Children's Oncology Group

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancer

Version 4.0 – October 2013

www.survivorshipguidelines.org

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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Contents

Contents (cont)

Contents (cont)

Contents (cont)

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COG Long-Term Follow-Up Guidelines Content Outline

Suggested Citations for COG Long-Term Follow-Up Guidelines

Guidelines

Children's Oncology Group. *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, Version 4.0*. Monrovia, CA: Children's Oncology Group; October 2013; Available on-line: ***www.survivorshipguidelines.org***.

Guidelines Methodology

Landier W, Bhatia S, Eshelman DA, Forte KJ, Sweeney T, Hester AL, Darling J, Armstrong FD, Blatt J, Constine LS, Freeman CR, Friedman DL, Green DM, Marina N, Meadows AT, Neglia JP, Oeffinger KC, Robison LL, Ruccione KS, Sklar CA, Hudson MM. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol* 2004; 22(24):4979-90.

Health Links Background and Application

Eshelman D, Landier W, Sweeney T, Hester AL, Forte K, Darling J & Hudson MM. Facilitating care for childhood cancer survivors: integrating Children's Oncology Group long-term follow-up guidelines and health links in clinical practice. *J Pediatr Oncol Nurs* 2004; 21(5): 271-280.

Abstract – Version 4.0
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Release date: October 2013

Status: Updated from Version 3.0 incorporating modifications based on recommendations from the Children's Oncology Group's Long- Term Follow-Up Guideline Core Committee and its ten associated multidisciplinary Task Forces.

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

Source: Version 4.0 of the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, and related Health Links*, can be downloaded in their entirety from ***www.survivorshipguidelines.org***.

Disclaimer and Notice of Proprietary Rights

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

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

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>
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for his in-depth expert review and extensive contributions to all radiation-related sections in all versions of the COG LTFU Guidelines

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Introductory Material

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Introduction – Version 4.0
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Overview	The Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (COG-LTFU Guidelines) are risk-based, exposure-related clinical practice guidelines for screening and management of late effects resulting from therapeutic exposures used during treatment for pediatric malignancies. These guidelines represent a statement of consensus from a panel of experts in the late effects of pediatric cancer treatment. The guidelines are both evidence-based (utilizing established associations between therapeutic exposures and late effects to identify high-risk categories) and grounded in the collective clinical experience of experts (matching the magnitude of the risk with the intensity of the screening recommendations). Since therapeutic interventions for a specific pediatric malignancy may vary considerably based on the patient's age, presenting features, and treatment era, a therapy-based design was chosen to permit modular formatting of the guidelines by therapeutic exposure. Importantly, the recommended periodic screening underscores the use of a thorough history and physical examination (H&P) as the primary assessment for cancer-related treatment effects. In this regard, 101 (74%) of the screening recommendations outlined for the 156 therapeutic exposures in the COG-LTFU Guidelines comprise assessments derived primarily from the H&P, with 80 (51%) relying solely on the H&P and 31 (20%) relying on the H&P plus a baseline diagnostic study (e.g., lab, imaging), whereas 41 (26%) include periodic laboratory, diagnostic imaging, or other testing, and 4 (3%) recommend no screening (agents with no known late effects). Interventions exceeding minimal screening are provided for consideration in individuals with positive screening tests. Medical citations supporting the association of each late effect with a specific therapeutic exposure are included. Patient education materials complementing the guidelines have been organized into Health Links that feature health protective counseling on 43 topics, enhancing patient follow-up visits and broadening application of the guidelines. Additional accompanying materials include detailed instructions, templates for cancer treatment summary forms, a radiation reference guide, and a tool to assist in identifying guideline applicability for individual patients based on therapeutic exposures.
Goal	Implementation of these guidelines is intended to increase quality of life and decrease complication-related healthcare costs for pediatric cancer survivors by providing standardized and enhanced follow-up care throughout the lifespan that (a) promotes healthy lifestyles, (b) provides for ongoing monitoring of health status, (c) facilitates early identification of late effects, and (d) provides timely intervention for late effects.
Target Population	The recommendations for periodic screening evaluations provided in the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* are appropriate for asymptomatic survivors of childhood, adolescent, or young adult cancers who present for routine exposure-related medical follow-up. More extensive evaluations are presumed, as clinically indicated, for survivors presenting with signs and symptoms suggesting illness or organ dysfunction.
Focus	These guidelines are intended for use ***beginning two or more years following the completion of cancer therapy***, and provide a framework for ongoing late effects monitoring in childhood cancer survivors; ***however, these guidelines are not intended to provide guidance for follow-up of the pediatric cancer survivor's primary disease***.

Introduction (cont)

Intended Users	The COG-LTFU Guidelines were developed as a resource for clinicians who provide ongoing healthcare to survivors of pediatric malignancies. The information within these guidelines is important for clinicians (e.g., physicians, nurse practitioners, physician assistants, nurses) in the fields of pediatrics, oncology, internal medicine, family practice, and gynecology, as well as subspecialists in many fields (e.g., endocrinology, cardiology, pulmonology). A basic knowledge of ongoing issues related to the long-term follow-up needs of this patient population is assumed. Healthcare professionals who do not regularly care for survivors of pediatric malignancies are encouraged to consult with a pediatric oncology long-term follow-up center if any questions or concerns arise when reviewing or using these guidelines. Although the information within the guidelines will certainly prove valuable to the survivors themselves, at this time the only version available is targeted to healthcare professionals. Therefore, survivors who choose to review these guidelines are strongly encouraged to do so with the assistance of a healthcare professional knowledgeable about long-term follow-up care for survivors of childhood, adolescent, and young adult cancers. This is important in order to put the recommendations in perspective, avoid over-testing, address potential anxieties, and provide a comprehensive evaluation of the survivor's health status. The Children's Oncology Group itself does not provide individualized treatment advice to patients or their families, and strongly recommends discussing this information with a qualified medical professional.
Developer	The COG-LTFU Guidelines were developed as a collaborative effort of the Children's Oncology Group Nursing Discipline and Late Effects Committee and are maintained and updated by the Children's Oncology Group's Long-Term Follow-Up Guidelines Core Committee and its associated Task Forces. All Children's Oncology Group members have complied with the COG conflict of interest policy, which requires disclosure of any potential financial or other conflicting interests.
Funding Source	This work was supported by the Children's Oncology Group Chair's Grant U10 CA098543 from the National Cancer Institute.
Evidence Collection	Pertinent information from the published medical literature over the past 20 years (updated as of October 2013) was retrieved and reviewed during the development and updating of these guidelines. For each therapeutic exposure, a complete search was performed via MEDLINE (National Library of Medicine, Bethesda, MD). Keywords included "childhood cancer therapy," "complications," and "late effects," combined with keywords for each therapeutic exposure. References from the bibliographies of selected articles were used to broaden the search.

Introduction (cont)

Methods	In 2002, the leadership of the Children's Oncology Group Late Effects Committee and Nursing Discipline appointed a 7-member task force, with representation from the Late Effects Committee, Nursing Discipline, and Patient Advocacy Committee. The task force was convened to review and summarize the medical literature and develop a draft of clinical practice guidelines to direct long-term follow-up care for pediatric cancer survivors. The task force followed a modified version of the guideline development process established by the National Comprehensive Cancer Network (NCCN), integrating available literature with expert opinion using reiterative feedback loops. The original draft went through several iterations within the task force prior to initial review. Multidisciplinary experts in the field, including nurses, physicians (pediatric oncologists and other subspecialists), patient advocates, behavioral specialists, and other healthcare professionals, were then recruited by the task force to provide an extensive, targeted review of the draft, including focused review of selected guideline sections. Revisions were made based on these recommendations. The revised draft was then sent out to additional multidisciplinary experts for further review. A total of 62 individuals participated in the review process. The guidelines subsequently underwent comprehensive review and scoring by a panel of experts in the late effects of pediatric malignancies, comprised of multidisciplinary representatives from the COG Late Effects Committee. In a parallel effort led by the Nursing Clinical Practice Subcommittee, complementary patient education materials (Health Links) were developed. Each Health Link underwent two levels of review; first by the Nursing Clinical Practice Subcommittee to verify accuracy of content and recommendations, and then by members of the Late Effects Committee (to provide expert medical review) and Patient Advocacy Committee (to provide feedback regarding presentation of content to the lay public).
Grading Criteria	The guidelines were scored by the multidisciplinary panel of experts using a modified version of the National Comprehensive Cancer Network "Categories of Consensus" system. Each score reflects the expert panel's assessment of the strength of data from the literature linking a specific late effect with a therapeutic exposure, coupled with an assessment of the appropriateness of the screening recommendation based on the expert panel's collective clinical experience. "High-level evidence" (category 1) was defined as evidence derived from high quality case control or cohort studies. "Lower-level evidence" (category 2A and 2B) was defined as evidence derived from non-analytic studies, case reports, case series and clinical experience. Rather than submitting recommendations representing major disagreements, items scored as "Category 3" were either deleted or revised by the panel of experts to provide at least a "Category 2B" score for all recommendations included in the guidelines.
Pre-Release Review	The initial version of the guidelines (Version 1.0 – Children's Oncology Group *Late Effects Screening Guidelines*) was released to the Children's Oncology Group membership in March 2003 for a six-month trial period. This allowed for initial feedback from the COG membership, resulting in additional review and revision of the guidelines by the Late Effects Committee prior to public release.

Introduction (cont)

Revisions	The guidelines were initially released to the public (Version 1.1 – *Childhood Cancer Survivor Long-Term Follow-Up Guidelines*) on the Children's Oncology Group Website in September 2003. Following this release, clarification regarding the applicability of the guidelines to the adolescent and young adult populations of cancer survivors was requested. In response, additional minor modifications were made and the title of the guidelines was changed. A revised version (Version 1.2 – *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*) was released to the public on the Children's Oncology Group Website in March 2004. In order to keep the guidelines current and clinically meaningful, the COG Late Effects Committee organized 18 multidisciplinary task forces in March 2004. These task forces are charged with the responsibility for monitoring the medical literature in regard to specific system-related clinical topics relevant to the guidelines (e.g., cardiovascular, neurocognitive, fertility/reproductive), providing periodic reports to the Late Effects Committee, and recommending revisions to the guidelines and their associated health education materials and references (including the addition of therapeutic exposures) as new information becomes available. In 2009, related task forces were merged, reducing the number of task forces to 10. Task force members are assigned according to their respective areas of expertise and clinical interest and membership is updated every 2 years. A list of these task forces and their membership is included in the "Contributors" section of this document, reflecting contributions and recommendations since the previous release of these guidelines. (Version 3.0 – October 2008). All revisions proposed by the task forces were evaluated by a panel of experts, and if accepted, assigned a score (see "Scoring Explanation" section of this document). Proposed revisions that were rejected by the expert panel were returned with explanation to the relevant task force chair. If desired, task force chairs were given an opportunity to respond by providing additional justification and resubmitting the rejected task force recommendation(s) for further consideration by the expert panel.
Plan for Updates	The 10 multidisciplinary task forces described above will continue to monitor the literature and report to the COG Long-Term Follow-Up Guideline Core Committee during each guideline review/update cycle. Periodic revisions to these guidelines are planned as new information becomes available, and at least every 5 years. Clinicians are advised to check the Children's Oncology Group website periodically for the latest updates and revisions to the guidelines, which will be posted at ***www.survivorshipguidelines.org***.
Definitions	"Late effects" are defined as therapy-related complications or adverse effects that persist or arise after completion of treatment for a pediatric malignancy. "Pediatric malignancies" are defined as those malignancies commonly associated with the pediatric population that may arise during childhood, adolescence or young adulthood. "Consensus" is defined as general agreement among the panel of experts.
Recommendations and Rationale:	Screening and follow-up recommendations are organized by therapeutic exposure and included throughout the guidelines. Pediatric cancer survivors represent a relatively small but growing population at high risk for various therapy-related complications. Although several well-conducted studies on large populations of childhood cancer survivors have demonstrated associations between specific exposures and late effects, the size of the survivor population and the rate of occurrence of late effects does not allow for clinical studies that would assess the impact of screening recommendations on the morbidity and mortality associated with the late effect. Therefore, scoring of each exposure reflects the expert panel's assessment of the level of literature support linking the therapeutic exposure with the late effect coupled with an assessment of the appropriateness of the recommended screening modality in identifying the potential late effect based on the panel's collective clinical experience.

Introduction (cont)

Potential Benefits and Harms	Potential benefits of implementing these guidelines into clinical practice include earlier identification of and intervention for late onset therapy-related complications in this at-risk population, potentially reducing or ameliorating the impact of late complications on the health status of survivors. In addition, ongoing healthcare that promotes healthy lifestyle choices and provides ongoing monitoring of health status is important for all cancer survivors. Potential harms of guideline implementation include increased patient anxiety related to enhanced awareness of possible complications, as well as the potential for false-positive screening evaluations, leading to unnecessary further workup. In addition, costs of long-term follow-up care may be prohibitive for some patients, particularly those lacking health insurance, or those with insurance that does not cover the recommended screening evaluations.
Patient Preferences	Ultimately, as with all clinical guidelines, decisions regarding screening and clinical management for any specific patient should be individually tailored, taking into consideration the patient's treatment history, risk factors, co-morbidities, and lifestyle. These guidelines are therefore not intended to replace clinical judgment or to exclude other reasonable alternative follow-up procedures. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.
Implementation Considerations:	Implementation of these guidelines is intended to standardize and enhance follow-up care provided to survivors of pediatric malignancies throughout the lifespan. Considerations in this regard include the practicality and efficiency of applying these broad guidelines in individual clinical situations. Studies to address guideline implementation and refinement are a top priority of the COG Long-Term Follow-Up Guideline Core Committee; studies of feasibility of guideline use have been reported in limited institutions and others are currently underway. Issues being addressed include description of anticipated barriers to application of the recommendations in the guidelines and development of review criteria for measuring changes in care when the guidelines are implemented. Additional concerns surround the lack of current evidence establishing the efficacy of screening for late complications in pediatric cancer survivors. While most clinicians believe that ongoing surveillance for these late complications is important in order to allow for early detection and intervention for complications that may arise, development of studies addressing the efficacy of this approach is imperative in order to determine which screening modalities are optimal for asymptomatic survivors. In addition, the clinical utility of this lengthy document has also been a top concern of the COG Long-Term Follow-Up Guideline Core Committee. While recognizing that the length and depth of these guidelines is important in order to provide clinically-relevant, evidence-based recommendations and supporting health education materials, clinician time limitations and the effort required to identify the specific recommendations relevant to individual patients have been identified as barriers to their clinical application. Therefore, the COG Long-Term Follow-Up Guideline Core Committee has partnered with the Baylor School of Medicine to develop a web-based interface, known as "Passport for Care," that generates individualized exposure-based recommendations from these guidelines in a clinician-focused format for ease of patient-specific application of the guidelines in the clinical setting. The Pasport for Care® application is available to Children's Oncology member institutions at no cost. For additional information, please contact Marc E. Horowitz, MD, (***mehorowi@txch.org***) or Susan Krause (***skrause@txch.org***).

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

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

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

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

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

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

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

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

Instructions for Use – Version 4.0
The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

Guideline Organization

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

Section Number	Unique identifier for each guideline section.
Therapeutic Agent	Therapeutic intervention for malignancy, including chemotherapy, radiation, surgery, blood/serum products, hematopoietic cell transplant, and other therapeutic modalities.
Potential Late Effects	Most common late treatment complications associated with specified therapeutic intervention.
Risk Factors	Host factors (e.g., age, sex, race, genetic predisposition), treatment factors (e.g., cumulative dose of therapeutic agent, mode of administration, combinations of agents), medical conditions (e.g., pre-morbid or co-morbid conditions), and health behaviors (e.g., diet, smoking, alcohol use) that may increase risk of developing the complication.
Highest Risk Factors	Conditions (host factors, treatment factors, medical conditions and/or health behaviors) associated with the highest risk for developing the complication.
Periodic Evaluations	Recommended screening evaluations, including health history, physical examination, laboratory evaluation, imaging, and psychosocial assessment. Recommendation for minimum frequency of periodic evaluations is based on risk factors and magnitude of risk, as supported by the medical literature and/or the combined clinical experience of the reviewers and panel of experts.
Health Counseling/ Further Considerations	**Health Links:** Health education materials developed specifically to accompany these guidelines. Title(s) of Health Link(s) relevant to each guideline section are referenced in this column. Health Link documents are included in Appendix II, and are also available on the COG website at ***www.survivorshipguidelines.org***. **Counseling:** Suggested patient counseling regarding measures to prevent/reduce risk or promote early detection of the potential treatment complication. **Resources:** Books and websites that may provide the clinician with additional relevant information. **Considerations for Further Testing and Intervention:** Recommendations for further diagnostic evaluations beyond minimum screening for individuals with positive screening tests, recommendations for consultation and/or referral, and recommendations for management of exacerbating or predisposing conditions.

Instructions for Use (cont)

System Score	Body system (e.g., auditory, musculoskeletal) most relevant to each guideline section. Score assigned by expert panel representing the strength of data from the literature linking a specific late effect with a therapeutic exposure coupled with an assessment of the appropriateness of the screening recommendation based on collective clinical experience.
Cancer Screening Recommendations	Sections 157–166 contain preventive screening recommendations for common adult-onset cancers, organized by column as follows: **Organ:** The organ at risk for developing malignancy. **Population Risk Factors:** Risk factors such as age, gender, genetic susceptibility, personal or family history, health-related behaviors or co-morbidities generally associated with increased risk for the specified malignancy in general populations. **Highest Risk Factors:** Populations considered by the panel of experts or other evaluating bodies (such as the American Cancer Society) as being at significantly increased risk for the specified malignancy. Risk factors may include therapeutic exposures resulting from cancer treatment, as well as other factors listed above (e.g., genetic susceptibility). **Periodic Evaluations:** **Standard Risk:** Guidelines provided under the "Standard Risk" category are per the American Cancer Society recommendations for standard-risk populations and are included here for reference. In addition, clinicians are encouraged to consult recommendations from other organizations, such as the U. S. Preventive Services Task Force (***www.ahrq.gov/clinic/serfiles.htm***). **Highest Risk:** Recommendations for high-risk populations, when applicable, are specified and may differ from recommendations for the standard risk groups due to the significantly increased risk of the specified malignancy within the high-risk group
References	References are listed immediately following each guideline section. Included are medical citations that provide evidence for the association of the therapeutic intervention with the specific treatment complication and/or evaluation of predisposing risk factors. In addition, some general review articles have been included in the Reference section for clinician convenience.
The following documents are also included to further assist with application of these guidelines:	
Explanation of Scoring	Elucidation of the process used by the panel of experts to assign scores to each guideline section.
Patient-Specific Guideline Identification Tool	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 Patient-Specific Guideline Identification Tool is imperative*** in order to determine each potential late effect associated with each therapeutic agent within this document (*see Appendix I*).

Using the COG LTFU Guidelines to Develop Individualized Screening Recommendations

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

1. Obtain the survivor's Cancer Treatment Summary (see templates for comprehensive and abbreviated summaries in Appendix 1). *Note: In order to generate accurate expo-*

Instructions for Use (cont)

sure-based follow-up recommendations from these guidelines, the following information regarding the survivor's diagnosis and treatment is required, ***at minimum***:

- Date of diagnosis
- Survivor's sex
- Survivor's date of birth
- Names of all chemotherapy agents received. For list of chemotherapeutic agents addressed by these guidelines (Sections 10–43), see the "Chemotherapy" portion of the Patient-Specific Guideline Identification Tool in Appendix I. For list of generic and brand names of chemotherapy agents, see Chemotherapy Agents in Appendix I.
- Cumulative dose of all anthracycline chemotherapy received (i.e., doxorubicin, daunorubicin, idarubicin, mitoxantrone and epirubicin), and age at first anthracycline dose (if unknown, age at first exposure is presumed to be age at diagnosis).
- For carboplatin: Whether patient received myeloablative dose (i.e., for hematopoietic cell transplant [HCT] conditioning).
- For cytarabine and methotrexate:
  - Route of administration (i.e., IV, IM, SQ, PO, IT, IO)
  - If IV: Designation of "high dose" (any single dose ≥ 1000 mg/m^2) versus "standard dose" (all single doses < 1000 mg/m^2)
- All radiation field(s) and total radiation dose (in Gy) to each field (for chest radiation, include age at first dose). For list of radiation fields addressed by these guidelines (Sections 44–102), see "Radiation" portion of the *Patient-Specific Guideline Identification Tool* in Appendix I. For clarification of anatomical areas included in common radiation fields, see *Radiation Fields by Anatomic Region and Radiation Fields* Defined in Appendix I. For clarification regarding radiation dose calculations for determining screening recommendations for individual patients, see *Determining Applicability of Radiation Sections for Specific Patients Based on Exposure* on page 56 of guidelines and in Appendix 1.
- Whether or not the survivor underwent a hematopoietic cell transplant (HCT), and if so, whether or not the survivor has a history of chronic graft-versus-host disease (cGVHD).
- Names of all relevant surgical procedures. For list of surgical procedures addressed by these guidelines (Sections 120–152), see "Surgery" portion of the *Patient-Specific Guideline Identification Tool* in Appendix I.
- Names of all other therapeutic modalities. For list of other therapeutic modalities addressed by these guidelines (Sections 153–156), see "Other Therapeutic Modalities" portion of the *Patient-Specific Guideline Identification Tool* in Appendix I.

2. Develop a list of guideline sections relevant to the survivor:
   - Sections 1–6 ("Any Cancer Experience") and 157 ("General Health Screening") are relevant to all survivors.
   - For survivors diagnosed prior to 1993, include relevant sections based on date of diagnosis:
     - If survivor was diagnosed prior to 1972, include Section 7
     - If survivor was diagnosed prior to 1993, include Section 8
     - If survivor was diagnosed between 1977 and 1985, include Section 9
   - For survivors who received chemotherapy, include relevant sections:

Instructions for Use (cont)

  - If survivor received any chemotherapy, include Section 10.
  - Review "Chemotherapy" portion of the *Patient-Specific Guideline Identification Tool* in Appendix I and include Sections 11–43 as applicable based on survivor's chemotherapy exposures (***Note:*** Some alkylating agent sections are gender-specific)
- For survivors who received radiation therapy, include relevant sections:
  - If survivor received any radiation therapy, include Sections 44–47. ***Exception:*** If the survivor's only radiation exposure was TBI, do NOT include Sections 46 or 47.
  - Review "Radiation" portion of the Patient-Specific Guideline Identification Tool in Appendix I and include Sections 48–102 as applicable based on survivor's radiation exposures (***Note:*** Some sections are gender-specific and some are relevant only for patients who received the minimum specified dose of radiation to the indicated field or anatomic area.
- For survivors who underwent hematopoietic cell transplant (HCT), include Sections 103–110. If the survivor has a history of chronic GVHD (cGVHD), also include Sections 111–119 (***Note:*** Section 116 is applicable only to survivors with currently active cGVHD; Section 118 is applicable only to females; Copies of the radiation sections applicable to TBI are reproduced and grouped together for convenience at the end of the HCT section on page 129).
- For survivors who underwent surgery, review "Surgery" portion of the *Patient-Specific Guideline Identification Tool* in Appendix I and include Sections 120–152 as applicable based on survivor's surgical history. (***Note:*** Some sections are gender-specific).
- For survivors who received other therapeutic modalities, review "Other Therapeutic Modalities" portion of the *Patient-Specific Guideline Identification Tool* in Appendix I and include Sections 153–156 as applicable.
- Include cancer screening guidelines (Sections 157–166) as applicable based on survivor's sex and current age. (***Note:*** For survivors whose radiation exposure triggers Section 77, there is no need to include Section 157; for survivors whose radiation exposure triggers Section 90, there is no need to include Section 159).

