsychological evaluation by a pediatric psychologist at entry into long-term follow-up:

- **Methotrexate**. High-dose intravenous (IV) or intrathecal (IT)
- **Cytarabine**. High-dose intravenous (IV)
- **Neurosurgery.** Surgery involving the brain or spinal cord
- **Radiation to the head/brain, including any of the following areas (fields):**
  - Total body irradiation (TBI)
  - Cranial (whole brain)
  - Craniospinal
  - Nasopharyngeal
  - Oropharyngeal
  - Orbital
  - Eye
  - Ear
  - Infratemporal (mid-facial area behind the cheekbones)

These tests usually take four to six hours, and can be done over two days for younger children or those who fatigue easily. The psychologist gives a series of general tests appropriate for age level, then another series of more and more specific subtests based on the results of the general ones. Pediatric psychologists usually make the testing fun for children. Parent(s) are usually interviewed separately. Neuropsychological tests are very different from tests that measure educational level. If problems are identified, referrals for appropriate educational interventions can then be initiated.

Even if the baseline neuropsychological evaluation is normal and the child is having no learning problems, it is important for parents and teachers to remain vigilant. Further neuropsychological evaluations may be indicated if:

- The child begins experiencing any of the learning problems listed earlier
- The child's school performance is declining
- It takes much longer than usual for the child to complete assignments
- The child is becoming frustrated with school

It is sometimes difficult to recognize the need for evaluation because children affected by radiation and/or chemotherapy can often think clearly and reason well and they may be above average academically in several areas. They may fall behind their classmates, however, on tasks that rely on processing skills, short-term memory, sequential operations, and organizational ability (especially visual). If a learning problem is identified, special accommodations or services can be requested to help maximize the child's learning potential. Many children with learning problems do extremely well in school with appropriate accommodations.

What can be done to help with learning problems?

The first step is usually to schedule a meeting with the child's school in order to develop a plan. An Individualized Educational Plan (IEP) will probably be needed (see further information about this below). Examples of strategies that are often helpful for children with learning problems related to cancer treatment include:

- Seating near the front of the classroom to diminish distraction.
- Minimizing the amount of written work required. Children with learning difficulties are often better able to demonstrate their knowledge verbally rather than in written form.
- Use of tape-recorded (audio) textbooks.
- Tape-recording classroom lectures instead of taking notes.
- Use of a computer keyboard instead of handwriting.
- Use of a calculator for math.
- Modification of test requirements, including extending or eliminating time limits and avoiding computerized answer sheets (such as "scan sheets" or "bubbles").
- Assignment of a classroom aide.
- Extra help with math, spelling, reading, and organizational skills.

Legal rights related to appropriate public education (in the United States)

In the United States, three public laws protect rights of people with disabilities, including learning problems related to cancer treatment. These laws are:

The Americans with Disabilities Act (ADA)
This law protects against discrimination in employment, transportation, communication, government and public accommodations for people with disabilities. Children who have had cancer are protected from discrimination under this law.

The Individuals with Disabilities Education Act (IDEA)
IDEA requires that every public school must provide free and appropriate education in the least restrictive environment to all eligible individuals between the ages of 3 and 21 years. This means that for children who qualify, the school must provide (free of charge) special education programs, speech therapy, occupational therapy, physical therapy, psychological services, augmentative communication techniques and technology, and other interventions as needed to help the child learn. The major provisions of these laws are as follows:

- All children, regardless of disability, are entitled to a free and appropriate public education and necessary related services. Schools are required to provide an individually designed instructional program for every eligible child, including early intervention programs for at-risk infants and toddlers.
- Children will receive fair testing to determine if they need special education services.
- Parents of children with disabilities may participate in the planning and decision-making for their child's special education.
- Children with disabilities will be educated in the least restrictive environment, usually with children who are not disabled.
- Parents have the right to challenge the decisions of the school system, with disputes being resolved by an impartial third party.

See http://www.ed.gov/offices/OSERS/IDEA/ for the full text of the IDEA act, with related information and updates.

The Rehabilitation Act ("Section 504")
Childhood cancer survivors may also be eligible for services and accommodations under Section 504 of the federal Rehabilitation Act. This law applies when the child does not meet the eligibility requirements for specially designed instruction, but still needs accommodations to perform successfully in school. For example, special accommodations to address health needs can include a water bottle on the desk, additional time to get to class, more time to finish written assignments, or elimination of timed test requirements.