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

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

The COG Long-Term Follow-Up Guidelines Core Committee recognizes that the time required to identify patient-specific recommendations from these guidelines is significant, and has been identified as a barrier to clinical use. Therefore, COG has partnered with the Baylor School of Medicine to develop a web-based interface, known as "Passport for

Instructions for Use (cont)

Care," that generates individualized exposure-based recommendations from these guidelines in a clinician-focused format for ease of patient-specific application in the clinical setting. The Pasport for Care® application is available to Children's Oncology member institutions at no cost. For additional information, please contact Marc E. Horowitz, MD, (***mehorowi@txch.org***) or Susan Krause (***skrause@txch.org***).

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

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New to Version 4.0 of the COG Long-Term Follow-Up Guidelines

All guideline sections have been reviewed by the Long-Term Follow-Up Guidelines Task Forces and modifications have been made per their recommendations and with the approval of the Expert Panel. The most significant modifications are detailed below.

- The following NEW sections have been added:
  - Impaired glucose metabolism/Diabetes mellitus related to abdominal radiation (Section 84)
  - Dyslipidemia related to TBI (Section 85)
  - Renal toxicity related to hematopoietic cell transplantation (Section 110)
  - Overweight/obesity related to neurosurgery affecting the hypothalamic-pituitary axis (Section 133)
  - Diabetes insipidus related to neurosurgery affecting the hypothalamic-pituitary axis (Section 134)
  - Scoliosis/kyphosis related to neurosurgery-spine (Section 139)
  - Scoliosis/kyphosis related to thoracic surgery (Section 151)
- The following existing sections from version 3.0 of the COG LTFU Guidelines have been *divided into more than one section* in version 4.0:
  - Psychosocial disorders; Mental health disorders; Risky behaviors; Psychosocial disability due to pain; Fatigue (Section 1, v3.0), now divided into: Adverse psychosocial/QoL effects (Section 1); Mental health disorders (Section 2); Risky behaviors (Section 3); Psychosocial disability due to pain (Section 4); Fatigue (Section 5); Limitations in healthcare and insurance access (Section 6)
  - Alkylating agents and gonadal dysfunction-testicular (Section 7 [male], v3.0), now divided into: Alkylating agents and reduced fertility (Section 11) and Alkylating agents and testosterone deficiency/insufficiency; delayed/arrested puberty (Section 12)
  - Ototoxicity related to radiation (Section 58, v3.0), now divided into: Tympanosclerosis; ototosclerosis, eustachian tube dysfunction; conductive hearing loss (Section 66) and Sensorineural hearing loss; tinnitus (Section 67)
  - Orchiectomy and gonadal dysfunction-testicular (Section 125, v3.0), now divided into: Unilateral orchiectomy; Reduced fertility, testosterone insufficiency (Section 143) and Bilateral orchiectomy; Infertility; testosterone deficiency (Section 144)
  - All sections previously divided into “Male” and “Female” sub-sections have been re-categorized as stand-alone male or female sections in version 4.0, as follows:
    - Alkylating agents and gonadal dysfunction (Section 7 [male and female], v3.0), now categorized as: Section 11 (male-reduced fertility), Section 12 (male-testosterone deficiency/insufficiency; delayed/arrested puberty) and Section 13 (female-delayed/arrested puberty; premature menopause; infertility)
    - Anthracyclines and cardiac toxicity (Section 28 [male and female], v.3.0), now categorized as: Section 33 (male) and Section 34 (female)
    - Cranial radiation and precocious puberty (Section 51 [male and female], v3.0), now categorized as: Section 56 (male) and Section 57 (female)
    - Cranial radiation and hyperprolactinemia (Section 52 [male and female], v3.0), now categorized as: Section 58 (male) and Section 59 (female)
    - Cranial radiation and gonadotropin deficiency (Section 54 [male and female], v3.0), now categorized as: Section 61 (male) and Section 62 (female)
    - Chest radiation and cardiac toxicity (Section 71 [male and female], v3.0), now categorized as: Section 80 (male) and Section 81 (female)
    - Hematopoietic cell transplant and solid tumors (Section 93 [male and female], v3.0), now categorized as: Section 104 (male) and Section 105 (female)

    - Nephrectomy (Section 114 [male-hydrocele/renal toxicity and female-renal toxicity], v3.0), now categorized as: Section 127 (male-hyrocele/renal toxicity) and Section 128 (female-renal toxicity)
    - Neurosurgery-spinal cord and psychosexual dysfunction (Section 121 [male and female], v3.0), now categorized as: Section 137 (male) and Section 138 (female)
    - Pelvic surgery or Cystectomy and sexual dysfunction (Section 128 [male and female], v3.0), now categorized as: Section 147 (male) and Section 148 (female)
- The following sections have been *removed* from version 4.0 of the COG LTFU Guidelines:
  - Dyslipidemia related to platinum chemotherapy (Section 17, v3.0)
  - Metabolic syndrome related to cranial radiation/TBI (Section 49, v3.0)
  - Kyphosis related to musculoskeletal radiation (Section 90, v 3.0): Kyphosis is now merged with Scoliosis in Section 101 of version 4.0 of the COG LTFU Guidelines
  - Hydrocele related to Pelvic Surgery or Cystectomy (Section 129 [male], v3.0)
- The following modifications have been made to *therapeutic exposures*:
  - Carboplatin at any dose added as a therapeutic exposure for ototoxicity in patients diagnosed at less than 1 year of age (Section 20; score = 1); Info Link added to provide rationale for this change
  - Radiation threshold for screening reduced from ≥ 40 Gy to ≥ 30 Gy for
    - Radiation to the neuroendocrine axis and gonadotropin deficiency: Section 61 (male; score = 1) and Section 62 (female; score = 1)
    - Radiation to the neuroendocrine axis and central adrenal insufficiency: Section 63 (score = 1)
  - Chest (thorax) and whole lung radiation removed as therapeutic exposures related to thyroid dysfunction, thyroid nodules, and thyroid cancer: Sections 71, 72, 73, 74 (score = 1 for each section)
  - Cranial and nasopharyngeal radiation removed as therapeutic exposures for hyperthyroidism: Section 74
  - "Autologous" specified as the sole type of hematopoietic cell transplant associated with the potential late effect of therapy-related acute myeloid leukemia/ myelo-dysplasia (Section 103; score = 1)
  - Pulmonary lobectomy, pulmonary metastasectomy, pulmonary wedge resection as therapeutic exposures for pulmonary dysfunction changed to: Thoracic surgery (includes thoracotomy, chest wall surgery, rib resection, pulmonary lobectomy, pulmonary metastasectomy, pulmonary wedge resection): Section 150 (score = 2A)
- The following modifications have been made to *potential late effects*:
  - "Psychosocial Disorders" re-categorized as "Adverse Psychosocial/QoL Effects" and additional potential late effects added: Dysfunctional marital relationships; Under-Unemployment; Dependent living (Section 1; score = 2A)
  - Additional potential late effect (suicidal ideation) added to: Mental health disorders (Section 2; score = 2A)
  - Additional potential late effect (microdontia) added to: Dental abnormalities (Section 10; score = 1)
  - Info Link added to explain that ifosfamide-related renal toxicity typically occurs during the acute treatment phase and improves or progresses over time (Section 19) (score = 1)
  - Additional potential late effect (hypertension) added to Renal toxicity related to Heavy metals (Section 22; score = 1)
  - Additional potential late effects (glomerular injury; hypertension) added to Renal toxicity related to Methotrexate/high-dose IV, IM, PO (Section 28; score = 2A)

  - Additional potential late effect (deficits in fine motor dexterity) added to Neurocognitive deficits related to: Cytarabine/high-dose IV (Section 23; score = 2A), Methotrexate/high-dose IV, IT, IO (Section 30; score = 1), and cranial/ear-infratemporal radiation/TBI (Section 49; score =1)
  - Additional potential late effect (language deficits) added to: Neurocognitive deficits related to cranial/ear-infratemporal radiation/TBI (Section 49; score = 1)
  - Additional potential late effect (cavernomas) added to: Cerebrovascular complications related to cranial radiation (Section 51; score = 1); Info link added to explain clinical implications of cavernomas
  - Additional potential late effect (focal nodular hyperplasia [FNH]) added to: Hepatic fibrosis/cirrhosis related to liver radiation (Section 86; score = 1); Info link added to explain clinical implications of FNH
  - Additional potential late effect (asymptomatic bacteriuria) added to: Cystectomy-related complications (Section 122; score = 1)
  - Potential late effect related to neurosurgery-spinal cord changed from "sexual dysfunction" to "psychosexual dysfunction" (Sections 137, 138; score = 2A)
- The following modifications have been made to *screening recommendations*:
  - CBC with differential yearly x 10 years removed as screening for t-AML/MDS and added to Considerations for further testing and intervention (as clinically indicated), in the following sections:
    - Alkylating agents (Section 14)
    - Anthracyclines (Section 32)
    - Epipodophyllotoxins (Section 43)
    - Autologous hematopoietic cell transplant (Section 103)
  - Chest x-ray (baseline, repeat as clinically indicated) removed as screening for pulmonary fibrosis from
    - Busulfan, carmustine [BCNU]), lomustine [CCNU] (Section 15)
    - Bleomycin (Section 35)
    - Radiation with potential impact to the lungs (Section 79)
    - Hematopoietic cell transplant with any history of chronic graft-versus-host disease (Section 114)
    - Thoracic surgery (Section 150)
  - Urinalysis (yearly) removed as screening for hemorrhagic cystitis and added to Considerations for further testing and intervention (for patients with a positive history) in the following sections:
    - Cyclophosphamide, ifosfamide (Section 17)
    - Radiation with potential impact to the bladder (Section 92)
  - Urinalysis (yearly) removed as screening for bladder cancer and added to Considerations for further testing and intervention (for patients with a positive history) in the following sections:
    - Cyclophosphamide (Section 18)
    - Radiation with potential impact to the bladder (Section 94)

- Serum testosterone (males at age 14 and as clinically indicated) modified to indicate that specimen is ideally obtained in the morning for
  - Alkylating agents and testosterone deficiency/insufficiency; delayed/arrested puberty (Section 12)
  - Radiation to the hypothalamic-pituitary axis and gonadotropin deficiency (Section 61)
  - Pelvic/testicular radiation and testosterone deficiency/insufficiency; delayed/ arrested puberty (Section 99)
  - Unilateral orchiectomy and testosterone insufficiency (Section 143)
- FSH, LH (males at age 14 and as clinically indicated) removed as screening for
  - Alkylating agents and testosterone deficiency/insufficiency; delayed/arrested puberty (Section 12)
  - Pelvic/testicular radiation and testosterone deficiency/insufficiency; delayed/arrested puberty (Section 99)
- FSH (males at age 14 and as clinically indicated) retained/ added as secondary screening for reduced fertility in sexually mature patients if unable to obtain semen analysis for:
  - Alkylating agents and gonadal dysfunction (testicular)—reduced fertility (Section 11)
  - Pelvic/testicular radiation and gonadal dysfunction (testicular)—reduced fertility (Section 98)
  - Unilateral orchiectomy and gonadal dysfunction (testicular)—reduced fertility (Section 143)
- Hemoglobin A1c (every 2 years) added as an option (in place of fasting blood glucose) for
  - Chest radiation and cardiac toxicity (Sections 80, 81)
- Endocrinology evaluation (yearly) replaces previous recommendation for "8:00 a.m. serum cortisol yearly $\times$ 15 years" for
  - Radiation to the hypothalamic-pituitary axis $\geq$30 Gy and central adrenal insufficiency (Section 63)
- Breast cancer screening (Sections 77 and 157):
  - Recommendation added for clinicians to discuss benefits and risks/harms of screening for patients who received TBI or 10–19 Gy radiation with potential impact to the breast
  - If decision is made to screen patients who received $<$ 20 Gy radiation with potential impact to the breast, screening recommendations are identical to those for patients who received $\geq$ 20 Gy and include: Mammogram and breast MRI yearly beginning 8 years after radiation or at age 25, whichever occurs last; Clinical breast exam yearly from puberty until age 25, then every 6 months; and Breast self-examination monthly
- Examination of external genitalia (yearly) and gynecological consultation when age-appropriate added as screening for
  - Hematopoietic cell transplant with any history of chronic graft-versus-host disease and vaginal fibrosis/stenosis (Section 118)
- Evaluation by neurologist modified to "as clinically indicated" rather than "every six months" for
  - Neurosurgery-brain and seizures (Section 131)
- Endocrinology consultation (or gynecology-females) for initiation of hormonal replacement therapy modified from "At age 11" to "At age 11 or immediately for post-pubertal patients" for
  - Bilateral oophorectomy (Section 142)
  - Bilateral orchiectomy (Section 144)

  - Cervical cancer screening recommendations (Section 158) updated to reflect current American Cancer Society recommendations (i.e., changes to PAP/HPV testing)
  - Lung cancer screening recommendations (Section 161) updated to include the following statement for patients at highest risk: "Clinician should discuss the benefits and risks/harms of spiral CT scanning"
- The following modifications have been made to *Health Counseling/Further Considerations*:
  - Added recommendations for minimum intake of Vitamin D as per the American Academy of Pediatrics to the following sections:
    - Methotrexate and reduced bone mineral density (Section 27)
    - Corticosteroids and reduced bone mineral density (Section 37)
    - Hematopoietic cell transplant and reduced bone mineral density (Section 109)
  - Added Info Link regarding metabolic syndrome, and recommendations to consider evaluation for other co-morbid conditions, including dyslipidemia, hypertension, or impaired glucose metabolism for
    - Overweight/obesity related to cranial radiation (Section 54)
  - Updated recommendations regarding monitoring growth and indications for endocrinology referrals for
    - Cranial radiation and growth hormone deficiency (Section 55)
  - Added information regarding induction of spermatogenesis with gonadotropins for
    - Radiation to the neuroendocrine axis and gonadotropin deficiency (Section 61)
  - Added recommendations for counseling patients regarding risk of life-threatening infections and indication for medical alert bracelets for
    - Splenic radiation and functional asplenia (Section 82)
    - Hematopoietic cell transplant with currently active chronic graft-versus-host disease and functional asplenia (Section 116)
    - Splenectomy and anatomic asplenia (Section 149)
  - Added recommendation for consideration of periodic monitoring of serum testosterone levels in males with low normal testosterone, as they age or if they become symptomatic, for
    - Pelvic/testicular radiation and testosterone deficiency/insufficiency; delayed/ arrested puberty (Section 99)
  - Updated antibiotic prophylaxis recommendations to indicate lack of current consensus for patients with orthopedic implants for
    - Limb sparing procedures (Section 126)
  - Revised sports/physical activity recommendations for
    - Nephrectomy and renal toxicity (Sections 127, 128)
  - Updated to reflect recommendations for sperm retrieval in men with erectile/ejaculatory dysfunction who desire paternity for
    - Neurosurgery-spinal cord and erectile dysfunction; ejaculatory dysfunction (Section 137)
    - Pelvic surgery/cystectomy and retrograde ejaculation; anejaculation; erectile dysfunction (Section 147)
  - Added consideration for gynecologic consultation in patients with positive history for
    - Neurosurgery-spinal cord and psychosexual dysfunction (Section 138)

  - Added importance of monitoring cardiovascular health in hypogonadal females for
    - Bilateral oophorectomy and hypogonadism/infertility (Section 142)
  - Added importance of monitoring for surgical complications after prosthesis placement and cautioned that orchiectomy can be associated with psychological distress related to altered body image for
    - Unilateral orchiectomy (Section 143)
    - Bilateral orchiectomy (Section 144)
- The following modifications have been made to the *Health Links*:
  - Added new Health Link: "Cardiovascular Risk Factors" (relevant to Sections 19, 22, 28, 33, 34, 54, 80, 81, 84, 85, 91, 110, 128, 133)
  - Modified the following Health Links:
    - Bone Health: Added recommendations for minimum daily intake of Vitamin D as per the American Academy of Pediatrics
    - Central Adrenal Insufficiency: Revised to reflect lower radiation dose for screening (> 30 Gy) and revised screening recommendations (endocrinology evaluation rather than yearly blood test)
    - Dental Health: Removed statement that xerostomia generally occurs only with radiation doses > 40 Gy.
    - Diet and Physical Activity: Updated "My Pyramid" to "My Plate"
    - Finding and Paying for Healthcare: Updated with information regarding new insurance options in the United States under the Affordable Care Act
    - Hearing Loss: Updated to indicate risk of hearing loss in survivors who received conventional doses of carboplatin prior to one year of age
    - Hypopituitarism: Updated to include antidiuretic hormone deficiency and diabetes insipidus related to neurosurgery
    - Limb Sparing Procedures: Updated to reflect lack of consensus regarding antibiotic prophylaxis recommendations
    - Pulmonary Health: Updated to remove chest x-ray, and to recommend avoidance of inhaled drugs (such as marijuana)
    - Scoliosis and Kyphosis: Added information regarding surgical procedures (thoracic and spinal surgeries) that may increase risk of developing scoliosis and kyphosis (from new Sections 139 and 151)
    - Reducing the Risk of Second Cancers: Updated with information regarding the role of vaccination in preventing Hepatitis B and HPV-related cancers
    - Single Kidney Health: Updated to reflect revised sports/physical activity recommendations for mononephric survivors; removed reference to Single Kidney Health Link from renal toxicity sections (Sections 19, 22, 28, 91)
    - Splenic Precautions: Updated to reflect current vaccine recommendations
    - Additional minor modifications made throughout Health Links to reflect current content of version 4.0 of the COG LTFU Guidelines
- Anthracycline isotoxic dose equivalent formula for Daunorubicin has been updated (see Sections 33, 34)
- The Info Link regarding prophylactic antibiotic therapy and immunizations for functionally or anatomically asplenic patients has been updated to indicate that clinicians should refer to the current edition of the AAP *Red Book* for recommendations (Sections 82, 116, 149)
- Information regarding the role of the human papillomavirus (HPV) vaccine in prevention of post-transplant malignancies has been added (Sections 104, 105)
- Radiation fields by anatomic area have been updated (see pages 56–57 of guidelines)

- The text that introduces the hematopoietic cell transplant sections (103–119) now precedes Section 103, since it is relevant to all hematopoietic cell transplant sections
- "Risk Factors" and "Highest Risk Factors" have been updated, based on current literature as reviewed by the Task Forces
- Links for general health screening have been updated (Section 166)
- Updated references have been added and outdated reference removed throughout the guidelines

In addition, the following modifications have been made to Version 4.0 of these guidelines:

- Links to all sections relevant to TBI have been added before the HCT section of the guidelines (see page 129)
- The "Radiation Reference Guide" has been updated to reflect modifications to section numbers and other changes as described above (see Appendix 1)
- The "Patient-Specific Guideline Identification Tool" has been updated to modifications to section numbers and other changes as described above (see Appendix 1)
- French translations of some Health Links have been added

Guidelines

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

ANY CANCER EXPERIENCE

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
1	**Any Cancer Experience** **Info Link** The Children's Oncology Group Long-Term Follow-Up Guidelines apply to patients who have been off therapy for a minimum of 2 years.	**Adverse Psychosocial/QoL Effects** Social withdrawal Educational problems Dysfunctional marital relationships Under-employment/ Unemployment Dependent living	**Host Factors** Female sex Family history of depression, anxiety, or mental illness Younger age at diagnosis Neurocognitive problems Physical limitations **Social Factors** Lower household income Lower educational achievement **Treatment Factors** Hematopoietic Cell Transplant	**Host Factors** CNS tumor CNS-directed therapy Hearing loss Premorbid learning or emotional difficulties **Social Factors** Failure to graduate from high school	**HISTORY** **Psychosocial assessment with attention to:** - **Educational and/or vocational progress** - **Social withdrawal** Yearly	**Health Links** **Introduction to Long-Term Follow-Up** **Emotional Issues** **Educational Issues** **Resources** 'Childhood Cancer Survivors' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012; 'Educating the Child with Cancer' edited by Nancy Keene, Candlelighters Childhood Cancer Foundation, Bethesda, MD, 2003. See also: ***www.cancer.gov*** ('Facing Forward' series for survivors) **Considerations for Further Testing and Intervention** Consider psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Consider social work consultation. Refer as indicated to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Psychosocial** **SCORE = 2A**

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ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
2	**Any Cancer Experience**	**Mental health disorders** Depression Anxiety Post-traumatic stress Suicidal ideation	**Host Factors** Female sex Family history of depression, anxiety, or mental illness **Social Factors** Lower household income Lower educational achievement **Treatment Factors** Hematopoietic Cell Transplant **Medical Conditions** Chronic pain	**Host Factors** CNS tumor CNS-directed therapy Premorbid learning or emotional difficulties Perceived poor physical health **Social Factors** Failure to graduate from high school	**HISTORY** **Psychosocial assessment with attention to:** - **Depression** - **Anxiety** - **Post-traumatic stress** - **Suicidal ideation** Yearly	**Health Links** **Emotional Issues** **Resources** 'Childhood Cancer Survivors' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 **Considerations for Further Testing and Intervention** Consider psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Consider appropriate psychotropic medications. Consider evaluation of parent for post-traumatic stress syndrome **SYSTEM = Psychosocial** **SCORE = 2A**

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ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
3	**Any Cancer Experience**	**Risky behaviors** Behaviors known to increase the likelihood of subsequent illness or injury	**Social Factors** Lower household income	**Host Factors** Older age at diagnosis **Social Factors** Lower educational achievement	**HISTORY** **Psychosocial assessment** Yearly	**Health Links** **Emotional Issues** **Resources** 'Childhood Cancer Survivors' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 See also: ***www.cancer.gov*** ('Facing Forward' series for survivors; smoking cessation information); ***www.cancer.org*** (smoking cessation) **SYSTEM = Psychosocial** **SCORE = 2A**

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ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
4	**Any Cancer Experience**	**Psychosocial disability due to pain**	**Treatment Factors** Amputation Radiation to bone/joint Limb-sparing surgery Vincristine exposure **Medical Conditions** Osteonecrosis	**Host Factors** CNS tumor Hodgkin lymphoma	**HISTORY** **Psychosocial assessment** Yearly	**Health Links** **Chronic Pain after Childhood Cancer** **Resources** 'Childhood Cancer Survivors' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 See also: ***www.nccn.org*** (chronic pain) **Considerations for Further Testing and Intervention** Consider psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Consider appropriate psychotropic medications. Consider referral to pain rehabilitation clinic. **SYSTEM = Psychosocial** **SCORE = 2A**

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ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
5	**Any Cancer Experience**	**Fatigue** **Info Link** Risk of sleep disturbance is increased for patients with CNS tumors and craniopharyngiomas.	**Host Factors** Female sex Depression Obesity Central CNS tumor (e.g., craniopharyngioma) **Social Factors** Unemployment **Medical Conditions** Sleep disturbance	**Host Factors** Pulmonary radiation	**HISTORY** **Psychosocial assessment** Yearly	**Resources** 'Childhood Cancer Survivors' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 See also: ***www.cancer.gov*** ('Facing Forward' series for survivors) **Considerations for Further Testing and Intervention** Screen for physical sources of fatigue, such as anemia, sleep disturbances, nutritional deficiencies, cardiomyopathy, pulmonary fibrosis, hypothyroidism, or other endocrinopathy. **SYSTEM = Psychosocial** **SCORE = 2A**

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ANY CANCER EXPERIENCE (CONT)

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

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BLOOD/SERUM PRODUCTS

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

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BLOOD/SERUM PRODUCTS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
8	**Diagnosed prior to 1993** **Info Link** • Exposure to blood/serum products prior to initiation of Hepatitis C screening of blood supply (1993 in the United States, considering more reliable EIA generation 2 released in the United States in 1992—dates may differ in other countries) is associated with risk of chronic hepatitis C. • Since the vast majority of patients received some type of blood product during childhood cancer treatment, screening based on date of diagnosis/treatment is recommended unless there is absolute certainty that the patient did not receive any blood or blood products. • Relevant exposures include packed red cells, whole blood, granulocytes, platelets, fresh frozen plasma, cryoprecipitate, IVIG, VZIG, factor concentrates, and allogeneic marrow, cord blood, or stem cells.	**Chronic hepatitis C**	**Host Factors** Living in hyperendemic area **Treatment Factors** Blood products before 1993 **Health Behaviors** IV drug use Unprotected sex Multiple partners High-risk sexual behavior Sexually transmitted diseases Tattoos Body piercing	**Host Factors** Chronic immunosuppression **Treatment Factors** Blood products prior to 1986 (when surrogate screening of blood donors with ALT was initiated and donors with self-reported high-risk behaviors were deferred)	**SCREENING** **Hepatitis C antibody** Once in patients who received treatment for cancer prior to 1993. **Note**: Date may vary for international patients. **Hepatitis C PCR (to establish chronic infection)** Once in patients with positive Hepatitis C antibody.	**Health Links** **Hepatitis** **Considerations for Further Testing and Intervention** Screen for viral hepatitis in patients with persistently abnormal liver function regardless of transfusion history. Consider HCV PCR screening in transfused at-risk HCV-antibody negative patients with abnormal liver function and/ or persistent immunosuppression (e.g., HCT recipients with chronic GVHD). Gastroenterology or hepatology consultation for management of patients with chronic hepatitis. Hepatitis A and B immunization in patients lacking immunity. **SYSTEM = Immune** **SCORE = 1**

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BLOOD/SERUM PRODUCTS (cont)

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

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CHEMOTHERAPY

ANY CHEMOTHERAPY

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

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CHEMOTHERAPY

ALKYLATING AGENTS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
11 (male)	**ALKYLATING AGENTS** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **HEAVY METALS** Carboplatin Cisplatin **NON-CLASSICAL ALKYLATORS** Dacarbazine (DTIC) Temozolomide	**Gonadal dysfunction (testicular)** Reduced fertility Oligospermia Azoospermia Infertility	**Host Factors** Testicular cancer Obesity Ejaculatory dysfunction Medications Occupational exposures (pesticides, heavy metals, solvents) **Treatment Factors** Higher cumulative doses of alkylators or combinations of alkylators Combined with radiation to: - abdomen/pelvis - testes - brain, cranium (neuroendocrine axis) - Genitourinary surgery **Health Behaviors** Tobacco/marijuana use History of sexually transmitted diseases **Info Link** • Doses that cause gonadal dysfunction show individual variation. • Germ cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function. • Prepubertal status does not protect from gonadal injury in males.	**Treatment Factors** MOPP ≥ 3 cycles Busulfan ≥ 600 mg/m^2 Cyclophosphamide cumulative dose ≥ 7.5 gm/m^2 or as conditioning for HCT Ifosfamide ≥ 60 gm/m^2 Any alkylators combined with: - testicular radiation - pelvic radiation - TBI	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchiometer** Yearly **SCREENING** **Semen analysis** At request of sexually mature patient Periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years post therapy **FSH** In sexually mature patient if unable to obtain semen analysis	**Health Links** **Male Health Issues** **Resources** Extensive information regarding infertility for patients and healthcare professionals is available on the following websites: American Society for Reproductive Medicine (***www.asrm.org***); Fertile Hope (***www.fertilehope.org***) **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to alkylating agents. Recovery of fertility may occur years after therapy. **Considerations for Further Testing and Intervention** Reproductive endocrinology/urology referral for infertility evaluation and consultation regarding assisted reproductive technologies. **SYSTEM = Reproductive (male)** **SCORE =** **Alkylating Agents = 1** **Heavy Metals = 2A** **Non-Classical Alkylators = 2A**

SECTION 11 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
12 (male)	**ALKYLATING AGENTS** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **HEAVY METALS** Carboplatin Cisplatin **NON-CLASSICAL ALKYLATORS** Dacarbazine (DTIC) Temozolomide	**Gonadal dysfunction (testicular)** Testosterone deficiency/ insufficiency Delayed/arrested puberty	**Host Factors** Testicular cancer Aging **Treatment Factors** Higher cumulative doses of alkylators or combinations of alkylators Combined with radiation to: - Abdomen/pelvis - Testes - Brain, cranium (neuroendocrine axis) Unilateral orchiectomy **Health Behaviors** Smoking **Info Link** • Doses that cause gonadal dysfunction show individual variation. • Germ cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function. • Prepubertal status does not protect from gonadal injury in males.	**Treatment Factors** MOPP Cyclophosphamide cumulative dose ≥ 20 gm/m^2 Conditioning for HCT; Ifosfamide ≥ 60 gm/m^2 Any alkylators combined with - Testicular radiation - Pelvic radiation - Neuroaxis radiation	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchiometer** Yearly **SCREENING** **Testosterone (ideally morning)** Baseline at age 14 AND as clinically indicated in patients with delayed or arrested puberty and/or clinical signs and symptoms of testosterone deficiency	**Health Links** **Male Health Issues** **Considerations for Further Testing and Intervention** Bone density evaluation in hypogonadal patients. Refer to endocrinology/urology for delayed puberty, persistently abnormal hormone levels or hormonal replacement for hypogonadal patients. Males with low normal testosterone should have periodic re-evaluation of testosterone as they age or if they become symptomatic. Testosterone insufficiency requiring hormone replacement therapy is rare after treatment wth alkylating agents only. **SYSTEM = Reproductive (male)** **SCORE =** **Alkylating Agents = 1** **Heavy Metals = 2A** **Non-Classical Alkylators = 2A**

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

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

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

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

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

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

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
19	**ALKYLATING AGENTS** Ifosfamide	**Renal toxicity** Glomerular injury Hypertension Tubular injury (renal tubular acidosis, Fanconi's syndrome, hypophosphatemic rickets) **Info Link** Ifosfamide-related renal toxicity typically occurs during the acute treatment phase and improves or progresses over time	**Host Factors** Younger age at treatment Mononephric **Treatment Factors** Higher cumulative dose Combined with other nephrotoxic agents such as: - Cisplatin - Carboplatin - Aminoglycosides Amphotericin - Immunosuppressants Methotrexate - Radiation impacting the kidney **Medical Conditions** Tumor infiltration of kidney(s) Pre-existing renal impairment Nephrectomy	**Host Factors** Age < 4 years at time of treatment **Treatment Factors** Ifosfamide dose ≥ 60 grams/m^2 Renal radiation dose ≥ 15 Gy	**PHYSICAL** **Blood pressure** Yearly **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** Baseline at entry into long-term follow-up, repeat as clinically indicated **Urinalysis** Yearly	**Health Links** **Kidney Health** **Cardiovascular Risk Factors** **Considerations for Further Testing and Intervention** Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 1**

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CHEMOTHERAPY

HEAVY METALS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
20	**HEAVY METALS** Carboplatin (myeloablative doses OR any dose if age at diagnosis < 1 year) Cisplatin **Info Link** • In general, patients who received carboplatin in nonmyeloablative doses do not appear to be at risk for clinically significant ototoxicity. • Some studies have observed hearing loss among infants (with retinoblastoma) exposed to nonmyeloablative doses of carboplatin.	**Ototoxicity** Sensorineural hearing loss Tinnitus Vertigo	**Host Factors** Age < 4 years at treatment **Treatment Factors** Combined with: - Cranial/ear radiation - Ototoxic drugs (e.g., aminoglycosides, loop diuretics) **Medical Conditions** Chronic otitis Cerumen impaction Renal dysfunction	**Host Factors** CNS neoplasm **Treatment Factors** Cumulative cisplatin dose ≥ 360 mg/m^2 High dose cisplatin (i.e., 40 mg/m^2 per day × 5 days per course) Cisplatin administered AFTER cranial/ear radiation Carboplatin conditioning for HCT Radiation involving ear ≥ 30 Gy	**HISTORY** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** Yearly **PHYSICAL** **Otoscopic exam** Yearly **SCREENING** **Complete audiological evaluation** Baseline at entry into long-term followup. If hearing loss is detected, test at least yearly, or as recommended by audiologist. If clinical suspicion of hearing loss at any time, test as clinically indicated. If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions [OAEs]. **Info Link** • A "complete audiological evaluation" includes pure tone air and bone conduction, speech audiometry, and tympanometry for both ears. • Frequency-specific auditory brainstem response (ABR) can be performed if the above is inconclusive.	**Health Links** **Hearing Loss** **Educational Issues** **Considerations for Further Testing and Intervention** Audiology consultation for amplification in patients with hearing loss. Speech and language therapy for children with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources. Consider specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
21	**HEAVY METALS** Carboplatin Cisplatin	**Peripheral sensory neuropathy** Paresthesias Dysesthesias **Info Link** • Acute toxicities most commonly occur and usually improve or resolve prior to patients entering long-term follow-up. • Neuropathy can persist after treatment and is typically not late in onset.	**Treatment Factors** Combined with: - Vincristine - Taxanes - Gemcitabine	**Treatment Factors** Cumulative cisplatin dose ≥ 300 mg/m^2	**HISTORY** **Numbness** **Tingling** **Paresthesias** **Dysesthesia** Yearly until 2 to 3 years after therapy, monitor yearly if symptoms persist **PHYSICAL** **Neurologic exam** Yearly	**Health Links** **Peripheral Neuropathy** **Considerations for Further Testing and Intervention** Physical therapy referral for patients with symptomatic neuropathy. Physical and occupational therapy assessment of hand function. Consider treatment with agent effective for neuropathic pain (e.g., gabapentin or amitriptyline). **SYSTEM = PNS** **SCORE = 2A**

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

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CHEMOTHERAPY

ANTIMETABOLITES

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

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

SECTION 24 REFERENCES

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CHEMOTHERAPY

ANTIMETABOLITES (cont)

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

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

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CHEMOTHERAPY

ANTIMETABOLITES (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
27	**ANTIMETABOLITES** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO **Info Link** High-dose IV is defined as any single dose ≥ 1000 mg/m^2.	**Reduced bone mineral density (BMD)** Defined as Z-score > 2.0 SD below the mean in survivors < 20 years old or T-score >1.0 SD below the mean in survivors ≥ 20 years old **Info Link** • The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density (BMD) of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the mean. • Current definitions of osteopenia (T-scores between 1.0 and 2.5 SD below the mean) and osteoporosis (T-scores > 2.5 SD below the mean) were developed primarily in the context of postmenopausal women. In this population, T-scores have a well validated correlation with fracture risk that increases with age. • The fracture risk associated with T-scores in younger populations, including cancer survivors with treatment-related hypogonadism, has not been established. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. • Pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. • The fracture risk in pediatric patients with low bone density for chronologic age based on Z-scores has not been established. There are no defined standards for referral or treatment of low BMD in children.	**Host Factors** Both genders are at risk Younger age at diagnosis Caucasian Lower weight and BMI **Treatment Factors** Corticosteroids Cyclosporine Tacrolimus Cranial radiation Craniospinal radiation HCT/TBI **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use Carbonated beverages	**Host Factors** Older age at time of treatment **Treatment Factors** Methotrexate cumulative dose ≥ 40 gm/m^2 Prolonged corticosteroid therapy (e.g., for chronic GVHD)	**SCREENING** **Bone density evaluation (DEXA or quantitative CT)** Baseline at entry into long-term follow-up, repeat as clinically indicated **Info Link** • The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. • Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. • Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	**Health Links** **Bone Health** **Resources** National Osteoporosis Foundation Website: ***www.nof.org*** **Considerations for Further Testing and Intervention** Ensure the AAP recommended minimum daily intake of Vitamin D (400 IU/day) for children, with possible considerations for high doses in selected patients (e.g., kidney disease or Vitamin D deficiency). Many experts recommend higher Vitamin D intake in adults as well. Also ensure adequate dietary calcium (see table in the "Bone Health" Health Link for age-appropriate recommendations). Supplements may be necessary if there are dietary restrictions. Advocate for regular weight-bearing exercises such as running and jumping. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency, correction of chronic metabolic acidosis that could accelerate bone loss). Endocrine consultation for patients with osteoporosis or history of multiple fractures for pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators). **SYSTEM = Musculoskeletal** **SCORE = 2B**

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

SECTION 28 REFERENCES

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

SECTION 29 REFERENCES

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

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

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ANTHRACYCLINE ANTIBIOTICS

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

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
33 (male)	**ANTHRACYCLINE ANTIBIOTICS** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Info Link (Mitoxantrone)** Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included here because of its cardiotoxic potential. **Info Link (Dose Conversion)** • Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of doxorubicin. There is a paucity of literature to support isotoxic dose conversion. • To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. **Doxorubicin**: Multiply total dose x 1 **Daunorubicin**: Multiply total dose x 1 **Epirubicin**: Multiply total dose x 0.67 **Idarubicin**: Multiply total dose x 5 **Mitoxantrone**: Multiply total dose x 4 • Clinical judgment should ultimately be used to determine indicated screening for individual patients.	**Cardiac toxicity** Cardiomyopathy Arrhythmias Subclinical left ventricular dysfunction **Info Link** • Dose levels correlating with cardiotoxicity are derived from adult studies. • Childhood cancer patients exhibit clinical and subclinical toxicity at lower levels. • Certain conditions (such as isometric exercise and viral infections) have been anecdotally reported to precipitate cardiac decompensation. • Prospective studies are needed to better define the contribution of these factors to cardiac disease risk.	**Treatment Factors** Combined with radiation involving the heart Combined with other cardiotoxic chemotherapy - Cyclophosphamide conditioning for HCT - Amsacrine **Medical Conditions** Obesity Congenital heart disease Febrile illness Hypertension Diabetes mellitus **Health Behaviors** Isometric exercise Smoking Drug use (e.g., cocaine, diet pills, ephedra, mahuang)	**Host Factors** Black/of African descent Younger than age 5 years at time of treatment **Treatment Factors** Higher cumulative anthracycline 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 Chest radiation ≥ 30 Gy Longer time elapsed	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **Info Link** • Exertional intolerance is uncommon in patients younger than 25 years old. • Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** Baseline at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated.	**Health Links** **Heart Health** **Cardiovascular Risk Factors** **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure and heart-healthy diet. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. High repetition weight lifting involving lighter weights is more likely to be safe. The number of repetitions should be limited to that which the survivor can perform with ease. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Consider excess risk of intensive isometric exercise program in any high risk patient (defined as needing screening every 1 or 2 years). **SYSTEM = Cardiovascular** **SCORE = 1**

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RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM (or comparable cardiac imaging)

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

*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 80], whichever was given first)
§See Section 80
†Based on doxorubicin isotoxic equivalent dose [see conversion factors on previous page, "Info Link (Dose Conversion)"]

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
34 (female)	**ANTHRACYCLINE ANTIBIOTICS** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Info Link (Mitoxantrone):** Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included here because of its cardiotoxic potential. **Info Link (Dose Conversion):** • Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of doxorubicin. There is a paucity of literature to support isotoxic dose conversion. • To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. **Doxorubicin**: Multiply total dose x 1 **Daunorubicin**: Multiply total dose x 1 **Epirubicin**: Multiply total dose x 0.67 **Idarubicin**: Multiply total dose x 5 **Mitoxantrone**: Multiply total dose x 4 • Clinical judgment should ultimately be used to determine indicated screening for individual patients.	**Cardiac toxicity** Cardiomyopathy Arrhythmias Subclinical left ventricular dysfunction **Info Link** • Dose levels correlating with cardiotoxicity are derived from adult studies. • Childhood cancer patients exhibit clinical and subclinical toxicity at lower levels. • Certain conditions (such as isometric exercise, pregnancy, and viral infections) have been anecdotally reported to precipitate cardiac decompensation. • Prospective studies are needed to better define the contribution of these factors to cardiac disease risk.	**Treatment Factors** Combined with radiation involving the heart Combined with other cardiotoxic chemotherapy - Cyclophosphamide conditioning for HCT - Amsacrine **Medical Conditions** Obesity Congenital heart disease Febrile illness Pregnancy Hypertension Diabetes mellitus **Health Behaviors** Isometric exercise Smoking Drug use (e.g., cocaine, diet pills, ephedra, mahuang)	**Host Factors** Female sex Black/of African descent Younger than age 5 years at time of treatment **Treatment Factors** Higher cumulative anthracycline doses: - ≥ 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 - Chest radiation ≥ 30 Gy Longer time elapsed	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **Info Link** • Exertional intolerance is uncommon in patients younger than 25 years old. • Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function))** Baseline at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated.	**Health Links** **Heart Health** **Cardiovascular Risk Factors** **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure and heart-healthy diet. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. High repetition weight lifting involving lighter weights is more likely to be safe. The number of repetitions should be limited to that which the survivor can perform with ease. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Consider excess risk of intensive isometric exercise program in any high risk patient (defined as needing screening every 1 or 2 years). 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. Evaluation to include an echocardiogram before and periodically during pregnancy (especially during third trimester) and monitoring during labor and delivery due to risk of cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

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Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. *J Clin Oncol*. Apr 1 2001;19(7):1926-1934.
Hudson MM, Rai SN, Nunez C, et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. *J Clin Oncol*. Aug 20 2007;25(24):3635-3643.
Kremer LC, van Dalen EC, Offringa M, Voute PA. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. *Ann Oncol*. Apr 2002;13(4):503-512.
Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voute PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. *Ann Oncol*. Jun 2002;13(6):819-829.
Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol*. Apr 20 2005;23(12):2629-2636.
Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009 339:b4606.
Shankar SM, Marina N, Hudson MM, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. *Pediatrics*. Feb 2008;121(2):e387-39.
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van Dalen EC, van der Pal HJ, van den Bos C, Kok WE, Caron HN, Kremer LC. Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. *Eur J Cancer*. Oct 2006;42(15):2549-2553.

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM (or comparable cardiac imaging)

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

*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 81], whichever was given first)
§See Section 81
†Based on doxorubicin isotoxic equivalent dose [see conversion factors on previous page, "Info Link (Dose Conversion)"]

CHEMOTHERAPY

ANTI-TUMOR ANTIBIOTICS

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

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

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CHEMOTHERAPY

CORTICOSTEROIDS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
37	**CORTICOSTEROIDS** Dexamethasone Prednisone	**Reduced bone mineral density (BMD)** Defined as Z-score > 2.0 SD below the mean in survivors < 20 years old or T-score >1.0 SD below the mean in survivors ≥ 20 years old **Info Link** • The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density (BMD) of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the mean. • Current definitions of osteopenia (T-scores between 1.0 and 2.5 SD below the mean) and osteoporosis (T-scores > 2.5 SD below the mean) were developed primarily in the context of postmenopausal women. In this population, T-scores have a well-validated correlation with fracture risk that increases with age. • The fracture risk associated with T-scores in younger populations, including cancer survivors with treatment-related hypogonadism, has not been established. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. • Pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. • The fracture risk in pediatric patients with low bone density for chronologic age based on Z-scores has not been established. There are no defined standards for referral or treatment of low BMD in children.	**Host Factors** Both genders are at risk Younger age at diagnosis Caucasian Lower weight and BMI **Treatment Factors** Corticosteroids Cyclosporine Tacrolimus Cranial radiation Craniospinal radiation HCT/TBI **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use Carbonated beverages	**Host Factors** Older age at time of treatment **Treatment Factors** Dexamethasone effect is more potent than prednisone Glucocorticoid cumulative dose ≥ 9 gm/m^2 prednisone equivalent	**SCREENING** **Bone density evaluation (DEXA or quantitative CT)** Baseline at entry into long-term follow-up, repeat as clinically indicated **Info Link** • The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. • Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. • Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	**Health Links** **Bone Health** **Resources** National Osteoporosis Foundation Website (***www.nof.org***) **Considerations for Further Testing and Intervention** Ensure the AAP recommended minimum daily intake of Vitamin D (400 IU/day) for children, with possible considerations for high doses in selected patients (e.g., kidney disease or Vitamin D deficiency). Many experts recommend higher Vitamin D intake in adults as well. Also ensure adequate dietary calcium (see table in the "Bone Health" Health Link for age-appropriate recommendations). Supplements may be necessary if there are dietary restrictions. Advocate for regular weight-bearing exercises such as running and jumping. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency, correction of chronic metabolic acidosis that could accelerate bone loss). Endocrine consultation for patients with osteoporosis or history of multiple fractures for pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators). **SYSTEM = Musculoskeletal** **SCORE = 2B**

SECTION 37 REFERENCES

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CHEMOTHERAPY

CORTICOSTEROIDS (cont)

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

SECTION 38 REFERENCES

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

SECTION 39 REFERENCES

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

SECTION 40 REFERENCES

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CHEMOTHERAPY

PLANT ALKALOIDS

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

SECTION 41 REFERENCES

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

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

SECTION 42 REFERENCES

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CHEMOTHERAPY

EPIPODOPHYLLOTOXINS

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

SECTION 43 REFERENCES

Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's Oncology Group. *Blood*. Jan 1 2007;109(1):46-51.

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DETERMINING APPLICABILITY OF RADIATION SECTIONS FOR SPECIFIC PATIENTS BASED ON EXPOSURE

GENERAL CONSIDERATIONS

- The radiation sections of the COG *Long-Term Follow-Up Guidelines* (Sections 44–102) are organized by anatomic region from the head downward. For specifics regarding relevant exposures to each anatomic region and radiation field, refer to the applicable pages of the "Radiation Reference Guide" in Appendix I and to the figures in this section.
- To determine specific screening guidelines by section number for an individual patient, use the "Patient-Specific Guideline Identification Tool" in Appendix I together with the "Radiation Reference Guide."

RADIATION DOSE CALCULATIONS

Some sections of the COG *Long-Term Follow-Up Guidelines* relevant to radiation exposure include dose specifications. These specifications indicate the minimum dose of radiation that is believed (based on available evidence and the recommendations of the expert panel) to place patients sufficiently at risk of the referenced late effect to recommend screening. For guideline sections that have a minimum specified dose, the following considerations apply in determining the applicability of the section for a patient based on his/her radiation exposure (see Appendix I—"Radiation Reference Guide"—for examples).