These laws cover survivors of cancer whose medical problems affect their educational performance, under the categories known as "other health impaired" (OHI), "traumatically brain injured," or "learning disabled." Special education services are also available for children with visual or hearing impairments or if the child's medical condition limits energy, alertness, or strength. Many survivors do not need special help in school, but those who do have a legal right to it.

If special educational services are needed, how can they be obtained?

Several steps are necessary in order to obtain specialized educational services: The steps needed are: (1) referral, (2) evaluation, (3) eligibility, (4) developing an individualized education plan (IEP) and (5) annual review.

Referral: Parents, teachers, or healthcare providers can make a referral by writing to the school principal to request special education testing. The request should state that the child is "health impaired" due to treatment for cancer,

provide an outline of relevant problems, and request assessments and an IEP meeting.

Evaluation: Once the referral is made, an evaluation is necessary to determine if the child needs additional help, and if so, what types of help would be most beneficial. Neuropsychological testing (if not yet performed) should be done at this time.

Eligibility: After the evaluation, a conference is held to discuss the results and reach conclusions about what actions will be necessary in the future.

Individualized Education Plan (IEP): This is a written document describing the special education program and any other related services specifically designed to meet the individual needs of the child identified with learning problems. Parents and professional educators develop it together. Any specific accommodations needed by the child should be included.

Annual Review: The written IEP plan should be reviewed and updated annually to assure that it continues to meet the child's educational needs.

Early intervention services for preschoolers

Federal law also mandates early intervention services for disabled infants and toddlers, and in some cases, children at risk of having developmental delays. Infants, toddlers, or preschoolers with cancer may be eligible for these services in order to avoid developmental delays caused by cancer treatments. These services are administered either by the school system or the state health department. You can find out which agency to contact by asking the hospital social worker or by calling the special education director for your school district. The law requires services not only for the infants or preschoolers, but for the family as well. Therefore, instead of an IEP, an Individualized Family Service Plan (IFSP) is developed.

Services for older students

Transition planning (for college or job training) should begin in the early years of middle school, when the student's peers are beginning to gain work skills and amass credits toward high school graduation. For some survivors, extra support will be needed to help make the transition from high school to adulthood go smoothly. The written transition plan is contained in the Individual Transition Plan (ITP). Students planning to attend trade school, a two-year community college program, or a four-year college program need information far in advance regarding which high school courses will be required for entry. This is especially important for those students with disabilities who carry a lighter course load, as they may need to make up some credits in summer school or via correspondence courses.

Transition programs should address the move from high school to trade school, community college, or a four-year college program. Students are eligible for publicly funded education and/or services until age 22 if needed. Tuition in some programs may be covered for some students, in full or in part. Special education services and help for students with learning disabilities are available on campus and in the dormitories at many colleges.

Additional information from the National Information Center for Children and Youth with Disabilities (phone: 1-800-695-0285, website: www.nichcy.org).

Adapted by Wendy Landier, CPNP, March 2003, from "Cognitive Late Effects in Leukemia Survivors" by Nancy Keene and Kevin Oeffinger MD, Candlelighters Quarterly, Summer 2001, and "Cognitive Late Effects to the Brain, Part II", by Nancy Keene and Kevin Oeffinger MD, Candlelighters Quarterly, Fall 2001, with permission from Candlelighters Childhood Cancer Foundation (phone: 800-366-2223, internet: www.candlelighters.org.)

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Thyroid Problems After Childhood Cancer

Treatment for childhood cancer sometimes damages the thyroid gland. Fortunately, late effects to the thyroid gland are usually very easy to treat. It is therefore important to find out if you are at risk so that problems can be identified early and treated appropriately.

What is the thyroid gland?

The thyroid is a small butterfly-shaped gland located in front of the trachea (windpipe) in the lower part of the neck. It is a very sensitive gland that enlarges and becomes more active during puberty, pregnancy, or times of great stress. It also alters its size and shape during women's menstrual cycles.

Some glands produce chemical messengers, called "hormones," that travel throughout the body to coordinate complicated processes such as growth, puberty, and reaction to stress. Disruptions in the balance of these chemical messengers can profoundly affect both health and quality of life.

Two hormones secreted by the thyroid gland, thyroxine (T4) and triiodothyronine (T3), have far-reaching effects on almost all tissues in the body and are intimately involved in physical growth, metabolism, and mental development. Basically, the thyroid hormones, T3 and T4, can be thought of as regulators of metabolism. Thus, when the thyroid hormones are low, the body's metabolism slows, resulting in fatigue, a lowered heart rate and blood pressure, slowing of the intestines (leading to constipation), and a constant feeling of being cold. On the other hand, when one or both of the thyroid hormone levels is high, the body's metabolism is increased, resulting in an increased heart rate and blood pressure, increased activity of the intestines (leading to diarrhea), and a constant feeling of being hot.