Sections with minimum dose specifications are applicable to a patient only if:

1. Patient received radiation to any field(s) relevant to the particular guideline section at ≥ the specified minimum dose[†]

OR

2. Patient received a combination of radiation to any relevant field(s)[†] ***plus*** relevant spinal radiation[‡] ***and/or*** TBI, the sum of which is ≥ the specified minimum dose[§]

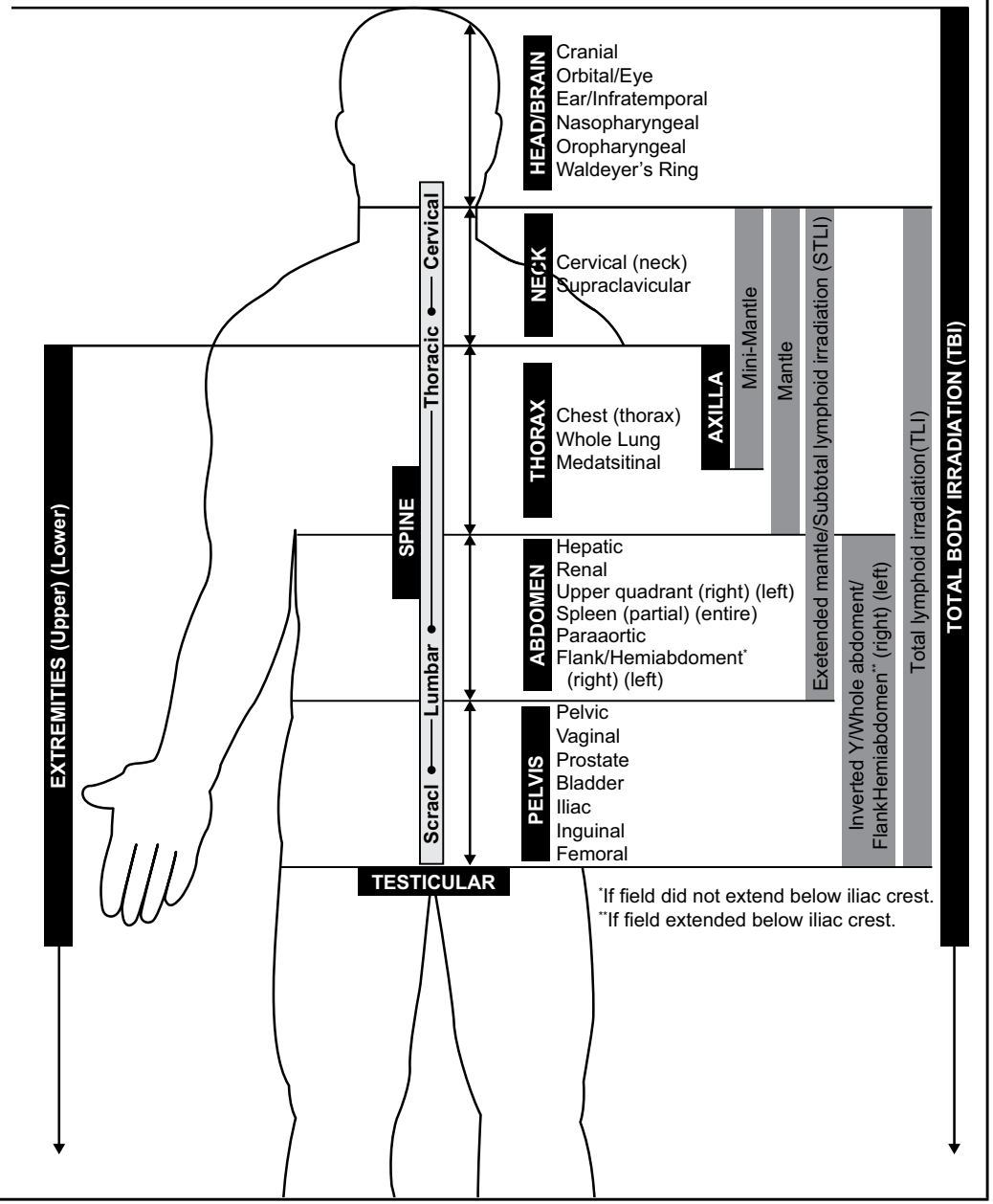
[†]Total dose to each field should include boost dose, if given. If patient received radiation to more than one field relevant to a particular guideline section during a single planned course of radiation treatment (excluding spinal radiation and TBI), ***the field that received the largest radiation dose should be used*** in making the determination as to the applicability of the indicated guideline section(s). ***Exception***: If patient received radiation ***to the same field at different times*** (e.g., at time of diagnosis AND at relapse), these doses should be added together when considering the applicability of the indicated guideline section.

[‡]Use the ***largest*** dose of radiation delivered to the spinal field(s) specified in the guideline section.

[§]Whole lung radiation, if given, should be included in minimum dose calculations for Sections 75–77, 83, 102.

GENERAL FACTORS INFLUENCING RADIATION TOXICITY

Include: daily fraction size, cumulative dose, age of patient at irradiation and type of radiation used. Toxicity may not be manifest until growth is completed or patient ages.

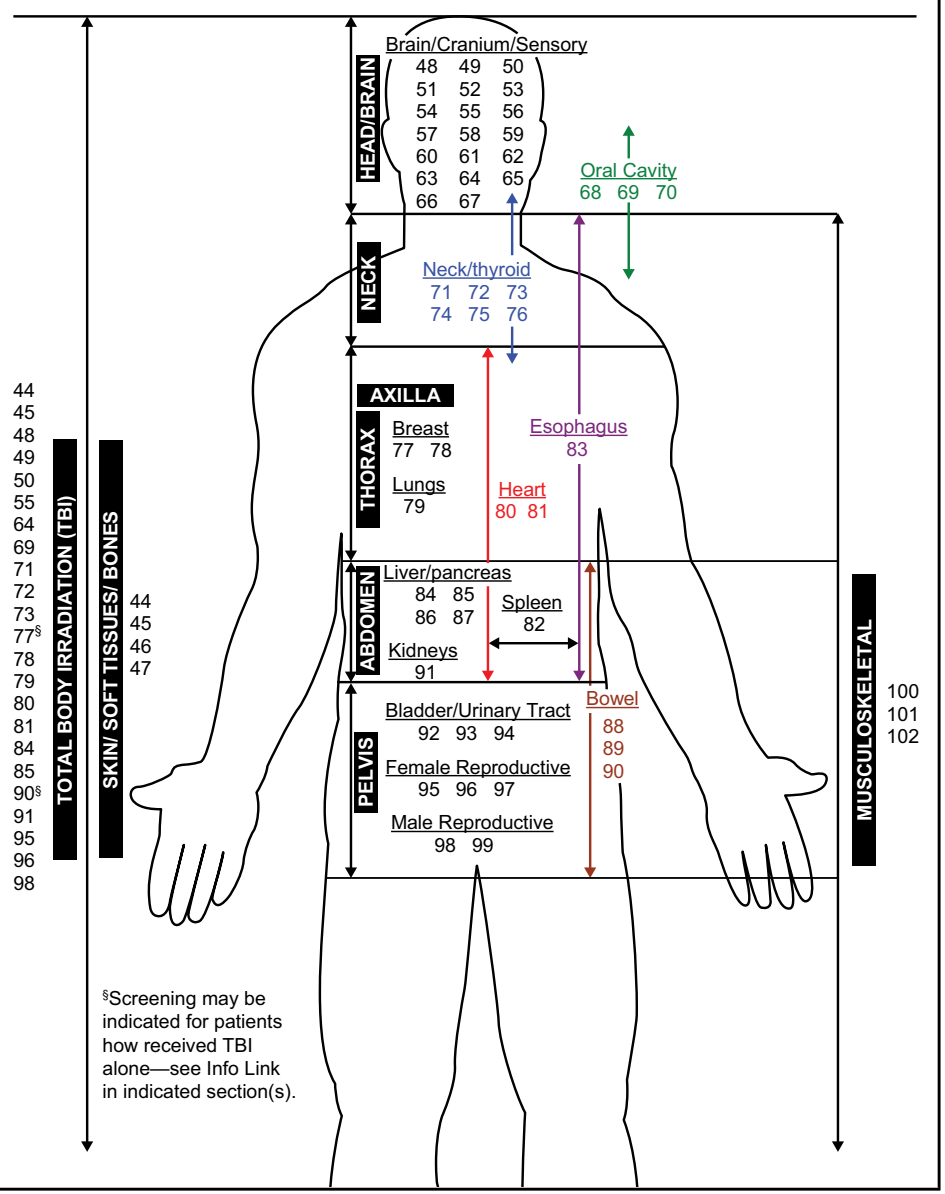


GUIDE TO RADIATION SECTION NUMBERS BY ANATOMIC REGION

NOTES

- This diagram provides an overview of the organization of the radiation sections of the COG *Long-Term Follow-Up Guidelines*.
- Radiation sections are arranged by anatomic region beginning with the cranium and proceeding downward.
- Arrows traversing multiple anatomic areas indicate body systems or organs (i.e., oral cavity, neck/thyroid, heart, esophagus, and bowel) that may be affected by radiation to any of the indicated anatomic regions.
- Additional detailed information, including examples of radiation dose calculations and diagrams of each body region are provided in the "Radiation Reference Guide" (Appendix I).
- Use the "Patient-Specific Guideline Identification Tool" in Appendix I together with the "Radiation Reference Guide" to determine specific screening guidelines by section number for individual patients.

Radiation Section Numbers by Anatomic Region



RADIATION

ALL FIELDS (INCLUDING TBI)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
44	**All Radiation Fields (Including TBI)**	**Secondary benign or malignant neoplasm** Occurring in or near radiation field **Info Link** Patients with bilateral or familial retinoblastoma (implying a germline mutation) are at increased risk for developing second malignant neoplasms.	**Host Factors** Cancer predisposing mutation (e.g., p53, RB1, NF1) Younger age at treatment **Treatment Factors** High cumulative radiation dose Large radiation treatment volumes Alkylating agent exposure	**Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Inspection and palpation of skin and soft tissues in irradiated field(s)** Yearly **SCREENING** **Other evaluations based on treatment volumes** See recommendations for specific fields	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Surgical and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

- See "Radiation Reference Guide" in Appendix I for list of all radiation fields applicable to this section.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 44 REFERENCES

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Armstrong GT, Liu W, Leisenring W, et al. Occurrence of multiple subsequent neoplasms in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Aug 1 2011;29(22):3056-3064.

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

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

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
45	**All Radiation Fields (Including TBI)** • See "Radiation Reference Guide" in Appendix I for list of all radiation fields applicable to this section. • See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.	**Dysplastic nevi** **Skin cancer** Basal cell carcinoma Squamous cell carcinoma Melanoma	**Host Factors** Gorlin's syndrome (nevoid basal cell carcinoma syndrome) **Health Behaviors** Sun exposure Tanning booths	**Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**HISTORY** **Skin lesions** **Changing moles (asymmetry, bleeding, increasing size, indistinct borders)** Yearly **PHYSICAL** **Dermatologic exam of irradiated fields** Yearly	**Health Links** **Skin Health** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Dermatology consultation for evaluation and monitoring of atypical nevi. Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 45 REFERENCES

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

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

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RADIATION

ALL FIELDS (EXCEPT TBI)

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

- See "Radiation Reference Guide" in Appendix I for list of all radiation fields applicable to this section.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 46 REFERENCES

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RADIATION

ALL FIELDS (EXCEPT TBI) (cont)

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

- See "Radiation Reference Guide" in Appendix I for list of all radiation fields applicable to this section.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

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

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

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

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
51	**≥ 18 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Cerebrovascular complications** Stroke Moyamoya Occlusive cerebral vasculopathy Cavernomas **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. • This condition reflects an attempt to revascularize the ischemic portion of the brain. • Cavernomas are a common late effect of cranial radiation, but the majority of patients with cavernomas are asymptomatic.	**Host Factors** Down syndrome **Treatment Factors** Suprasellar radiation **Medical Conditions** Sickle cell disease Neurofibromatosis	**Host Factors** Parasellar tumor **Treatment Factors** Radiation dose ≥ 50 Gy Circle of Willis in radiation field	**HISTORY** **Hemiparesis** **Hemiplegia** **Weakness** **Aphasia** Yearly **PHYSICAL** **Neurologic exam** Yearly	**Considerations for Further Testing and Intervention** Brain MRI with diffusion-weighted imaging with MR angiography as clinically indicated. Neurology/neurosurgery consultation and follow-up. Physical and occupational therapy as clinically indicated. Note: Revascularization procedures are likely helpful for moyamoya. Aspirin prophylaxis has not yet been shown to be beneficial for moyamoya or occlusive cerebral vasculopathy. **SYSTEM = CNS** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 18 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 18 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 52 REFERENCES

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RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO BRAIN/CRANIUM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
54	**Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring**	**Overweight** **Obesity** **Info Link** Overweight: Age 2–20 years: BMI for age ≥ 85th–< 95th percentile Age ≥ 21 years: BMI ≥ 25–29.9 Obesity: Age 2–20 years: BMI for age ≥ 95th percentile Age ≥ 21 years: BMI ≥ 30 BMI=wt(kg)/ht(M^2) BMI calculator available on-line at: ***www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm/*** Growth charts for patients < 21 years of age available on-line at: ***www.cdc.gov/growthcharts***	**Host Factors** Younger at treatment **Treatment Factors** Higher cranial radiation dose Surgery in suprasellar region Combined with corticosteroids Prolonged corticosteriod therapy (e.g., for chronic GVHD) **Medical Conditions** Familial dyslipidemia Growth hormone deficiency Hypothyroidism Hypogonadism	**Host Factors** Age < 4 years old at time of treatment Female sex **Treatment Factors** Cranial radiation dose ≥ 18 Gy **Medical Conditions** Inability to exercise	**PHYSICAL** **Height** **Weight** **BMI** **Blood pressure** Yearly	**Health Links** **Diet and Physical Activity** **Cardiovascular Risk Factors** **Counseling** Counsel regarding obesity-related health risks **Considerations for Further Testing and Intervention** Consider evaluation for other co-morbid conditions, including dyslipidemia, hypertension, or impaired glucose metabolism. Nutritional counseling. **Info Link** • Overweight/obesity may occur in a constellation of conditions known as the metabolic syndrome. • Definitions of the metabolic syndrome are evolving, but generally include a combination of central (abdominal) obesity with at least 2 or more of the following: - hypertension - atherogenic dyslipidemia (elevated triglycerides, reduced HDL cholesterol), and - abnormal glucose metabolism (fasting hyperglycemia, hyperinsulinism, insulin resistance, diabetes mellitus type II). **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 54 REFERENCES

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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
55	**Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **Total Body Irradiation (TBI)**	**Growth hormone deficiency** **Info Link** Growth charts available on-line at ***www.cdc.gov/growthcharts/***	**Host Factors** Younger age at treatment **Treatment Factors** Higher radiation doses Surgery in suprasellar region Pretransplant radiation TBI ≥ 10 Gy in single fraction, ≥ 12 Gy fractionated	**Treatment Factors** Radiation dose ≥ 18 Gy Pretransplant cranial radiation TBI given in single fraction	**HISTORY** **Assessment of nutritional status** Every 6 months until growth is completed, then yearly. **PHYSICAL** **Tanner staging** Every 6 months until sexually mature **Height** **Weight** **BMI** Every 6 months until growth is completed, then yearly	**Health Links** **Growth Hormone Deficiency** See also: **Hypopituitarism** **Resources** ***www.magicfoundation.org*** **Considerations for Further Testing and Intervention** For skeletally immature children, refer to endocrinology if radiation dose ≥ 30 Gy. For those treated with < 30 Gy, obtain x-ray for bone age in poorly growing children. Endocrine consultation for: Poor growth for age or stage of puberty as evidenced by decline in growth velocity and change in percentile rankings on growth chart; weight below 3rd percdentile on growth chart. Evaluate thyroid function in any poorly growing child. Consult with endocrinologist regarding risks/benefits of adult growth hormone replacement therapy. Consider bone density testing in patients who are growth hormone deficient. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
57 (female)	**Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring**	**Precocious puberty**	**Host Factors** Female sex Younger age at treatment **Treatment Factors** Radiation doses ≥ 18 Gy		**PHYSICAL** **Height** **Weight** **Tanner staging** Yearly until sexually mature	**Health Links** **Precocious Puberty** **Resources** ***www.magicfoundation.org*** **Considerations for Further Testing and Intervention** Obtain FSH, LH, estradiol as clinically indicated in patients with signs of accelerated pubertal progression and growth. Obtain x-ray for bone age in rapidly growing children. Endocrine consultation for accelerated puberty (puberty in girl < 8 years old). **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
58 (male)	**≥ 40 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Hyperprolactinemia**	**Treatment Factors** Higher radiation dose Surgery or tumor in hypothalamic area	**Treatment Factors** Radiation dose ≥ 50 Gy	**HISTORY** **Decreased libido** **Galactorrhea** Yearly **SCREENING** **Prolactin level** In patients with galactorrhea or decreased libido.	**Health Links** **Hyperprolactinemia** **Resources** ***www.magicfoundation.org*** **Considerations for Further Testing and Intervention** CT evaluation of sella turcica for pituitary adenoma in patients with hyperprolactinemia. Endocrine consultation for patients with hyperprolactinemia or galactorrhea. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 58 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
59 (female)	**≥ 40 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Hyperprolactinemia**	**Treatment Factors** Higher radiation dose Surgery or tumor in hypothalamic area	**Treatment Factors** Radiation dose ≥ 50 Gy	**HISTORY** **Galactorrhea** **Menstrual history** Yearly **SCREENING** **Prolactin level** In patients with galactorrhea or amenorrhea.	**Health Links** **Hyperprolactinemia** **Resources** ***www.magicfoundation.org*** **Considerations for Further Testing and Intervention** CT evaluation of sella turcica for pituitary adenoma in patients with hyperprolactinemia. Endocrine consultation for patients with hyperprolactinemia or galactorrhea. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 59 REFERENCES

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

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
60	**≥ 40 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Central hypothyroidism** **Info Link** Central hypothyroidism includes thyroid-releasing and thyroid-stimulating hormone deficiency	**Treatment Factors** Higher radiation dose		**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**Health Links** **Thyroid Problems** See also: **Hypopituitarism** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
61 (male)	**≥ 30 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Gonadotropin deficiency** **Info Link** Gonadotropin deficiency includes LH and FSH deficiency.	**Treatment Factors** Higher radiation dose		**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchiometer** Yearly **SCREENING** **Semen analysis** At request of sexually mature patient **FSH** **LH** **Testosterone** (ideally morning) Baseline at age 14 ***and*** as clinically indicated in patients with delayed/arrested puberty and/or clinical signs and symptoms of testosterone deficiency	**Health Links** **Male Health Issues** See also: **Hypopituitarism** **Resources** American Society for Reproductive Medicine: ***www.asrm.org*** Fertile Hope: ***www.fertilehope.org*** **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Spermatogenesis can be induced with gonadotropins in men with hypogonadotropic hypogonadism. Consider bone density testing in patients who are gonadotropin deficient. **SYSTEM = Reproductive (male)** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 61 REFERENCES

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RADIATION

POTENTIAL IMPACT TO NEUROENDOCRINE AXIS (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
62 (female)	**≥ 30 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Gonadotropin deficiency** **Info Link** Gonadotropin deficiency includes LH and FSH deficiency.	**Treatment Factors** Higher radiation dose		**HISTORY** **Pubertal (onset, tempo)** **Menstrual/pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging** Yearly until sexually mature **SCREENING** **FSH** **LH** **Estradiol** Baseline at age 13, ***and*** as clinically indicated in patients with delayed or arrested puberty, irregular menses, primary or secondary amenorrhea, or clinical signs and symptoms of estrogen deficiency	**Health Links** **Female Health Issues** See also: **Hypopituitarism** **Resources** American Society for Reproductive Medicine: ***www.asrm.org*** Fertile Hope: ***www.fertilehope.org*** **Considerations for Further Testing and Intervention** Refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Consider bone density testing in patients who are gonadotropin deficient. **SYSTEM = Reproductive (female)** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 62 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
63	**≥ 30 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Orbital/Eye** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Central adrenal insufficiency**	**Treatment Factors** Higher radiation dose Surgery or tumor in the suprasellar region	**Treatment Factors** Prior development of another hypothalamic-pituitary endocrinopathy	**HISTORY** **Failure to thrive** **Anorexia** **Dehydration** **Hypoglycemia** **Lethargy** **Unexplained hypotension** Yearly **SCREENING** Refer for yearly endocrinology evaluation if dose to hypothalamic-pituitary axis ≥30 Gy	**Health Links** **Central Adrenal Insufficiency** See also: **Hypopituitarism** **Resources** ***www.magicfoundation.org*** **Counseling** Counsel regarding corticosteroid replacement therapy and stress dosing. Counsel regarding Medical Alert bracelet. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 63 REFERENCES

Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. *Nat Clin Pract Endocrinol Metab*. Feb 2009 5(2):88-99.
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RADIATION

POTENTIAL IMPACT TO EYE

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

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO EYE (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
65	**≥ 30 Gy to:** **Cranial** **Orbital/Eye** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone. **Info Link** • Radiation-related ocular complications other than cataracts are generally associated only with orbital/eye radiation or higher dose cranial radiation. • Patients with a history of an ocular tumor (e.g., retinoblastoma) are at higher risk for late-onset ocular complications and should receive ongoing follow-up by an ophthalmologist at least annually, and more frequently if clinically indicated.	**Ocular toxicity** Orbital hypoplasia Lacrimal duct atrophy Xerophthalmia (keratoconjunctivitis sicca) Keratitis Telangiectasias Retinopathy Optic chiasm neuropathy Enophthalmos Chronic painful eye Maculopathy Papillopathy Glaucoma **Info Link** Reduced visual acuity may be associated with cataracts, retinal damage, and optic nerve damage.	**Treatment Factors** Higher radiation dose Higher daily fraction dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) [problems related to tearing]	**Host Factors** Chronic GVHD (xerophthalmia only) **Treatment Factors** Total dose ≥ 50 Gy Fraction dose ≥ 2 Gy	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** **Dry eye** **Persistent eye irritation** **Excessive tearing** **Light sensitivity** **Poor night vision** **Painful eye** Yearly **PHYSICAL** **Visual acuity** **Funduscopic exam** Yearly **SCREENING** **Evaluation by ophthalmologist** Yearly	**Health Links** **Eye Health** **Resources** FACES–The National Craniofacial Association website: ***www.faces-cranio.org/*** **Considerations for Further Testing and Intervention** Refer patients with visual deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. **SYSTEM = Ocular** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO EAR

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
66	**≥ 30 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Ototoxicity** Tympanosclerosis Otosclerosis Eustachian tube dysfunction Conductive hearing loss	**Host Factors** Younger age at treatment **Treatment Factors** Higher radiation dose **Medical Conditions** Chronic otitis Chronic cerumen impaction	**Treatment Factors** Dose ≥ 50 Gy	**HISTORY** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** Yearly **PHYSICAL** **Otoscopic exam** Yearly **SCREENING** **Complete audiological evaluation** Yearly after completion of therapy for 5 years [for patients < 10 years old, continue yearly until age 10], then every 5 years If hearing loss is detected, test at least yearly or as recommended by audiologist If clinical suspicion of hearing loss at any time, test as clinically indicated If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions [OAEs] **Info Link** • A "complete audiological evaluation" includes pure tone air and bone conduction, speech audiometry, and tympanometry for both ears. • Frequency-specific auditory brainstem response (ABR) can be performed if the above is inconclusive.	**Health Links** **Hearing Loss** **Educational Issues** **Considerations for Further Testing and Intervention** Audiology consultation for patients with hearing loss. Otolaryngology consultation for patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Speech and language therapy for children with hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources. Consider specialized evaluation for specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 66 REFERENCES

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RADIATION

POTENTIAL IMPACT TO EAR (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
67	**≥ 30 Gy to:** **Cranial** **Ear/Infratemporal** **Nasopharyngeal** **Waldeyer's Ring** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Ototoxicity** Sensorineural hearing loss Tinnitus	**Host Factors** Younger age at treatment CNS tumor **Treatment Factors** Higher radiation dose Conventional (non-conformal) radiation **Medical Conditions** CSF shunting	**Treatment Factors** Radiation administered prior to platinum chemotherapy Combined with other ototoxic agents such as: - Cisplatin - Carboplatin in myeloablative doses - Aminoglycosides	**HISTORY** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** Yearly **PHYSICAL** **Otoscopic exam** Yearly **SCREENING** **Complete audiological evaluation** Yearly after completion of therapy for 5 years [for patients <10 years old, continue yearly until age 10], then every 5 years If hearing loss is detected, test at least yearly or as recommended by audiologist If clinical suspicion of hearing loss at any time, test as clinically indicated If audiogram is inconclusive or unevaluable, refer to audiologist for consideration of electrophysiologic testing e.g., otoacoustic emissions [OAEs] **Info Link** • A "complete audiological evaluation" includes pure tone air and bone conduction, speech audiometry, and tympanometry for both ears. • Frequency-specific auditory brainstem response (ABR) can be performed if the above is inconclusive.	**Health Links** **Hearing Loss** **Educational Issues** **Considerations for Further Testing and Intervention** Audiology consultation for patients with hearing loss. Otolaryngology consultation for patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Speech and language therapy for children with hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources. Consider specialized evaluation for specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 67 REFERENCES

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RADIATION

POTENTIAL IMPACT TO ORAL CAVITY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
68	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Waldeyer's Ring** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Mantle** **Mini-Mantle** **Total Lymphoid Irradiation (TLI)**	**Xerostomia** **Salivary gland dysfunction**	**Treatment Factors** Head and neck radiation involving the parotid gland Higher radiation doses Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Salivary gland dose ≥ 30 Gy **Medical Conditions** Chronic GVHD	**HISTORY** **Xerostomia** Yearly **PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine) Regular dental care including fluoride applications **SYSTEM = Dental** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 68 REFERENCES

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RADIATION

POTENTIAL IMPACT TO ORAL CAVITY (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
69	**Cranial** **Nasopharyngeal** **Oropharyngeal** **Waldeyer's Ring** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Mantle** **Mini-Mantle** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)**	**Dental abnormalities** Tooth/root agenesis Microdontia Root thinning/shortening Enamel dysplasia Periodontal disease Dental caries Malocclusion Temporomandibular joint dysfunction	**Host Factors** Younger age at treatment Gorlin's syndrome (nevoid basal cell carcinoma syndrome) **Treatment Factors** Higher radiation dose	**Host Factors** Age < 5 years at time of treatment **Treatment Factors** Dose ≥ 10 Gy	**PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Regular dental care including fluoride applications. Consultation with orthodontist experienced in management of irradiated childhood cancer survivors. Baseline panorex prior to dental procedures to evaluate root development. **SYSTEM = Dental** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 69 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
70	**≥ 40 Gy to:** **Cranial** **Nasopharyngeal** **Oropharyngeal** **Waldeyer's Ring** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Mantle** **Mini-Mantle** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Osteoradionecrosis**	**Treatment Factors** Radiation dose to bone ≥ 45 Gy	**Treatment Factors** Dose ≥ 50 Gy	**HISTORY** **Impaired or delayed healing following dental work** **Persistent jaw pain or swelling** **Trismus** As clinically indicated **PHYSICAL** **Impaired wound healing** **Jaw swelling** **Trismus** As clinically indicated	**Health Links** **Osteoradionecrosis** **Considerations for Further Testing and Intervention** Imaging studies (x-ray, CT scan and/or MRI) may assist in making diagnosis. Surgical biopsy may be needed to confirm diagnosis. Consider hyperbaric oxygen treatments. **SYSTEM = Dental** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 70 REFERENCES

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RADIATION

POTENTIAL IMPACT TO NECK/THYROID

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 71 REFERENCES

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RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

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

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
74	≥ **40 Gy to:** **Oropharyngeal** **Waldeyer's Ring** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Mantle** **Mediastinal** **Mini-Mantle** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Hyperthyroidism**	**Treatment Factors** Higher radiation dose		**HISTORY** **Heat intolerance** **Tachycardia** **Palpitations** **Weight loss** **Emotional lability** **Muscular weakness** **Hyperphagia** Yearly **PHYSICAL** **Eyes** **Skin** **Thyroid** **Cardiac** **Neurologic** Yearly **SCREENING** **TSH** **Free T4** Yearly	**Health Links** **Thyroid Problems** **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
75	≥ **40 Gy to:** **Cranial** **Nasopharyngeal** **Oropharyngeal** **Waldeyer's Ring** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Mini~Mantle** **Whole lung** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Carotid artery disease**	**Medical Conditions** Hypertension Diabetes mellitus Hypercholesterolemia		**HISTORY** **Memory impairment** **Yearly** **PHYSICAL** **Diminished carotid pulses** **Carotid bruits** **Abnormal neurologic exam (compromise of blood flow to brain)** Yearly	**Considerations for Further Testing and Intervention** Doppler ultrasound of carotid vessels as clinically indicated. MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated. Consider color Doppler 10 years after completion of radiation therapy to the neck as a baseline refer to cardiologist if abnormal. **SYSTEM = Cardiovascular** **SCORE = 2A**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO NECK/THYROID (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
76	**≥ 40 Gy to:** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Mini-Mantle** **Whole lung** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Subclavian artery disease**			**PHYSICAL** **Diminished brachial and radial pulses** **Pallor of upper extremities** **Coolness of skin** **Unequal blood pressure** Yearly	**Considerations for Further Testing and Intervention** Doppler ultrasound of subclavian vessels as clinically indicated. MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated. Consider color Doppler 10 years after completion of radiation therapy to the neck as a baseline refer to cardiologist if abnormal. **SYSTEM = Cardiovascular** **SCORE = 2A**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 76 REFERENCES

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RADIATION

POTENTIAL IMPACT TO BREAST

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
77 (female)	≥ **10 Gy to:** **Subtotal Lymphoid Irradiation (STLI)** **Axilla** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Mini~Mantle** **Whole lung** **Total Body Irradiation (TBI)*** **Total Lymphoid Irradiation (TLI)**	**Breast cancer**	**Host Factors** Family history of breast cancer **Treatment Factors** Higher radiation dose Longer time since radiation (> 5 years) Decreased risk in women treated with alkylating agents	**Host Factors** *BRACA1*, *BRACA2*, ATM mutation	**PHYSICAL** **Breast exam** Yearly, beginning at puberty until age 25, then every 6 months **SCREENING** **≥ 20 Gy** Mammogram Yearly, beginning 8 years after radiation or at age 25, whichever occurs last. **Breast MRI** Yearly, as an adjunct to mammography beginning 8 years after radiation or at age 25, whichever occurs last. **10–19 Gy or TBI alone** Clinician to discuss benefits and risks/ harms of screening with patient. If decision is made to screen, then follow screening recommendations for ≥ 20 Gy.	**Health Links** **Breast Cancer** **Counseling** Teach breast self-exam and counsel to perform monthly beginning at puberty. **Considerations for Further Testing and Intervention** Surgical consultation for diagnostic procedure in patients with breast mass or suspicious radiographic finding. Decisions regarding the use of HRT should be based on current literature and should take into consideration the risk/benefit ratio for individual patients. **SYSTEM = SMN** **SCORE = 1**

Info Link

- **Important*: The risk of breast cancer in patients who received 10–19 Gy of radiation with potential impact to the breast or those who received TBI alone is of a lower magnitude compared to those who received ≥ 20 Gy of radiation with potential impact to the breast (e.g.,thorax, axilla).
- *Monitoring of patients who received 10-19 Gy of radiation with potential impact to the breast, or those who received TBI without additional radiation,should be determined on an individual basis.*
- After the clinician discusses the benefits and risks/ harms of screening with the patient, if a decision is made to screen, then follow the recommendations for patients who received ≥ 20 Gy.

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 10 Gy
     OR
  2) Received a combination of radiation to any of the specified fields, the sum of which is ≥ 10 Gy
     OR
  3) Received TBI alone
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

Info Link

- Mammography is currently limited in its ability to evaluate the premenopausal breast.
- MRI is now recommended as an adjunct to mammography in women treated with chest radiation for childhood cancer similar to screening of other populations at high risk for breast cancer (e.g., premenopausal known or likely carriers of gene mutation of known penetrance).
- The upper age limit at which both modalities should be used for breast cancer surveillance has not been established.

SECTION 77 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
78 (female)	**Subtotal Lymphoid Irradiation (STLI)** **Axilla** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Mini~Mantle** **Whole lung** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)**	**Breast tissue hypoplasia**	**Host Factors** Prepubertal at time of breast irradiation Treatment Factors **Treatment Factors** Radiation dose ≥ 10 Gy to prepubertal breast bud may cause failure of development (hypoplasia)	**Treatment Factors** ≥ 20 Gy to prepubertal breast bud may ablate development	**PHYSICAL** **Breast exam** Yearly	**Considerations for Further Testing and Intervention** Surgical consultation for breast reconstruction after completion of growth. **SYSTEM = Reproductive (female)** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 78 REFERENCES

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RADIATION

POTENTIAL IMPACT TO LUNGS

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

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SYSTEM = Pulmonary

SCORE = 1

SECTION 79 REFERENCES

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RADIATION

POTENTIAL IMPACT TO HEART

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
80 (male)	**Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Whole lung** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)**	**Cardiac toxicity** Congestive heart failure Cardiomyopathy Pericarditis Pericardial fibrosis Valvular disease Myocardial infarction Arrhythmia Atherosclerotic heart disease	**Host Factors** Younger age at irradiation Family history of dyslipidemia Coronary artery disease **Treatment Factors** Radiation dose ≥ 20 Gy to chest TBI Combined with radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Combined with other cardiotoxic chemotherapy: - Anthracyclines - Cyclophosphamide conditioning for HCT - Amsacrine **Medical Conditions** Hypertension Obesity Dyslipidemia Diabetes mellitus Congenital heart disease Febrile illness **Health Behaviors** Smoking Isometric exercise Drug use (e.g., cocaine, diet pills, ephedra)	**Host Factors** Black/of African descent Younger than age 5 years at treatment **Treatment Factors** Anteriorly-weighted radiation fields Lack of subcarinal shielding Doses ≥ 30 Gy in patients who have received anthracyclines Doses ≥ 40 Gy in patients who have not received anthracyclines Longer time since treatment	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **Info Link** • Exertional intolerance is uncommon in patients younger than 25 years old. • Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** Yearly **SCREENING** **Fasting blood glucose OR HbA1c and lipid profile** Every 2 years If abnormal, refer for ongoing management **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated **ECHO (or comparable imaging to evaluate cardiac anatomy and function)** Baseline at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose.	**Health Links** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **Dental Health** **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure and heart-healthy diet. Counsel regarding endocarditis prophylaxis if at highest risk. Note: The AHA now limits their recommendation regarding endocarditis prophylaxis only to patients whose cardiac conditions are associated with the highest risk of adverse outcome, which includes, but is not limited to the following four categories: (1) prosthetic heart valves, (2) previous history of infective endocarditis, (3) certain patients with congenital heart disease, and (4) valvulopathy following cardiac transplantation. Survivors diagnosed with heart valve disorders should discuss the need for endocarditis prophylaxis with their cardiologist. See Wilson et al. (2007) for specifics. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. High repetition weight lifting involving lighter weights is more likely to be safe. The number of repetitions should be limited to that which the survivor can perform with ease. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation for patients with subclinical abnormalities on screening evaluations or with left ventricular dysfunction, dysrhythmia or prolonged QTc interval. Consider cardiology consultation (5 to 10 years after radiation) to evaluate risk for coronary artery disease in patients who received ≥ 40 Gy chest radiation alone or ≥ 30 Gy chest radiation plus anthracycline. Consider excess risk of intensive isometric exercise program in any high risk patient defined as needing screening every 1 or 2 years. **SYSTEM = Cardiovascular** **SCORE = 1**

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM

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

*Age at time of first cardiotoxic therapy (anthracycline or radiation with potential to impacte heart, whichever was given first)

†Based on doxorubicin isotoxic equivalent dose [see conversion factors in Section 33 "Info Link (Dose Conversion)"]

‡If patient received radiation to more than one specified field, see dose calculation rules on page 56.

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO HEART (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
81 (female)	**Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Whole lung** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)**	**Cardiac toxicity** Congestive heart failure Cardiomyopathy Pericarditis Pericardial fibrosis Valvular disease Myocardial infarction Arrhythmia Atherosclerotic heart disease	**Host Factors** Younger age at irradiation Family history of dyslipidemia Coronary artery disease **Treatment Factors** Radiation dose ≥ 20 Gy to chest TBI Combined with radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Combined with other cardiotoxic chemotherapy: - Anthracyclines - Cyclophosphamide conditioning for HCT - Amsacrine **Medical Conditions** Hypertension Obesity Dyslipidemia Diabetes mellitus Congenital heart disease Febrile illness Pregnancy Premature ovarian failure (untreated) **Health Behaviors** Smoking Isometric exercise Drug use (e.g., cocaine, diet pills, ephedra)	**Host Factors** Female sex Black/of African descent Younger than age 5 years at treatment **Treatment Factors** Anteriorly-weighted radiation fields Lack of subcarinal shielding Doses ≥ 30 Gy in patients who have received anthracyclines Doses ≥ 40 Gy in patients who have not received anthracyclines Longer time since treatment	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **Info Link** • Exertional intolerance is uncommon in patients younger than 25 years old. • Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** Yearly **SCREENING** **Fasting blood glucose OR HbA1c and lipid profile** Every 2 years If abnormal, refer for ongoing management **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated **ECHO (or comparable imaging to evaluate cardiac anatomy and function)** Baseline at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose.	**Health Links** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **Dental Health** **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure, and heart-healthy diet. Counsel regarding endocarditis prophylaxis if at highest risk. **Note**: The AHA now limits their recommendation regarding endocarditis prophylaxis only to patients whose cardiac conditions are associated with the highest risk of adverse outcome, which includes, but is not limited to the following four categories: (1) prosthetic heart valves, (2) previous history of infective endocarditis, (3) certain patients with congenital heart disease, and (4) valvulopathy following cardiac transplantation. Survivors diagnosed with heart valve disorders should discuss the need for endocarditis prophylaxis with their cardiologist. See Wilson et al. (2007) for specifics. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. High repetition weight lifting involving lighter weights is more likely to be safe. The number of repetitions should be limited to that which the survivor can perform with ease. Patients who choose to engage in strenuous or varsity team sports should discuss appropriate guidelines and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation for patients with subclinical abnormalities on screening evaluations or with left ventricular dysfunction, dysrhythmia or prolonged QTc interval. Additional cardiology evaluation for patients who are pregnant or planning pregnancy who: (1) received ≥ 30 Gy chest radiation, or (2) received chest radiation in combination with cardiotoxic chemotherapy (anthracyclines or high-dose cyclophosphamide).Evaluation to include echocardiogram before and periodically during pregnancy (especially during third trimester) and monitoring during labor and delivery due to risk of cardiac failure. Consider cardiology consultation (5 to 10 years after radiation) to evaluate risk for coronary artery disease in patients who received ≥ 40 Gy chest radiation alone or ≥ 30 Gy chest radiation plus anthracycline. Consider excess risk of intensive isometric exercise program in any high-risk patient defined as needing screening every 1 or 2 years. **SYSTEM = Cardiovascular** **SCORE = 1**

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM

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

*Age at time of first cardiotoxic therapy (anthracycline or radiation with potential to impacte heart, whichever was given first)

†Based on doxorubicin isotoxic equivalent dose [see conversion factors in Section 34 "Info Link (Dose Conversion)"]

‡If patient received radiation to more than one specified field, see dose calculation rules on page 56.

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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Heidenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. *J Clin Oncol*. Jan 1 2007;25(1):43-49.

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

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

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

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

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

Qureshi AI, Alexandrov AV, Tegeler CH, Hobson RW, 2nd, Dennis Baker J, Hopkins LN. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging cosponsored by the Society of Vascular and Interventional Neurology. *J Neuroimaging*. Jan 2007;17(1):19-47.

Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst*. Feb 7 2007;99(3):206-214.

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RADIATION

POTENTIAL IMPACT TO SPLEEN

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
82	**≥ 40 Gy to:** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Spleen (entire)** **Whole abdomen** **Subtotal Lymphoid Irradiation (STLI)** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone. **Info Link** • Not all paraaortic and inverted Y treatment fields include the spleen. • Survivors are at risk for functional asplenia only if the spleen was included in the radiation field.	**Functional asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*, meningococcus)	**Treatment Factors** Higher radiation dose to entire spleen		**PHYSICAL** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** When febrile T ≥ 101ºF **SCREENING** **Blood culture** When febrile T ≥ 101°F	**Health Links** **Splenic Precautions** **Counseling** Medical alert bracelet/card noting functional asplenia Counsel regarding risk of life-threatening infections with encapsulated organisms. Also counsel regarding risk associated with malaria and tick-borne diseases if living in or visiting endemic areas. **Considerations for Further Testing and Intervention** In patients with T ≥ 101° (38.3° C) or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC toxic clinical appearance fever ≥ 104°F meningitis, pneumonia, or other serious focus of infection signs of septic shock or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines according to current ACIP recommendations. Discuss with dental provider potential need for antibiotic prophylaxis based on planned procedure. **Info Link** See current edition of AAP *Red Book* for current recommendations regarding antibiotic prophylaxis and immunizations **SYSTEM = Immune** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
83	**≥ 30 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Cervical (neck)** **Supraclavicular** **Spine (cervical)** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Mini~Mantle** **Whole lung** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Esophageal stricture**	**Treatment Factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, actinomycin) **Medical Conditions** Gastroesophageal reflux History of Candida esophagitis	**Treatment Factors** Radiation dose ≥ 40 Gy **Medical Conditions** Gut GVHD	**HISTORY** **Dysphagia** **Heartburn** Yearly	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Surgical and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
84	**[Abdominal radiation]** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Lymphoid Irradiation (TLI)** **Total Body Irradiation (TBI)**	**Impaired Glucose Metabolism/Diabetes Mellitus** **Info Link** • Impaired glucose metabolism may occur in a constellation of conditions known as the metabolic syndrome. • Definitions of the metabolic syndrome are evolving but generally include a combination of central (abdominal) obesity with at least 2 or more of the following: - hypertension - atherogenic dyslipidemia (elevated triglycerides reduced HDL cholesterol) - abnormal glucose metabolism (fasting hyperglycemia, hyperinsulinism, insulin resistance, diabetes mellitus type II). • **Note**: Patients who received TBI may develop features of metabolic syndrome without associated obesity	**Host Factors** Family history of diabetes mellitus **Treatment Factors** Prolonged corticosteriod therapy (e.g., for chronic GVHD)	**Medical Conditions** Obesity (not *necessary* in HCT survivors who received TBI)	**SCREENING** **Fasting blood glucose *OR* HbA1c** Every 2 years. More frequently if indicated based on patient evaluation	**Health Links** **Diet and Physical Activity** **Cardiovascular Risk Factors** **Counseling** Counsel regarding obesity-related health risks and nutrition. **Considerations for Further Testing and Intervention** Consider endocrine consultation if impaired glucose metabolism is suspected. Consider evaluation for other co-morbid conditions, including overweight/obesity, hypertension, and dyslipidemia. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

• See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
85	**Total Body Irradiation (TBI)** **Note**: For all guideline sections relevant to patients who received TBI please see page 129.	**Dyslipidemia**	**Host Factors** Family history of dyslipidemia **Treatment Factors** Prolonged corticosteriod therapy (e.g., for chronic GVHD)	**Medical Conditions**	**SCREENING** **Fasting lipid profile** Every 2 years and as clinically indicated	**Health Links** **Diet and Physical Activity** **Cardiovascular Risk Factors** **Counseling** Counsel regarding nutrition. **Considerations for Further Testing and Intervention** Consider evaluation for other co-morbid conditions including hypertension, impaired glucose metabolism, and overweight/ obesity.