The pituitary, a gland in the brain, makes a chemical called thyroid-stimulating hormone (TSH), which travels in the bloodstream to the thyroid. As you might guess from the name, thyroid-stimulating hormone stimulates the thyroid gland to make the thyroid hormones T3 and T4. When levels of T3 and T4 are low, then the brain increases the production of TSH, which in turn stimulates the thyroid gland to produce more T3 and T4. Conversely, if the level of either T3 or T4 is too high, the brain senses this and decreases the production of TSH, which leads to less production of T3 and T4.

The possible late effects

Damage to the thyroid gland resulting from childhood cancer therapy is usually the result of radiation to the brain or neck. Several different types of thyroid problems can develop.

Primary hypothyroidism. (primary = damage to the thyroid gland; hypo = low; thyroidism = disease of the thyroid). In this type of hypothyroidism, the TSH is elevated in response to low levels of thyroid hormone (T3 and T4), resulting from direct damage to the thyroid gland.

Central hypothyroidism. (central = damage in the pituitary gland/brain). In this type of hypothyroidism, both the TSH and T4 levels are low due to damage to the thyroid's control center (pituitary gland) in the brain.

Compensated hypothyroidism. This occurs when the thyroid is working too hard trying to maintain the correct hormone levels. There are usually no symptoms, but blood tests show normal T4 with slightly elevated TSH levels. An over-stimulated thyroid gland is at increased risk for developing tumors, both benign and malignant. Survivors with compensated hypothyroidism are sometimes given supplemental thyroid hormone to allow the gland to rest.

Hyperthyroidism. (hyper = high) This occurs when too much T3 or T4 is produced, causing the body to use energy faster than it should.

Thyroid nodules and thyroid cancer. Radiation to the neck can cause abnormal growths (nodules) or cancer of the thyroid gland.

What are the symptoms of thyroid damage?

Signs and symptoms of an under active thyroid (hypothyroidism) can include:

- Fatigue or lethargy
- Hoarseness
- Difficulty concentrating
- Depression or mood changes
- Constipation
- Weakness
- Intolerance to cold
- Swelling around the eyes
- Poor growth
- Delayed puberty
- Puffy face and hands
- Weight gain
- Dry or rough skin
- Brittle hair
- Joint or muscle aches
- Slow heart rate
- Low blood pressure
- High cholesterol
- Decreased tolerance for exercise

Signs and symptoms of an overactive thyroid (hyperthyroidism) can include:

- Nervousness or anxiety
- Difficulty concentrating
- Fatigue
- Muscle weakness or tremor
- Rapid or irregular heartbeat

- Excessive perspiration
- Heat intolerance
- Diarrhea
- Weight loss
- Menstrual irregularities
- Protruding eyes
- Tenderness in the neck
- Decreased tolerance for exercise

Thyroid cancer is generally a slow-growing cancer with few signs or symptoms. Usually, a painless, hard mass (lump) in the thyroid gland can be felt. One might also experience hoarseness, problems with swallowing, enlarged lymph nodes in the neck and difficulty breathing.

Who is at risk?

People who received radiation that may have affected the thyroid gland directly are at risk for primary hypothyroidism, compensated hypothyroidism, hyperthyroidism, thyroid nodules, and/or thyroid cancer. The following radiation fields have the potential to impact the thyroid gland directly:

- Neck (cervical or mantle)
- Head/brain (cranial)
- Spine
- Nose, mouth, and/or throat (nasopharyngeal, oropharyngeal)
- Chest (mediastinal, whole lung)
- Total body irradiation (TBI)

People who received radiation that may have affected the pituitary gland in the brain are at risk for central hypothyroidism. The following radiation fields have the potential to impact the pituitary gland:

- Head/brain (cranial)
- Eye/orbit
- Ear/infratemporal region (midfacial area behind the cheekbones)
- Nose, mouth, and/or throat (nasopharyngeal, oropharyngeal)
- Total body irradiation (TBI)

Female gender, higher radiation dose, and treatment at a young age also increase the likelihood of developing a thyroid problem after childhood cancer treatment. Thyroid dysfunction can occur soon after radiation, but generally does not occur until several years later. If treated promptly, thyroid problems are easily managed.

What follow up is needed for those at risk?