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SYSTEM = Endocrine/Metabolic

SCORE = 1

SECTION 85 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
86	**≥ 30 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Hepatic fibrosis** **Cirrhosis** **Focal nodular hyperplasia** **Info Link** • Focal nodular hyperplasia (FNH) is a benign change that represents a scar in the liver. • FNH is usually an asymptomatic finding noted on MRI or ultrasound of the liver. • Continued observation or biopsy may be indicated depending on individual patient factors and imaging features.	**Treatment Factors** Higher radiation dose **Medical Conditions** Chronic hepatitis History of VOD **Health Behaviors** Alcohol use	**Treatment Factors** Dose ≥ 40 Gy to at least 1/3 of liver volume Dose 20-30 Gy to entire liver	**PHYSICAL** **Jaundice** **Spider angiomas** **Palmar erythema** **Xanthomata** **Hepatomegaly** **Splenomegaly** Yearly **SCREENING** **ALT** **AST** **Bilirubin** Baseline at entry into long-term follow-up, repeat as clinically indicated	**Health Links** **Liver Health** **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/ hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
87	**≥ 30 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Cholelithiasis**	**Host Factors** Ileal conduit Obesity Pregnancy Family history of cholelithiasis **Treatment Factors** Abdominal surgery Abdominal radiation TPN		**HISTORY** **Colicky abdominal pain related to fatty food intake** **Excessive flatulence** Yearly and as clinically indicated **PHYSICAL** **RUQ or epigastric tenderness** **Positive Murphy's sign** Yearly and as clinically indicated	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Consider gallbladder ultrasound in patients with chronic abdominal pain **SYSTEM = GI/Hepatic** **SCORE = 2B**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 87 REFERENCES

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
88	**≥ 30 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Bladder** **Femoral** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (lumbar)** **Spine (sacral)** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Bowel obstruction**	**Treatment Factors** Higher radiation dose to bowel Abdominal surgery **Info Link** Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery	**Treatment Factors** Radiation dose ≥ 45 Gy (Obstruction may occur in people who received lower doses of abdominal radiation during childhood)	**HISTORY** **Abdominal pain** **Distention** **Vomiting** **Constipation** With clinical symptoms of obstruction **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** With clinical symptoms of obstruction	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Obtain KUB in patients with clinical symptoms of obstruction. Surgical consultation in patients unresponsive to medical management. **SYSTEM = GI/Hepatic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
89	**≥ 30 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Bladder** **Femoral** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (lumbar)** **Spine (sacral)** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Chronic enterocolitis** **Fistula** **Strictures**	**Treatment Factors** Higher radiation dose to bowel Abdominal surgery	**Treatment Factors** Radiation dose ≥ 45 Gy	**HISTORY** **Nausea** **Vomiting** **Abdominal pain** **Diarrhea** Yearly	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Serum protein and albumin yearly in patients with chronic diarrhea or fistula. Surgical and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 89 REFERENCES

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RADIATION

POTENTIAL IMPACT TO GI/HEPATIC SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
90	**≥ 30 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Bladder** **Femoral** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (lumbar)** **Spine (sacral)** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Body Irradiation (TBI)*** **Total Lymphoid Irradiation (TLI)**	**Colorectal cancer** **Info Link** • Reports of colorectal cancer in cohorts of long-term survivors suggest that radiation likely increases risk but the median age of onset is not as well established as that of secondary breast cancer following chest radiation. • The expert panel agreed that early onset of screening is likely beneficial and that a prudent course would be to initiate screening for colorectal cancer for those at highest risk (abdominal pelvic and/or spinal radiation ≥ 30 Gy) at age 35 or 10 years post radiation whichever occurs last. • Surveillance should be done via colonoscopy as per recommendations for populations at highest risk with information from the first colonoscopy informing the frequency of follow-up testing.	**Host Factors** Current age ≥ 50 years **Treatment Factors** Higher radiation dose to bowel Higher daily dose fraction Combined with chemotherapy (especially alkylators) **Medical Conditions** Obesity **Health Behaviors** High fat/low fiber diet	**Host Factors** Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps, or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps in first degree relative	**SCREENING** **Colonoscopy** Every 5 years [minimum] beginning at 10 years after radiation or at age 35 years [whichever occurs last] More frequently if indicated based on colonoscopy results Per the ACS, begin screening earlier for the following high-risk groups—HNPCC: at puberty FAP: at age 21 years IBD: 8 years after diagnosis of IBD Information from the first colonoscopy will inform frequency of follow-up testing	**Health Links** **Colorectal Cancer** **Considerations for Further Testing and Intervention** Surgical and/or oncology consultation as needed. **SYSTEM = SMN** **SCORE = 2A**
	Info Link • *Reports of colorectal cancer in cohorts of long-term survivors suggest that radiation likely increases risk however the risk related to TBI alone has not been established. • *Monitoring of patients who received TBI without additional radiation potentially impacting the colon/rectum should be determined on an individual basis.* (See Info Link in next column.)					

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO URINARY TRACT

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
91	**Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Subtotal Lymphoid Irradiation (STLI)** **Extended Mantle** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)** • See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.	**Renal toxicity** **Renal insufficiency** **Hypertension**	**Host Factors** Bilateral Wilms tumor Mononephric **Treatment Factors** Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Radiation dose ≥ 10 Gy TBI combined with radiation to the kidney Combined with other nephrotoxic agents, such as: - Cisplatin - Carboplatin - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants **Medical Conditions** Diabetes mellitus Hypertension Nephrectomy	**Treatment Factors** Radiation dose ≥ 15 Gy TBI ≥ 6 Gy in single fraction or ≥ 12 Gy fractionated	**PHYSICAL** **Blood pressure** Yearly **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** Baseline at entry into long-term follow-up, repeat as clinically indicated **Urinalysis** Yearly	**Health Links** **Kidney Health** **Cardiovascular Risk Factors** **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Urinary** **SCORE = 1**

SECTION 91 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
92	**≥ 30 Gy to:** **Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (sacral)** **Spine (whole)** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone. **Info Link** The bladder is included in the left and right flank/ hemiabdomen treatment fields only if the fields extended below iliac crest.	**Hemorrhagic cystitis**	**Treatment Factors** Higher radiation dose (≥ 30 Gy to entire bladder, ≥ 60 Gy to portion of bladder)	**Treatment Factors** Combined with cyclophosphamide and/or ifosfamide	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**Health Links** **Bladder Health** **Counseling** Counsel to promptly report dysuria or gross hematuria **Considerations for Further Testing and Intervention** For patients with positive history, obtain urinalysis and consider urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as > 5 RBC/HFP on at least 2 occasions). Nephrology or Urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/ creatinine ratio. Urology referral for patients with culture negative macroscopic hematuria. **SYSTEM = Urinary** **SCORE = 2A**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 92 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
93	**≥ 30 Gy to:** **Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (sacral)** **Spine (whole)** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone. **Info Link** The bladder is included in the left and right flank/ hemiabdomen treatment fields only if the fields extended below iliac crest.	**Urinary tract toxicity** Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis	**Treatment Factors** Higher cumulative radiation dose (≥ 45 Gy) Radiation to entire bladder Combined with: - Cyclophosphamide - Ifosfamide - Vincristine		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly **SCREENING** **Urinalysis** Yearly	**Health Links** **Bladder Health** **Considerations for Further Testing and Intervention** Urologic consultation for patients with incontinence or dysfunctional voiding. **SYSTEM = Urinary** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 30 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 30 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 93 REFERENCES

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

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
94	**Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (sacral)** **Spine (whole)** **Total Lymphoid Irradiation (TLI)** **Info Link** The bladder is included in the left and right flank/ hemiabdomen treatment fields only if the fields extended below iliac crest.	**Bladder malignancy**	**Treatment Factors** Radiation to pelvis Combined with: - Cyclophosphamide - Ifosfamide **Health Behaviors** Alcohol use Smoking		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**Health Links** **Bladder Health** **Counseling** Counsel to promptly report dysuria or gross hematuria **Considerations for Further Testing and Intervention** For patients with positive history, obtain urinalysis and consider urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as > 5 RBC/HFP on at least 2 occasions). Nephrology or Urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/ creatinine ratio. Urology referral for patients with culture negative macroscopic hematuria. **SYSTEM = SMN** **SCORE = 2A**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SECTION 94 REFERENCES

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RADIATION

POTENTIAL IMPACT TO FEMALE REPRODUCTIVE SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
95 (female)	**Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Pelvic** **Vaginal** **Spine (lumbar)** **Spine (sacral)** **Spine (whole)** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)**	**Uterine vascular insufficiency** Resulting in adverse pregnancy outcomes, such as spontaneous abortion, neonatal death, low-birth weight infant, fetal malposition, and premature labor **Info Link** 10% of girls with Wilms tumor have congenital uterine anomalies.	**Host Factors** Females with Wilms tumor and associated Müllerian anomalies **Treatment Factors** Higher radiation dose to pelvis	**Host Factors** Prepubertal at treatment **Treatment Factors** Radiation dose ≥ 30 Gy TBI	**HISTORY** **Pregnancy** Yearly and as clinically indicated **Childbirth history** Yearly and as clinically indicated	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine: ***www.asrm.org*** Fertile Hope: ***www.fertilehope.org*** **Considerations for Further Testing and Intervention** Consider high-level ultrasound evaluation of genitourinary tract after pubertal development as clinically indicated in patients contemplating pregnancy. High-risk obstetrical care during pregnancy.
	Info Link The uterus is included in the left and right flank/ hemiabdomen fields only if the fields extended below iliac crest.					

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

SYSTEM = Reproductive (Female)

SCORE = 2B

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RADIATION

POTENTIAL IMPACT TO FEMALE REPRODUCTIVE SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
96 (female)	**Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Pelvic** **Vaginal** **Spine (lumbar)** **Spine (sacral)** **Spine (whole)** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)** **Info Link** The ovaries are included in the left and right flank/ hemiabdomen treatment fields only if the fields extended below iliac crest.	**Gonadal dysfunction (ovarian)** Delayed/arrested puberty Premature menopause Infertility	**Host Factors** Older age at irradiation **Treatment Factors** Radiation dose ≥ 5 Gy if pubertal, ≥ 10 Gy if prepubertal Combined with alkylating agent chemotherapy Longer time since treatment	**Treatment Factors** Radiation dose ≥ 10 Gy if pubertal, ≥ 15 Gy if prepubertal Combined with cyclophosphamide conditioning for HCT	**HISTORY** **Pubertal (onset, tempo), menstrual, pregnancy history** **Sexual function (vaginal dryness, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging** Yearly until sexually mature **SCREENING** **FSH** **LH** **Estradiol** Baseline at age 13 AND as clinically indicated in patients with delayed or arrested puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine: ***www.asrm.org*** Fertile Hope: ***www.fertilehope.org*** **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to radiation. Recovery of fertility may occur years after therapy. Counsel regarding risks and benefits of HRT. **Considerations for Further Testing and Intervention** Bone density evaluation in hypogonadal patients. Refer to endocrinology/gynecology for delayed puberty, persistently abnormal hormone levels or hormonal replacement for hypogonadal patients. Reproductive endocrinology referral for infertility evaluation and consultation regarding assisted reproductive technologies. **SYSTEM = Reproductive (Female)** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
97 (female)	**Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Iliac** **Pelvic** **Vaginal** **Total Lymphoid Irradiation (TLI)**	**Vaginal fibrosis/stenosis**	**Host Factors** Vaginal tumor or pelvic tumor adjacent to vagina **Treatment Factors** Radiation dose ≥ 50 Gy in postpubertal female Radiation dose ≥ 25 Gy in prepubertal female **Medical Conditions** Chronic GVHD	**Treatment Factors** Radiation dose ≥ 55 Gy in postpubertal female Radiation dose ≥ 35 Gy in prepubertal female	**HISTORY** **Psychosocial assessment** **Dyspareunia** **Vulvar pain** **Post-coital bleeding** **Difficulty with tampon insertion** Yearly	**Considerations for Further Testing and Intervention** Gynecologic consultation for management. Psychological consultation in patients with emotional difficulties. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Info Link
The vagina is included in the left and right flank/ hemiabdomen treatment fields only if the fields extended below iliac crest.

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO MALE REPRODUCTIVE SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
98 (male)	**Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Femoral** **Iliac** **Inguinal** **Pelvic** **Prostate** **Testicular** **Total Body Irradiation (TBI)** **Total Lymphoid Irradiation (TLI)** **Info Link** The testes are included in the left and right flank/ hemiabdomen only if the fields extended below iliac crest. • See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.	**Gonadal dysfunction (testicular)** Reduced fertility Oligospermia Azoospermia Infertility	**Host Factors** Testicular cancer Obesity Ejaculatory dysfunction Medications Occupational exposures (pesticides, heavy metals, solvents) **Treatment Factors** Radiation dose to testes: - 1 to 3 Gy—azoospermia may be reversible - 3 to 6 Gy—azoospermia possibly reversible (but unlikely) - 8 to 10 Gy—azoospermia likely permanent Fractionated small doses greater risk than single large doses Combined with alkylating agents Genitourinary surgery **Medical Conditions** Chronic GVHD **Health Behaviors** Tobacco/marijuana use History of sexually transmitted diseases	**Treatment Factors** Radiation dose to testes ≥ 6 Gy—azoospermia likely permanent	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchiometer** Yearly **SCREENING** **Semen analysis** At request of sexually mature patient Periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years post therapy **FSH** In sexually mature patient if unable to obtain semen analysis	**Health Links** **Male Health Issues** **Resources** American Society for Reproductive Medicine: ***www.asrm.org*** Fertile Hope: ***www.fertilehope.org*** **Counseling** Counsel regarding the need for contraception, since there is tremendous individual variability in gonadal toxicity after exposure to radiation. Recovery of fertility may occur years after therapy. **Considerations for Further Testing and Intervention** Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies. **SYSTEM = Reproductive (Male)** **SCORE = 1**

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RADIATION

POTENTIAL IMPACT TO MALE REPRODUCTIVE SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
99 (male)	≥ **20 Gy to:** **Inverted Y** **Left Flank/Hemiabdomen** **Right Flank/Hemiabdomen** **Whole abdomen** **Bladder** **Femoral** **Iliac** **Inguinal** **Pelvic** **Prostate** **Testicular** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone. **Info Link** The testes are included in the left and right flank/ hemiabdomen only if the fields extended below iliac crest.	**Gonadal dysfunction (testicular): Testosterone deficiency/insufficiency** Delayed/arrested puberty	**Host Factors** Testicular cancer Aging **Treatment Factors** Testicular irradiation combined with head/brain irradiation Combined with unilateral orchiectomy	**Treatment Factors** Combined with alkylating agents Combined with cyclophosphamide conditioning for HCT	**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchiometer** Yearly **SCREENING** **Testosterone** (ideally morning) Baseline at age 14 ***AND*** as clinically indicated in patients with delayed or arrested puberty and/or clinical signs and symptoms of testosterone deficiency	**Health Links** **Male Health Issues** **Considerations for Further Testing and Intervention** Bone density evaluation in hypogonadal patients. Refer to endocrinology/urology for delayed puberty, persistently abnormal hormone levels or hormonal replacement for hypogonadal patients. Males with low normal testosterone should have periodic repeat measurements of testosterone as they age or if they become symptomatic. **SYSTEM = Reproductive (Male)** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 20 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***and*** TBI, the sum of which is ≥ 20 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
100	**All Radiation Fields (including TBI)**	**Musculoskeletal growth problems** Hypoplasia Fibrosis Reduced or uneven growth Shortened trunk height (trunk radiation) Limb length discrepancy (extremity radiation)	**Host Factors** Younger age at treatment **Treatment Factors** Higher cumulative radiation dose Larger radiation treatment field Higher radiation dose per fraction	**Host Factors** Prepubertal at treatment **Treatment Factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones Epiphysis in treatment field Dose ≥ 20 Gy	**PHYSICAL** **Limb lengths** Yearly for patients who had extremity radiation **Height** **Weight** Yearly **Sitting height** Yearly for patients who had trunk radiation	**Counseling** Counsel regarding increased risk of fractures in weight-bearing irradiated bones **Considerations for Further Testing and Intervention** Orthopedic consultation for any deficit noted in growing child. Consider plastic surgery consult for reconstruction. **SYSTEM = Musculoskeletal** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
101	**Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Whole lung** **Total Lymphoid Irradiation (TLI)**	**Scoliosis/Kyphosis**	**Host Factors** Younger age at irradiation Paraspinal malignancies Neurofibromatosis **Treatment Factors** Hemithoracic or abdominal radiation Hemithoracic, abdominal or spinal surgery Radiation of only a portion of (rather than whole) vertebral body **Info Link** With contemporary treatment approaches, scoliosis is infrequently seen as a consequence of radiation unless the patient has also undergone surgery to the hemithorax, abdomen or spine.	**Treatment Factors** Radiation doses ≥ 20 Gy (lower doses for infants) Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones	**PHYSICAL** **Spine exam for scoliosis and kyphosis** Yearly until growth completed, may need more frequent assessment during puberty or if curve detected	**Health Links** **Scoliosis and Kyphosis** **Considerations for Further Testing and Intervention** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on radiographic exam. **SYSTEM = Musculoskeletal** **SCORE = 1**

- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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RADIATION

POTENTIAL IMPACT TO MUSCULOSKELETAL SYSTEM (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
102	**≥ 40 Gy to:** **Hepatic** **Inverted Y** **Left Flank/Hemiabdomen** **Left upper quadrant** **Paraaortic** **Renal** **Right Flank/Hemiabdomen** **Right Upper quadrant** **Spleen (entire)** **Spleen (partial)** **Whole abdomen** **Lower extremity** **Upper extremity** **Cervical (neck)** **Supraclavicular** **Bladder** **Femoral** **Iliac** **Inguinal** **Pelvic** **Prostate** **Vaginal** **Spine (cervical)** **Spine (lumbar)** **Spine (sacral)** **Spine (thoracic)** **Spine (whole)** **Subtotal Lymphoid Irradiation (STLI)** **Axilla** **Chest (thorax)** **Extended Mantle** **Mantle** **Mediastinal** **Mini~Mantle** **Whole lung** **Total Lymphoid Irradiation (TLI)** **TBI*** *TBI is included for dose calculation purposes only; this section is not applicable to patients who received TBI alone.	**Radiation-induced fracture**	**Treatment Factors** History of surgery to cortex of bone	**Treatment Factors** Radiation dose ≥ 50 Gy to bone	**PHYSICAL** **Pain, swelling, deformity of bone** As indicated	**Considerations for Further Testing and Intervention** Radiograph of affected bone as clinically indicated. Orthopedic evaluation as clinically indicated. **SYSTEM = Musculoskeletal** **SCORE = 1**

- This section is only applicable to patients who:
  1) Received radiation to any of the specified fields at ≥ 40 Gy
     OR
  2) Received a combination of radiation to any of the specified fields ***plus*** relevant spinal radiation ***and/or*** TBI, the sum of which is ≥ 40 Gy
- See dose calculation rules on page 56 for patients who received: (a) radiation to more than one of the specified fields, or (b) more than one planned course of treatment to the same field.
- See "Patient-Specific Guideline Identification Tool" in Appendix I to determine specific screening guidelines by section number for individual patients.

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HEMATOPOIETIC CELL TRANSPLANT INTRODUCTORY INFORMATION/TBI-RELATED POTENTIAL LATE EFFECTS

Info Link: Hematopoietic Cell Transplant Introductory Information

- Complications after hematopoietic cell transplantation have multifactorial etiology: prior therapy for primary malignancy intensity of transplant conditioning, stem cell product (e.g., marrow, cord blood, peripheral stem cells), donor (e.g., autologous, allogeneic, unrelated), quality of donor to recipient match, complication of transplant process (immunosuppression and GVHD), complications in the post-transplant period, underlying disease, host genetic factors, lifestyle behaviors.
- This section includes late treatment complications that may be observed in hematopoietic cell transplant recipients not covered elsewhere in these guidelines.
- Refer to other sections of these guidelines for specific details related to late complications of radiation and of specific chemotherapeutic agents.
- For HCT follow-up recommendations from the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and the American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT), see: Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant*. Mar 2012;47(3):337-341.

TBI-Related Potential Late Effects

The complete list of potential late effects and associated Guideline section numbers are included here for clinician convenience when evaluating patients who received TBI. For details regarding each potential late effect and indicated screening, please refer to the relevant section within these Guidelines.

Section #	Gender	Potential Late Effect
44	Both	***Secondary benign or malignant neoplasms***
45	Both	***Dysplastic nevi/skin cancer***
48	Both	***Brain tumor (benign or malignant)***
49	Both	***Neurocognitive deficits***
50	Both	***Clinical leukoencephalopathy***
55	Both	***Growth hormone deficiency***
64	Both	***Cataracts***
69	Both	***Dental abnormalities***
71	Both	***Thyroid nodules***
72	Both	***Thyroid cancer***
73	Both	***Hypothyroidism***
77*	Female	***Breast cancer***
78	Female	***Breast tissue hypoplasia***
79	Both	***Pulmonary toxicity***
80	Male	***Cardiac toxicity***
81	Female	***Cardiac toxicity***
84	Both	***Impaired glucose metabolism/diabetes mellitus***
85	Both	***Dyslipidemia***
90*	Both	***Colorectal cancer***
91	Both	***Renal toxicity***
95	Female	***Uterine vascular insufficiency***
96	Female	***Gonadal dysfunction (ovarian)***
98	Male	***Gonadal dysfunction (testicular)***
100	Both	***Musculoskeletal growth problems***

*Screening may be indicated for patients who received TBI alone – see Info Link in this section

HEMATOPOIETIC CELL TRANSPLANT

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
103	**Autologous Hematopoietic Cell Transplant (HCT)**	**Myelodysplasia** **Acute myeloid leukemia**	**Treatment Factors** Radiation therapy Stem cell mobilization with etoposide Alkylating agent chemotherapy Epipodophyllotoxins Anthracyclines Autologous transplant	**Host Factors** Older age **Treatment Factors** Autologous transplant for non-Hodgkin and Hodgkin lymphoma Peripheral blood stem cells	**HISTORY** **Fatigue** **Bleeding** **Easy bruising** Yearly, up to 10 years after transplant **PHYSICAL** **Dermatologic exam (pallor, petechiae, purpura)** Yearly, up to 10 years after transplant	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Counsel to promptly report fatigue, pallor, petechiae or bone pain. **Considerations for Further Testing and Intervention** CBC and bone marrow exam as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 103 REFERENCES

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
104 (male)	**Hematopoietic Cell Transplant (HCT)**	**Solid tumors**	**Host Factors** Younger age at transplant Fanconi's anemia **Treatment Factors** Radiation therapy **Medical Conditions** Hepatitis C infection Chronic GVHD Human Papillomavirus (HPV) infection	**Treatment Factors** TBI	**PHYSICAL** **Evaluation for benign or malignant neoplasms** Yearly	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Avoid excessive sun exposure and tanning booths. Counsel regarding safer sexual practices. **Considerations for Further Testing and Intervention** Oncology consultation as clinically indicated. HPV vaccination per current recommendations. **SYSTEM = SMN** **SCORE = 1**

SECTION 104 REFERENCES

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
105 (female)	**Hematopoietic Cell Transplant (HCT)**	**Solid tumors**	**Host Factors** Younger age at transplant Fanconi's anemia **Treatment Factors** Radiation therapy **Medical Conditions** Hepatitis C infection Chronic GVHD Human Papillomavirus (HPV) infection	**Treatment Factors** TBI	**PHYSICAL** **Evaluation for benign or malignant neoplasms** Yearly	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** Avoid excessive sun exposure and tanning booths. Counsel regarding safer sexual practices. **Considerations for Further Testing and Intervention** Females with cGVHD appear to be at increased risk for cervical cancer and should, at minimum, have pelvic exams and PAP testing according to ACS recommendations (see Section 158) with more aggressive monitoring as clinically indicated. Oncology consultation as clinically indicated. HPV vaccination per current recommendations. **SYSTEM = SMN** **SCORE = 1**

SECTION 105 REFERENCES

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

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
106	**Hematopoietic Cell Transplant (HCT)**	**Lymphoma**	**Medical Conditions** Chronic GVHD	**Host Factors** Diagnosis of primary immune deficiency **Treatment Factors** HLA mismatch Unrelated donor transplant T-cell depletion ATG	**PHYSICAL** **Lymphadenopathy** Yearly **Splenomegaly** Yearly	**Considerations for Further Testing and Intervention** Oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

SECTION 106 REFERENCES

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

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
107	**Hematopoietic Cell Transplant (HCT)**	**Hepatic toxicity** Chronic hepatitis Cirrhosis Iron overload	**Treatment Factors** History of multiple transfusions Radiation to the liver Antimetabolite therapy **Medical Conditions** Chronic GVHD Viral hepatitis History of VOD **Health Behaviors** Alcohol use	**Medical Conditions** Chronic hepatitis C with siderosis and steatosis	**SCREENING** **ALT** **AST** **Bilirubin** **Ferritin** Baseline at entry into long-term follow-up, repeat as clinically indicated	**Health Links** **Liver Health** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. **Note**: PCR testing for HCV may be required in immunosuppressed patients who are negative for antibody. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction or known hepatitis. Hepatitis A and B immunizations in patients lacking immunity. Consider liver biopsy in patients with persistent elevation of ferritin (based on clinical context and magnitude of elevation). Consider phlebotomy or chelation therapy for treatment of iron overload. **SYSTEM = GI/Hepatic** **SCORE = 1**

SECTION 107 REFERENCES

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
108	**Hematopoietic Cell Transplant (HCT)**	**Osteonecrosis (Avascular Necrosis)** **Info Link** • Osteonecrosis typically occurs during the acute treatment phase, and may progress over time or resolve. • Multifocal osteonecrosis is significantly more common (3:1) than unifocal.	**Treatment Factors** Corticosteroids (dexamethasone effect is more potent than prednisone) Other immunosuppressants TBI High-dose radiation to any bone Allogeneic HCT > autologous	**Host Factors** Pubertal or post-pubertal at time of transplant **Treatment Factors** Prolonged immunosuppressive therapy (e.g., for chronic GVHD) **Medical Conditions** Chronic GVHD	**HISTORY** **Joint pain** **Swelling** **Immobility** **Limited range of motion** Yearly **PHYSICAL** **Musculoskeletal exam** Yearly	**Health Links** **Osteonecrosis** **Considerations for Further Testing and Intervention** MRI as clinically indicated in patients with history suggestive of osteonecrosis (should be done soon after symptom onset). Orthopedic consultation in patients with positive imaging and/or symptoms of osteonecrosis. Symptomatic lesions confer the greatest risk for collapse. Physical therapy evaluation (for non-pharmacologic pain management, range of motion, strengthening, stretching, functional mobility). **SYSTEM = Musculoskeletal** **SCORE = 1**

SECTION 108 REFERENCES

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
109	**Hematopoietic Cell Transplant (HCT)**	**Reduced bone mineral density (BMD)** Defined as Z-score > 2.0 SD below the mean in survivors < 20 years old or T-score > 1.0 SD below the mean in survivors ≥ 20 years old **Info Link** • The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density (BMD) of young adults at peak bone age and defined as a T-score. A T-score is the number of standard deviations the BMD measurement is above or below the mean. • Current definitions of osteopenia (T-scores between 1.0 and 2.5 SD below the mean) and osteoporosis (T-scores > 2.5 SD below the mean) were developed primarily in the context of postmenopausal women. In this population, T-scores have a well-validated correlation with fracture risk that increases with age. • The fracture risk associated with T-scores in younger populations, including cancer survivors with treatment-related hypogonadism, has not been established. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. • Pediatric BMD reference data sets calculate Z-scores based on age and gender. A Z-score is the number of standard deviations the measurement is above or below the AGE-MATCHED MEAN BMD. • The fracture risk in pediatric patients with low bone density for chronologic age based on Z-scores has not been established. There are no defined standards for referral or treatment of low BMD in children.	**Host Factors** Both genders are at risk Younger age at diagnosis Caucasian Lower weight and BMI **Treatment Factors** Corticosteroids Cyclosporine Tacrolimus Cranial radiation Craniospinal radiation HCT/TBI **Medical Conditions** Growth hormone deficiency Hypogonadism/delayed puberty Hyperthyroidism **Health Behaviors** Inadequate intake of calcium and vitamin D Lack of weight bearing exercise Smoking Alcohol use Carbonated beverages	**Host Factors** Older age at time of treatment **Treatment Factors** Prolonged corticosteroid therapy (e.g., for chronic GVHD)	**SCREENING** **Bone density evaluation (DEXA or quantitative CT)** Baseline at entry into long-term follow-up, repeat as clinically indicated **Info Link** • The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. • Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. • Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	**Health Links** **Bone Health** **Resources** National Osteoporosis Foundation website: ***www.nof.org*** **Considerations for Further Testing and Intervention** Ensure the AAP recommended minimum daily intake of Vitamin D (400 IU/day) for children, with possible considerations for high doses in selected patients (e.g., kidney disease or Vitamin D deficiency). Many experts recommend higher Vitamin D intake in adults as well. Also ensure adequate dietary calcium (see table in the "Bone Health" Health Link for age-appropriate recommendations). Supplements may be necessary if there are dietary restrictions. Advocate for regular weight-bearing exercises such as running and jumping. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency, correction of chronic metabolic acidosis that could accelerate bone loss). Endocrine consultation for patients with osteoporosis or history of multiple fractures for pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators). **SYSTEM = Musculoskeletal** **SCORE = 2B**

SECTION 109 REFERENCES

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HEMATOPOIETIC CELL TRANSPLANT (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
110	**Hematopoietic Cell Transplant (HCT)**	**Renal toxicity** Glomerular injury Tubular injury Hypertension	**Treatment Factors** Chronic cyclosporine use	**Host Factors** Older age at transplant **Treatment Factors** TBI **Medical Conditions** Acute kidney injury within 6 months of HCT History of cGVHD	**PHYSICAL** **Blood pressure** Yearly **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** Baseline at entry into long-term follow-up, repeat as clinically indicated **Urinalysis** Yearly	**Health Links** **Kidney Health** **Cardiovascular Risk Factors** **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency **SYSTEM = Renal** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
111	**HCT with *any history* of Chronic GVHD**	**Dermatologic toxicity** Permanent alopecia Nail dysplasia Vitiligo Scleroderma Squamous cell carcinoma of the skin **Info Link** Dermatologic toxicity is more common in presence of active cGVHD; effects may persist after cGVHD resolves.			**PHYSICAL** **Hair (alopecia)** **Nails (hypoplasia)** **Skin (vitiligo, scleroderma)** Yearly	**Health Links** **Skin Health** **SYSTEM = Dermatologic** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
112	**HCT with *any history* of Chronic GVHD**	**Xerophthalmia (keratoconjunctivitis sicca)** **Info Link** Xerophthalmia is more common in presence of active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Cranial radiation Eye radiation Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Radiation dose to eye ≥ 30 Gy Radiation fraction ≥ 2 Gy	**HISTORY** **Dry eyes (burning, itching, foreign body sensation, inflammation)** Yearly **PHYSICAL** **Eye exam** Yearly	**Health Links** **Eye Health** **Considerations for Further Testing and Intervention** Supportive care with artificial tears. Schirmer's testing as clinically indicated. Ongoing ophthalmology follow-up for identified problems. Consider every six month ophthalmology evaluation for patients with corneal damage. **SYSTEM = Ocular** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
113	**HCT with *any history* of Chronic GVHD**	**Xerostomia** **Salivary gland dysfunction** **Dental caries** **Periodontal disease** **Oral cancer (squamous cell carcinoma)** **Info Link** Oral-dental late effects are more common in presence of active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Head and neck radiation involving the parotid gland Higher radiation doses Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment Factors** Salivary gland radiation dose ≥ 30 Gy Use of azathioprine for cGVHD management **Medical Conditions** High grade of cGVHD Fanconi anemia	**HISTORY** **Xerostomia** Yearly **PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**Health Links** **Dental Health** **Considerations for Further Testing and Intervention** Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine). Regular dental care including fluoride applications and regular screening for intraoral malignancy. **SYSTEM = Dental** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
114	**HCT with *any history* of Chronic GVHD**	**Pulmonary toxicity** **Bronchiolitis obliterans** **Chronic bronchitis** **Bronchiectasis** **Info Link** Pulmonary late effects are more common in presence of active cGVHD; effects may persist after cGVHD resolves.	**Treatment Factors** Chest radiation TBI Pulmonary toxic chemotherapy: - Busulfan - Bleomycin - Carmustine (BCNU) - Lomustine (CCNU) **Health Behaviors** Smoking Inhaled illicit drug use	**Medical Conditions** Prolonged immunosuppression related to cGVHD and its treatment	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** Yearly **PHYSICAL** **Pulmonary exam** Yearly **SCREENING** **PFTs (including DLCO and spirometry)** Baseline at entry into long-term follow-up, repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: ***www.smokefree.gov*** **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Patients who desire to SCUBA dive should be advised to obtain medical clearance from a pulmonologist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations. **SYSTEM = Pulmonary** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
115	**HCT with *any history* of Chronic GVHD**	**Immunologic complications** Secretory IgA deficiency Hypogammaglobulinemia Decreased B cells T cell dysfunction Chronic infections (e.g., conjunctivitis, sinusitis, and bronchitis associated with chronic GVHD) **Info Link** Immunologic complications related to cGVHD may persist or resolve over time.		**Host Factors** Active cGVHD **Medical Conditions** Prolonged immunosuppression related to cGVHD and its treatment	**HISTORY** **Chronic conjunctivitis** **Chronic sinusitis** **Chronic bronchitis** **Recurrent or unusual infections** **Sepsis** Yearly **PHYSICAL** **Pulmonary exam** Yearly **Eye exam** Yearly **Nasal exam** Yearly	**Considerations for Further Testing and Intervention** Consider PCP and anti-fungal prophylaxis in patients with active cGVHD for duration of immunosuppressive therapy. Immunology or infectious diseases consultation for assistance with management of infections. Immunologic abnormalities may persist for up to 20 years post transplant. **SYSTEM = Immune** **SCORE = 1**

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HEMATOPOIETIC CELL TRANSPLANT

WITH CHRONIC GVHD (cont)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
116	**HCT with *currently active* chronic GVHD**	**Functional asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*, meningococcus) **Info Link** This section applies only to patients who have active cGVHD.	**Treatment Factors** Splenic radiation Ongoing immunosuppression	**Host Factors** Hypogammaglobulinemia	**PHYSICAL** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** When febrile T ≥ 101ºF as indicated for patients with active chronic GVHD **SCREENING** **Blood culture** When febrile T ≥ 101ºF as indicated for patients with active chronic GVHD	**Health Links** **Splenic Precautions** **Counseling** Advise obtaining medical alert bracelet/card noting functional asplenia. Counsel regarding risk of life-threatening infections with encapsulated organisms. Also counsel regarding risk associated with malaria and tick-borne diseases if living in or visiting endemic areas **Considerations for Further Testing and Intervention** Consider antibiotic prophylaxis for encapsulated organisms and bacteremia/endocarditis prophylaxis for duration of immunosuppressive therapy for chronic GVHD (see: American Academy of Pediatric Dentistry, Guideline on Antibiotic Prophylaxis for Dental Patients at Risk for Infection). In patients with T ≥ 101° (38.3° C) or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC, toxic clinical appearance; fever ≥ 104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines according to current ACIP recommendations. **Info Link** See current edition of AAP *Red Book* for current recommendations regarding antibiotic prophylaxis and immunizations **SYSTEM = Immune** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
117	**HCT with *any history* of chronic GVHD**	**Esophageal stricture** **Info Link** Esophageal stricture related to cGVHD is generally not reversible over time.	**Treatment Factors** Radiation involving the esophagus Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical Conditions** Gastroesophageal reflux History of Candida esophagitis	**Treatment Factors** Radiation dose ≥ 40 Gy **Medical Conditions** Gut GVHD	**HISTORY** **Dysphagia** **Heartburn** Yearly	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** Surgery and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
118 (female)	**HCT with *any history* of chronic GVHD**	**Vaginal fibrosis/stenosis** **Info Link** Vaginal fibrosis/stenosis related to cGVHD is generally not reversible over time.	**Treatment Factors** Pelvic radiation		**HISTORY** **Psychosocial assessment** **Dyspareunia** **Vulvar pain** **Post-coital bleeding** **Difficulty with tampon insertion** Yearly **PHYSICAL** **Examine genitalia for lichen planus-like features as well as erosions, fissures, and ulcers** Yearly **SCREENING** **Gynecologic consultation when age appropriate**	**Considerations for Further Testing and Intervention** Psychological consultation in patients with emotional difficulties. **SYSTEM = Reproductive (female)** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
119	**HCT with *any history* of chronic GVHD**	**Joint contractures** **Info Link** Joint contractures related to cGVHD are generally not reversible over time.			**Musculoskeletal exam** Yearly	**Considerations for Further Testing and Intervention** Consultation with physical therapy, rehabilitation medicine/ physiatrist. **SYSTEM = Musculoskeletal** **SCORE = 1**

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SURGERY

AMPUTATION

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
120	**Amputation**	**Amputation-related complications** Impaired cosmesis Functional and activity limitations Residual limb integrity problems Phantom pain Neuropathic pain Musculoskeletal pain Increased energy expenditure Impaired quality of life and functional status Psychological maladjustment	**Host Factors** Skeletally immature/growing children **Treatment Factors** Site of amputation: Hemipelvectomy > Trans-femur amputation > Trans-tibia amputation **Medical Conditions** Obesity Diabetes Poor residual limb healing		**HISTORY** **Phantom pain** **Functional and activity limitations** Yearly **PHYSICAL** **Residual limb integrity** Yearly **SCREENING** **Prosthetic evaluation** Every 6 months until skeletally mature, then yearly	**Health Links** **Amputation** **Counseling** Counsel regarding skin checks, signs of poor prosthetic fit, residual limb and prosthetic hygiene, physical fitness and importance of maintaining a healthy weight and lifestyle. **Considerations for Further Testing and Intervention** Physical therapy consultation as needed per changing physical status such as weight gain or gait training with a new prosthesis, and for non-pharmacological pain management. Occupational therapy consultation as needed to assist with activities of daily living. Psychological/social work consultation to assist with emotional difficulties related to body image, marriage, pregnancy, parenting, employment, insurance and depression. Vocational counseling/training to identify vocations that will not produce/exacerbate functional limitations. **SYSTEM = Musculoskeletal** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
121	**Central venous catheter**	**Thrombosis** **Vascular insufficiency** **Infection of retained cuff or line tract**			**HISTORY** **Tenderness or swelling at previous catheter site** Yearly **PHYSICAL** **Venous stasis** **Swelling** **Tenderness at previous catheter site** Yearly and as clinically indicated	**SYSTEM = Cardiovascular** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
122	**Cystectomy** **Info Link** All potential late effects for pelvic surgery apply to Cystectomy (see also Sections 145–148).	**Cystectomy-related complications** Asymptomatic bacteriuria Chronic urinary tract infection Renal dysfunction Vesicoureteral reflux Hydronephrosis Reservoir calculi Spontaneous neobladder perforation Vitamin B12/folate/carotene deficiency (patients with ileal entercystoplasty only) **Info Link** Reservoir calculi are stones in the neobladder (a reservoir for urine usually constructed of ileum/colon)			**SCREENING** **Vitamin B12 level** Yearly starting 5 years after cystectomy (patients with ileal enterocystoplasty only) **Urology evaluation** Yearly	**Health Links** **Cystectomy** **Kidney Health** **SYSTEM = Urinary** **SCORE =** **Asymptomatic bacteriuria: 1** **Chronic urinary tract infection: 1** **Renal dysfunction: 1** **Vesicoureteral reflux: 1** **Hydronephrosis: 1** **Spontaneous neobladder perforation: 1** **Reservoir calculi: 2A** **Vitamin B12/folate/carotene deficiency: 2B**

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SURGERY

ENUCLEATION

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
123	**Enucleation**	**Impaired cosmesis** **Poor prosthetic fit** **Orbital hypoplasia**	**Host Factors** Younger age at enucleation **Treatment Factors** Combined with radiation		**SCREENING** **Evaluation by ocularist** Yearly **Evaluation by ophthalmologist** Yearly	**Health Links** **Eye Health** **Considerations for Further Testing and Intervention** Psychological consultation in patients with emotional difficulties related to cosmetic and visual impairment. Vocational rehabilitation referral as indicated. **SYSTEM = Ocular** **SCORE = 1**

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SURGERY

HYSTERECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
124 (female)	**Hysterectomy** **Info Link** For patients who also underwent oophorectomy, see also: Section 141 (unilateral oophorectomy) or Section 142 (bilateral oophorectomy)	**Pelvic floor dysfunction** **Urinary incontinence** **Sexual dysfunction**	**Treatment Factors** Pelvic radiation		**HISTORY** **Urinary leakage** **Abdominal pain** **Dyspareunia** **Psychosocial assessment** Yearly	**Health Links** **Female Health Issues** **Counseling** Counsel patients with ovaries regarding potential for biologic parenthood using gestational surrogate. **Considerations for Further Testing and Intervention** Reproductive endocrinology consultation for patients wishing to pursue pregnancy via gestational surrogate. **SYSTEM = Reproductive (female)** **SCORE = 2A**

SECTION 124 REFERENCES

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SURGERY

LAPAROTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
125	**Laparotomy**	**Adhesions** **Bowel obstruction**	**Treatment Factors** Combined with radiation		**HISTORY** **Abdominal pain** **Distention** **Vomiting** **Constipation** With clinical symptoms of obstruction **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** With clinical symptoms of obstruction	**Health Links** **Gastrointestinal Health** **Considerations for Further Testing and Intervention** KUB as clinically indicated for suspected obstruction. Surgical consultation for patients unresponsive to medical management. **SYSTEM = GI/Hepatic** **SCORE = 1**

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SURGERY

LIMB SPARING PROCEDURE

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
126	**Limb sparing procedure**	**Complications related to limb sparing procedure** Functional and activity limitations Contractures Chronic infection Chronic pain Limb length discrepancy Musculoskeletal pain Increased energy expenditure Fibrosis Prosthetic malfunction (loosening, non-union, fracture) requiring revision, replacement or amputation Prosthetic revision required due to growth Impaired quality of life Complications with pregnancy/delivery (in female patients with internal hemipelvectomy)	**Host Factors** Younger age at surgery Rapid growth spurt Skeletally immature **Treatment Factors** Tibial endoprosthesis Use of biologic material (allograft or autograft) for reconstruction **Medical Conditions** Endoprosthetic infection Obesity **Health Behaviors** High level of physical activity (associated with higher risk loosening) Low level of physical activity (associated with higher risk of contractures or functional limitations)	**Treatment Factors** Radiation to extremity **Medical Conditions** Poor healing; Infection of reconstruction	**HISTORY** **Functional and activity limitations** Yearly and as clinically indicated **PHYSICAL** **Residual limb integrity** Yearly and as clinically indicated **SCREENING** **Radiograph of affected limb** Yearly **Evaluation by orthopedic surgeon (ideally by an orthopedic oncologist)** Every 6 months until skeletally mature, then yearly	**Health Links** **Limb Sparing Procedures** **Counseling** Counsel regarding need for antibiotic prophylaxis prior to dental and invasive procedures if applicable. **Considerations for Further Testing and Intervention** There is not consensus at the present time regarding antibiotic prophylaxis for patients with orthopedic implants undergoing dental procedures; guidelines are currently under development by the American Dental Association (ADA) and American Academy of Orthopedic Surgery (AAOS). Counsel patients to discuss the potential need for antibiotic prophylaxis prior to dental and invasive procedures with their treating dentist/ orthopedic surgeon. Physical therapy consultation as needed per changes in functional status (such as post-lengthening, revisions, life changes such as pregnancy), and for non-pharmacological pain management. Consider psychological consultation as needed to assist with emotional difficulties related to body image, marriage, pregnancy, parenting, employment, insurance and depression. Vocational counseling/ training to identify vocations that will not produce/exacerbate functional limitations. **SYSTEM = Musculoskeletal** **SCORE = 1**