TSH and Free T4 levels should be checked (by blood test) every year and any time symptoms develop. During yearly follow-up visits, the thyroid gland should be palpated (felt by hand) and growth for children and teens should be plotted on a growth chart. During periods of rapid growth, healthcare providers may recommend more frequent

monitoring of thyroid levels. Thyroid problems can occur years or decades after cancer treatment, so a yearly check is necessary for the rest of your life if you are at risk.

Female survivors at risk for thyroid problems who are planning to become pregnant should have their thyroid levels checked before attempting pregnancy. It is important to do this before becoming pregnant, because mothers with thyroid disease have a higher chance of having babies with neurological defects. It is also important to monitor thyroid levels periodically during pregnancy.

How is damage to the thyroid treated?

Treatment for thyroid problems is generally easy and effective. If problems with thyroid levels are identified, you may be referred to an endocrinologist (hormone specialist) for continuing treatment. If a lump is detected on the thyroid, you may be referred to a surgeon or other specialist for evaluation and management.

Primary hypothyroidism (high TSH, low or normal T4): Daily treatment with synthetic thyroid hormone (levothyroxine) in pill form is required. Treatment is for life. Stopping the medication will result in a recurrence of the symptoms of hypothyroidism.

Compensated hypothyroidism (mildly elevated TSH, normal T4): Daily treatment with levothyroxine (pills) may be used to suppress an overactive gland.

Central hypothyroidism (low TSH, low T4): Daily treatment with levothyroxine.

Hyperthyroidism (low TSH, high T3 or T4): The overproduction of the thyroid hormones, T3 or T4, can cause life-threatening changes to the body, so more aggressive therapies are required to make the thyroid produce less thyroid hormone, or to completely stop thyroid hormone production. There are three options to treat hyperthyroidism:

- Medication that prevents thyroid hormone production (generally only a temporary treatment).
- Surgery to remove most of the gland.
- Thyroid ablation (destroying the hormone-producing cells in the gland by drinking a radioactive liquid called I-131).

The goal of treatment for hyperthyroidism is to make the patient either euthyroid (normal thyroid level) or hypothyroid (low thyroid level), which can then be treated with a daily pill of levothyroxine.

Thyroid nodules: People with nodules detected by palpation need additional testing. This is generally done with an ultrasound (picture made using sound-waves) and biopsy (sampling the thyroid tissue to check for cancer cells).

Thyroid cancer: Thyroid cancer is usually very treatable. Depending upon the type and stage of thyroid cancer, treatment generally includes surgery to remove almost all of the

gland followed by thyroid gland ablation (destroying any remaining thyroid tissue by drinking a radioactive liquid called I-131). The person then takes daily levothyroxine pills and gets periodic check ups.

Thyroid problems are common in childhood cancer survivors who had head or neck radiation. However, treatment is generally easy and effective. Be sure to discuss your thyroid gland with your healthcare provider at your yearly follow-up visits.

Adapted by Wendy Landier, CPNP, March 2003, from "Late Effects to the Thyroid Gland" by Nancy Keene and Kevin Oeffinger MD, Candlelighters Quarterly, Spring 2001, with permission from Candlelighters Childhood Cancer Foundation (phone: 800-366-2223, internet: www.candlelighters.org).

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PRECAUTIONS FOR PEOPLE WITH SINGLE KIDNEY

- To avoid injury to the remaining kidney, it is best NOT to participate in martial arts and boxing. (If you insist on participating in these sports, USE A KIDNEY GUARD).
- USE A KIDNEY GUARD for other sports such as football, soccer, baseball, basketball, etc.
- DRINK PLENTY OF WATER, WATER, WATER, especially when playing sports, while out in the sun, and during hot weather.
- CALL THE DOCTOR IMMEDIATELY if you have symptoms of a possible urinary tract infection (burning when you urinate, having to urinate more frequently than usual, having the sensation when you have to urinate that you need to urinate immediately—you cannot "wait" or "hold it").
- **DO NOT TAKE** ANY NEW MEDICINES (prescription, over-the-counter, or herbal) WITHOUT CHECKING WITH YOUR DOCTOR AND/OR PHARMACIST—and make sure they know that you only have one kidney.
- **DO NOT TAKE** any non-steroidal anti-inflammatory drugs, (for example, **ASPIRIN, BUFFERIN, ASCRIPTIN, IBUPROFEN, ADVIL, MOTRIN, ALEVE, NAPROXEN, NUPRIN),** unless your doctor advises you to.
- Remind all healthcare providers that you had a nephrectomy (kidney removal) and the reason why.
- Have a health checkup at least once a year that includes a blood pressure measurement, a urine test for protein, and a blood test measuring kidney function.