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SURGERY

NEPHRECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
127 (male)	**Nephrectomy**	**Hydrocele** **Renal toxicity** Proteinuria Hyperfiltration Renal insufficiency **Info Link** • Surgery-induced renal atrophy (vanishing kidney) is a rare complication reported in survivors who have undergone retroperitoneal tumor resections. • Once this diagnosis is established, annual screening should include evaluations recommended for children treated with nephrectomy.	**Host Factors** Denys-Drash syndrome WAGR syndrome Hypospadias Cryptorchidism Bilateral Wilms tumor **Treatment Factors** Combined with other nephrotoxic therapy such as: - Cisplatin - Carboplatin - Ifosfamide - Aminoglycosides - Amphotericin - Immunosuppressants - Methotrexate - Radiation impacting the kidneys		**PHYSICAL** **Blood pressure** Yearly **Testicular exam to evaluate for hydrocele** Yearly **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** Baseline at entry into long-term follow-up. Repeat as clinically indicated **Urinalysis** Yearly	**Health Links** **Single Kidney Health** **See also: Kidney Health** **Cardiovascular Risk Factors** **Counseling** Counsel mononephric survivors regarding sports and activity safety, stressing the importance of physical fitness, and proper use of seatbelts (i.e., wearing lapbelts around hips, not waist). Consideration should be given to survivor health status, current kidney health (position, size, function), and acceptability of unlikely risk of renal injury to the survivor and/or family. Counsel to use NSAIDS with caution. Documentation of this discussion is recommended. **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
128 (female)	**Nephrectomy**	**Renal toxicity** Proteinuria Hyperfiltration Renal insufficiency **Info Link** • Surgery-induced renal atrophy (vanishing kidney) is a rare complication reported in survivors who have undergone retroperitoneal tumor resections. • Once this diagnosis is established, annual screening should include evaluations recommended for children treated with nephrectomy.	**Host Factors** Denys-Drash syndrome WAGR syndrome Bilateral Wilms tumor **Treatment Factors** Combined with other nephrotoxic therapy such as: Cisplatin Carboplatin Ifosfamide Aminoglycosides Amphotericin Immunosuppressants Methotrexate Radiation impacting the kidneys		**PHYSICAL** **Blood pressure** Yearly **SCREENING** **BUN** **Creatinine** **Na, K, Cl, CO_2** **Ca, Mg, PO_4** Baseline at entry into long-term follow-up. Repeat as clinically indicated **Urinalysis** Yearly	**Health Links** **Single Kidney Health** **See also: Kidney Health** **Cardiovascular Risk Factors** **Counseling** Counsel mononephric survivors regarding sports and activity safety, stressing the importance of physical fitness, and proper use of seatbelts (i.e., wearing lapbelts around hips, not waist). Consideration should be given to survivor health status, current kidney health (position, size, function), and acceptability of unlikely risk of renal injury to the survivor and/or family. Counsel to use NSAIDS with caution. Documentation of this discussion is recommended. **Considerations for Further Testing and Intervention** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
129	**Neurosurgery–Brain**	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change **Info Link** • Neurocognitive deficits vary with extent of surgery and postoperative complications. • In general, mild delays occur in most areas of neuropsychological function compared to healthy children. • Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. • New deficits may emerge over time. • Neurosensory deficits (i.e., vision, hearing) due to tumor or its therapy may complicate neurocognitive outcomes.	**Host Factors** Younger age at treatment Primary CNS tumor **Treatment Factors** In combination with: - TBI - Cranial radiation; Methotrexate (IT, IO, high-dose IV) - Cytarabine (high-dose IV) Longer elapsed time since therapy Extent and location of resection **Medical Conditions** Hydrocephalus/history of shunt placement	**Host Factors** Age < 3 years at time of treatment Predisposing family history of learning or attention problems **Treatment Factors** Radiation dose ≥ 24 Gy to whole brain Radiation dose ≥ 40 Gy to local fields **Medical Conditions** Posterior fossa syndrome CNS infection	**HISTORY** **Educational and/or vocational progress** Yearly **SCREENING** **Referral for formal neuropsychological evaluation** Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**Health Links** **Educational Issues** **Considerations for Further Testing and Intervention** Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Refer patients with neurocognitive deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Consider use of psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
130	**Neurosurgery–Brain**	**Motor and/or sensory deficits** Paralysis Movement disorders Ataxia Eye problems (ocular nerve palsy, gaze paresis, nystagmus, papilledema, optic atrophy)	**Host Factors** Primary CNS tumor **Medical Conditions** Hydrocephalus	**Host Factors** Optic pathway tumor; Hypothalamic tumor; Suprasellar tumor (eye problems)	**SCREENING** **Evaluation by neurologist** Yearly, until 2 to 3 years after surgery or stable; Continue to monitor if symptoms persist **Evaluation by physiatrist/rehabilitation medicine specialist** Yearly, or more frequently as clinically indicated in patients with motor dysfunction	**Considerations for Further Testing and Intervention** Speech, physical, and occupational therapy in patients with persistent deficits. Consider consultations with nutrition, endocrine, and psychiatry (for obsessive-compulsive behaviors) in patients with hypothalamic-pituitary axis tumors. Ophthalmology evaluation as clinically indicated. **SYSTEM = CNS** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
131	**Neurosurgery–Brain**	**Seizures**	**Host Factors** Primary CNS tumor **Treatment Factors** Methotrexate (IV, IT, IO)		**SCREENING** **Evaluation by neurologist** As clinically indicated	**SYSTEM = CNS** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
132	**Neurosurgery–Brain**	**Hydrocephalus** **Shunt malfunction**	**Host Factors** Primary CNS tumor		**SCREENING** **Abdominal x-ray** After pubertal growth spurt for patients with shunts to assure distal shunt tubing in peritoneum **Evaluation by neurologist** Yearly for patients with shunts	**Counseling** Education patient/family regarding potential symptoms of shunt malfunction. **Considerations for Further Testing and Intervention** Per the American Academy of Pediatric Dentistry endocarditis prophylaxis guidelines, antibiotics are not indicated prior to dental work for patients with V-P shunts (indicated for V-A and V-V shunts only). **SYSTEM = CNS** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
133	**Neurosurgery–Brain** (applies only to neurosurgery with potential to affect the Hypothalamic-Pituitary Axis)	**Overweight/obesity** **Info Link** Overweight - Age 2–20 years: BMI for age ≥ 85th–< 95th percentile - Age ≥ 21 years: BMI ≥ 25–29.9; Obesity - Age 2–20 years: BMI for age ≥ 95th percentile - Age ≥ 21 years: BMI ≥ 30 BMI = wt(kg)/ht(M^2) BMI calculator available on-line at: ***www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm//*** Growth charts for patients < 21 years of age available on-line at: ***www.cdc.gov/growthcharts***	**Treatment Factors** Surgery in suprasellar region	**Host Factors** Extension of tumor into hypothalamus Pre-treatment obesity Craniopharyngioma	**PHYSICAL** **Height** **Weight** **BMI** Yearly	**Health Links** **Diet and Physical Activity** **Cardiovascular Risk Factors** **Counseling** Nutritional counseling. Counsel regarding obesity-related health risks **Considerations for Further Testing and Intervention** Consider evaluation for central endocrinopathies, including growth hormone deficiency, central hypothyroidism, central adrenal insufficiency, precocious puberty, and gonadotropin deficiency. Refer to endocrine to manage hormonal dysfunction. Consider evaluation for other co-morbid conditions, including dyslipidemia, hypertension, and impaired glucose metabolism/ diabetes mellitus. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
134	**Neurosurgery–Brain** (applies only to neurosurgery with potential to affect the Hypothalamic-Pituitary Axis)	**Diabetes insipidus**	**Treatment Factors** Surgery in suprasellar region Reoperation for recurrent tumor	**Host Factors** Extension of tumor into hypothalamus Craniopharyngioma	**HISTORY** Assessment of excessive thirst/polyuria Yearly **SCREENING** **Na, K, Cl, CO_2** **Serum Osmolality** **Urine Osmolality** As clinically indicated if history consistent with excessive thirst and/or polyuria	**Health Links** **Hypopituitarism** **Considerations for Further Testing and Intervention** Consider evaluation for other central endocrinopathies, including growth hormone deficiency, central hypothyroidism, central adrenal insufficiency, precocious puberty, and gonadotropin deficiency. Refer to endocrine to manage hormonal dysfunction. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
135	**Neurosurgery–Spinal cord**	**Neurogenic bladder** **Urinary incontinence**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation dose ≥ 45 Gy to lumbar and/or sacral spine and/or cauda equina	**Host Factors** Injury above the level of the sacrum **Treatment Factors** Radiation dose ≥ 50 Gy to lumbar and/or sacral spine and/or cauda equina	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**Health Links** **Neurogenic Bladder** **Counseling** Counsel regarding adequate fluid intake, regular voiding, seeking medical attention for symptoms of voiding dysfunction or urinary tract infection and compliance with recommended bladder catheterization regimen. **Considerations for Further Testing and Intervention** Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections. **SYSTEM = CNS** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
136	**Neurosurgery–Spinal cord**	**Neurogenic bowel** **Fecal incontinence**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation dose ≥ 50 Gy to bladder, pelvis, or spine	**Host Factors** Injury above the level of the sacrum	**HISTORY** **Chronic constipation** **Fecal soiling** Yearly **PHYSICAL** **Rectal exam** As clinically indicated	**Counseling** Counsel regarding benefits of adherence to bowel regimen, including adequate hydration, fiber, laxatives/enemas as clinically indicated. **Considerations for Further Testing and Intervention** GI consultation to establish bowel regimen for patients with chronic impaction or fecal soiling. **SYSTEM = CNS** **SCORE = 1**

SECTION 136 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
137 (male)	**Neurosurgery–Spinal cord**	**Psychosexual dysfunction** Erectile dysfunction Ejaculatory dysfunction	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation to bladder, pelvis, or spine **Medical Conditions** Hypogonadism	**Host Factors** Injury above the level of the sacrum **Treatment Factors** Radiation dose ≥ 55 Gy to penile bulb in adult and ≥ 45 Gy in prepubertal child	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** Yearly **Medication use** Yearly	**Health Links** **Male Health Issues** **Counseling** Men with erectile/ejaculatory dysfunction desiring paternity can consider assisted reproductive technology for sperm retrieval Resources. ***www.urologychannel.com*** **Considerations for Further Testing and Intervention** Urologic consultation in patients with positive history. **SYSTEM = CNS** **SCORE = 2A**

SECTION 137 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
138 (female)	**Neurosurgery–Spinal cord**	**Psychosexual dysfunction**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation to bladder, pelvis, or spine **Medical Conditions** Hypogonadism Vaginal fibrosis/stenosis Chronic GVHD	**Host Factors** Injury above the level of the sacrum	**HISTORY** **Altered or diminished sensation, loss of sensation)** **Dyspareunia** **Medication use** Yearly	**Considerations for Further Testing and Intervention** Gynecologic consultation in patients with positive history. **SYSTEM = CNS** **SCORE = 2A**

SECTION 138 REFERENCES

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
139	**Neurosurgery–Spinal cord** Laminectomy Laminoplasty	**Scoliosis/Kyphosis**	**Host Factors** Preoperative deformity Young age (deformity can still develop even if skeletally mature at time of surgery) **Treatment Factors** Radiation to the spine Increasing number of laminae removed Facetectomy Laminectomy (versus laminotomy) Laminectomy without fusion	**Treatment Factors** > 3 laminae removed; Increasing number of resections Surgery of thoracolumbar junction	**PHYSICAL** **Spine exam for scoliosis and kyphosis** Yearly until growth completed, may need more frequent assessment during puberty or if curve detected	**Health Links** **Scoliosis and Kyphosis** **Considerations for Further Testing and Intervention** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on radiographic exam. **SYSTEM = Musculoskeletal** **SCORE = 1**

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OOPHOROPEXY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
140 (female)	**Oophoropexy** **Info Link** Also see Section 96 if shielding from radiation was incomplete.	**Oophoropexy-related complications** Inability to conceive despite normal ovarian function Dyspareunia Symptomatic ovarian cysts Bowel obstruction Pelvic adhesions	**Treatment Factors** Ovarian radiation Tubo-ovarian dislocation, especially with lateral ovarian transposition		**HISTORY** **Inability to conceive despite normal ovarian function** **Dyspareunia** **Abdominal pain** **Pelvic pain** Yearly	**Considerations for Further Testing and Intervention** Gynecologic consultation for patients with positive history and/or physical findings. **SYSTEM = Reproductive (female)** **SCORE = 2A**

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SURGERY

OOOPHORECTOMY (UNILATERAL)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
141 (female)	**Oophorectomy** (unilateral)	**Premature menopause** **Info Link** Evidence for premature menopause following unilateral oophorectomy is limited and has been extrapolated from the adult literature.	**Health Behaviors** Smoking	**Treatment Factors** - Combined with: - Pelvic radiation - Alkylating agents - TBI	**SCREENING** **FSH** **LH** **Estradiol** Baseline at age 13 AND as clinically indicated in patients with delayed or arrested puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine (***www.asrm.org***) Fertile Hope (***www.fertilehope.org***) **Counseling** Counsel currently menstruating women to be cautious about delaying childbearing. Counsel regarding need for contraception. **Considerations for Further Testing and Intervention** Refer to reproductive endocrinology for counseling regarding oocyte cryopreservation in patients wishing to preserve options for future fertility. **SYSTEM = Reproductive (female)** **SCORE = 2A**

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SURGERY

OOOPHORECTOMY (BILATERAL)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
142 (female)	**Oophorectomy** (bilateral)	**Hypogonadism** **Infertility**			**SCREENING** **Gynecologic or endocrinologic consultation for initiation of hormonal replacement therapy** At age 11 or immediately for post-pubertal patients	**Health Links** **Female Health Issues** **Resources** American Society for Reproductive Medicine (***www.asrm.org***) Fertile Hope (***www.fertilehope.org***) **Counseling** Counsel regarding benefits of HRT in promoting pubertal progression, bone and cardiovascular health. Counsel women regarding pregnancy potential with donor eggs (if uterus is intact). **Considerations for Further Testing and Intervention** Bone density evaluation in hypogonadal patients. Reproductive endocrinology referral regarding assisted reproductive technologies. Monitor cardiovascular health. **SYSTEM = Reproductive (female)** **SCORE = 1**

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SURGERY

ORCHIECTOMY (UNILATERAL)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
143 (male)	**Orchiectomy** unilateral	**Gonadal dysfunction (testicular)** Reduced fertility Testosterone insufficiency	**Host Factors** Testicular cancer Obesity Ejaculatory dysfunction Medications Occupational exposures (pesticides, heavy metals, solvents) **Treatment Factors** Unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents **Health Behaviors** Tobacco/marijuana use History of sexually transmitted diseases		**HISTORY** **Pubertal (onset, tempo)** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging** Until sexually mature **Testicular volume by Prader orchiometer; Testicular examination (including prosthesis)** Yearly **SCREENING** **Screening for reduced fertility: Semen analysis** As requested by sexually mature patient **FSH** In sexually mature patient if unable to obtain semen analysis **Screening for testosterone insufficiency: Testosterone** (ideally morning) As clinically indicated in patients with delayed or arrested puberty and/or clinical signs and symptoms of testosterone deficiency	**Health Links** **Male Health Issues** **Counseling** Counsel to wear athletic supporter with protective cup during athletic activities. **Considerations for Further Testing and Intervention** Consider surgical placement of testicular prosthesis and ongoing monitoring for surgical complications after prosthesis placement. Orchiectomy can be associated with psychological distress related to altered body image. **SYSTEM = Reproductive (male)** **SCORE = 1**

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SURGERY

ORCHIECTOMY (BILATERAL)

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
144 (male)	**Orchiectomy** bilateral	**Gonadal dysfunction (testicular)** Infertility Testosterone Deficiency			**PHYSICAL** **Examination of testicular prostheses** Yearly **SCREENING** Refer to endocrinology at age 11 for initiation of hormonal replacement therapy to induce puberty (or immediately for post-pubertal patients)	**Health Links** **Male Health Issues** **Considerations for Further Testing and Intervention** Consider surgical placement of testicular prostheses and ongoing monitoring for surgical complications after prostheses placement. Orchiectomy can be associated with psychological distress related to altered body image. **SYSTEM = Reproductive (male)** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
145	**Pelvic surgery** **Cystectomy** **Info Link** For patients with cystectomy: See also Section 122	**Urinary incontinence** **Urinary tract obstruction**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Retroperitoneal node dissection Extensive pelvic dissection (e.g., bilateral ureteral re-implantation, retroperitoneal tumor resection) Radiation to the bladder, pelvis, and/or lumbar-sacral spine		**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**Counseling** Counsel regarding adequate fluid intake, regular voiding, seeking medical attention for symptoms of voiding dysfunction or urinary tract infection and compliance with recommended bladder catheterization regimen. **Considerations for Further Testing and Intervention** Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections. **SYSTEM = Urinary** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
146	**Pelvic surgery** **Cystectomy**	**Fecal incontinence**	**Host Factors** Tumor adjacent to or compressing spinal cord or cauda equina **Treatment Factors** Radiation to the bladder, pelvis, or spine		**HISTORY** **Chronic constipation** **Fecal soiling** Yearly **PHYSICAL** **Rectal exam** As clinically indicated	**Counseling** Counsel regarding benefits of adherence to bowel regimen, including adequate hydration, fiber, laxatives/enemas as clinically indicated. **Considerations for Further Testing and Intervention** GI consultation to establish bowel regimen for patients with chronic impaction or fecal soiling. **SYSTEM = GI/Hepatic** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
147 (male)	**Pelvic surgery** **Cystectomy**	**Sexual dysfunction (male)** Retrograde ejaculation Anejaculation Erectile dysfunction	**Treatment Factors** Retroperitoneal node dissection Retroperitoneal tumor resection Cystectomy Radical prostatectomy Tumor adjacent to spine; Radiation to bladder, pelvis, or spine **Medical Conditions** Hypogonadism	**Host Factors** Extensive presacral tumor resection or dissection; Radiation dose ≥ 55 Gy to penile bulb in adult and ≥ 45 Gy in prepubertal child	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** **Quality of ejaculate (frothy white urine with first void after intercourse suggests retrograde ejaculation)** Yearly	**Health Links** **Male Health Issues** **Resources** ***www.urologychannel.com*** **Counseling** Men with erectile/ejaculatory dysfunction desiring paternity can consider assisted reproductive technology for sperm retrieval. **Considerations for Further Testing and Intervention** Urologic consultation in patients with positive history and/or physical exam findings. **SYSTEM = Reproductive (male)** **SCORE = 2A**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
148 (female)	**Pelvic surgery** **Cystectomy**	**Sexual dysfunction (female)**	**Host Factors** Chronic GVHD Hypogonadism Tumor adjacent to spine **Medical Conditions** Radiation to bladder, pelvis, or spine		**HISTORY** **Altered or diminished sensation, loss of sensation** **Dyspareunia** **Medication use** Yearly	**SYSTEM = Reproductive (female)** **SCORE = 2A**

SECTION 148 REFERENCES

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SURGERY

SPLENECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
149	**Splenectomy**	**Asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*, *meningococcus*)			**PHYSICAL** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** When febrile T ≥ 101ºF **SCREENING** **Blood culture** When febrile T ≥ 101ºF	**Health Links** **Splenic Precautions** **Counseling** Advise obtaining medical alert bracelet/card noting asplenia. Counsel regarding risk of life-threatening infections with encapsulated organisms. Also counsel regarding risk associated with malaria and tick-borne diseases if living in or visiting endemic areas. **Considerations for Further Testing and Intervention** In patients with T ≥ 101° (38.3° C) or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC; toxic clinical appearance; fever ≥ 104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines according to current ACIP recommendations. Discuss with dental provider potential need for antibiotic prophylaxis based on planned procedure. **Info Link** See current edition of AAP *Red Book* for recommendations regarding antibiotic prophylaxis and immunizations **SYSTEM = Immune** **SCORE = 2A**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
150	**Thoracic surgery (includes thoracotomy, chest wall surgery, rib resection, pulmonary lobectomy, pulmonary metastasectomy, pulmonary wedge resection)**	**Pulmonary dysfunction**	**Treatment Factors** Combined with pulmonary toxic therapy: - Bleomycin - Busulfan - Carmustine (BCNU) - Lomustine (CCNU) **Medical Conditions** Atopic history **Health Behaviors** Smoking Inhaled illicit drug use	**Treatment Factors** Combined with: - Chest radiation - TBI	**HISTORY** **Cough** **SOB** **DOE** **Wheezing** Yearly **PHYSICAL** **Pulmonary exam** Yearly **SCREENING** **PFTs (including DLCO and spirometry)** Baseline at entry into long-term follow-up, repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction	**Health Links** **Pulmonary Health** **Resources** Extensive information regarding smoking cessation is available for patients on the NCI's website: ***www.smokefree.gov*** **Counseling** Counsel regarding tobacco avoidance/smoking cessation. Patients who desire to SCUBA dive should be advised to obtain medical clearance from a pulmonologist. **Considerations for Further Testing and Intervention** In patients with abnormal PFTs, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for patients with symptomatic pulmonary dysfunction; Influenza and pneumococcal vaccinations . **SYSTEM = Pulmonary** **SCORE = 2A**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
151	**Thoracic surgery (includes thoracotomy, chest wall surgery, rib resection, pulmonary lobectomy, pulmonary metastasectomy, pulmonary wedge resection)**	**Scoliosis/Kyphosis**	**Host Factors** Young age (deformity can still develop even if skeletally mature at time of surgery) Preoperative deformity Treatment Factors Radiation to the spine	**Treatment Factors** Greater number of ribs resected	**PHYSICAL** **Spine exam for scoliosis and kyphosis** Yearly until growth completed, may need more frequent assessment during puberty or if curve detected	**Health Links** **Scoliosis and Kyphosis** **Considerations for Further Testing and Intervention** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on radiographic exam **SYSTEM = Musculoskeletal** **SCORE = 2A**

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THYROIDECTOMY

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
152	**Thyroidectomy** **Info Link** • Total thyroidectomy is uncommon, but if done is associated with the risk of hypoparathyroidism. This complication generally occurs in the early postoperative period and may persist. • Patients with a history of total thyroidectomy should be monitored for signs and symptoms of hypoparathyroidism (e.g., paresthesias, muscle cramping, altered mental status, hyperreflexia, tetany, hypocalcemia, and hyperphosphatemia).	**Hypothyroidism**			**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly **PHYSICAL** **Height** **Weight** **Hair and skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
153	**Radioiodine therapy (I-131 thyroid ablation)**	**Lacrimal duct atrophy**			**HISTORY** **Excessive tearing** Yearly	**Considerations for Further Testing and Intervention** Ophthalmology consultation as clinically indicated. **SYSTEM = Ocular** **SCORE = 2A**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
154	**Radioiodine therapy (I-131 thyroid ablation)**	**Hypothyroidism**			**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair and skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
155	**Systemic MIBG (in therapeutic doses)** **Info Link** MIBG used for diagnostic purposes (i.e., MIBG scanning) does NOT put patients at risk for hypothyroidism.	**Hypothyroidism**			**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair and skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**Health Links** **Thyroid Problems** **Counseling** Counsel at-risk females of childbearing potential to have their thyroid levels checked prior to attempting pregnancy and periodically throughout pregnancy. **Considerations for Further Testing and Intervention** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

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Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
156	**Bioimmunotherapy** (e.g., G-CSF,IL-2, erythropoietin)	**Insufficient information currently available regarding late effects of biological agents.**			**SCREENING** **No Known Late Effects**	**SYSTEM = No Known Late Effects** **SCORE = N/A**

SECTION 156 REFERENCES

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CANCER SCREENING GUIDELINES

BREAST CANCER

Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
157 (female)	**Breast**	Over age 40 Family history of breast cancer in first degree relative Early onset of menstruation Late onset of menopause (age 55 or older) Older than 30 at birth of first child Never pregnant Obesity Previous breast biopsy with atypical hyperplasia Hormone replacement therapy	Chest radiation with potential impact to the breast (see Section 77), including ≥ 20 Gy to the following fields: - Chest (thorax) - Whole lung - Mediastinal - Axilla - Mini-Mantle - Mantle - Extended Mantle - TLI - STLI - TBI* *BRACA1*, *BRACA2*, ATM mutation **Info Link** • ***Important*: The risk of breast cancer in patients who received 10–19 Gy of radiation with potential impact to the breast or those who received TBI alone is of a lower magnitude compared to those who received ≥20 Gy of radiation with potential impact to the breast (e.g.,thorax, axilla).** • **Monitoring of patients who received 10–19 Gy of radiation with potential impact to the breast or those who received TBI without additional radiation should be determined on an individual basis.** • **After the clinician discusses the benefits and risks/harms of screening with the patient, if a decision is made to screen, then follow the recommendations for patients who received ≥ 20 Gy.**	***PATIENTS AT STANDARD RISK (ACS Recommendation)*** **PHYSICAL** **Clinical breast exam** Every 3 years between ages 20–39, then yearly beginning at age 40 **SCREENING** **Mammogram** Yearly, beginning at age 40 ***PATIENTS AT HIGHEST RISK*** (≥ 20 Gy radiation with potential impact to the breast) **PHYSICAL** **Breast self exam** Monthly, beginning at puberty **Clinical breast exam** Yearly, beginning at puberty until age 25, then every 6 months **SCREENING** **Mammogram** Yearly, beginning 8 years after radiation or at age 25, whichever occurs last. **Breast MRI** Yearly, as an adjunct to mammography beginning 8 years after radiation or at age 25, whichever occurs last. **Info Link** • Mammography is currently limited in its ability to evaluate the premenopausal breast. • MRI is now recommended as an adjunct to mammography in women treated with chest radiation for childhood cancer similar to screening of other populations at high risk for breast cancer (e.g., premenopausal known or likely carriers of gene mutation of known penetrance). • The upper age limit at which both modalities should be used for breast cancer surveillance has not been established.	**Health Links** **Breast Cancer** (for patients at highest risk only) **Counseling** For patients at highest risk, counsel to perform breast self-examination monthly, beginning at puberty. For standard risk patients, provide general guidance regarding routine screening beginning at age 40 per current ACS guidelines. **Considerations for Further Testing and Interventions** Surgery and/or oncology consultation as clinically indicated

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
158 (female)	**Cervical**	Early age at first intercourse Multiple lifetime sex partners Smoking Sexually transmitted diseases	Personal history of cervical dysplasia Prenatal DES exposure HPV infection Immunosuppression Chronic steroid use HIV positive Chronic GVHD	***PATIENTS AT STANDARD RISK (ACS Recommendation)*** **PHYSICAL** **Pelvic exam** Every 3–5 years beginning at age 21 (see "Screening" below for specific recommendations) **SCREENING** **Cervical PAP smear** • Cervical cancer screening should begin at age 21 y. • For women aged 21–29 y, screening should be done every 3 y with conventional or liquid-based Pap tests. • For women aged 30–65 y, screening should be done every 5 y with both the HPV test and the Pap test (preferred), or every 3 y with the Pap test alone (acceptable). • Women aged > 65 y who have had > 3 consecutive negative Pap tests or > 2 consecutive negative HPV and Pap tests within the last 10 y, with the most recent test occurring within the last 5 y, and women who have had a total hysterectomy should stop cervical cancer screening. • Women at any age should not be screened annually by any screening method.	**Health Links** **Reducing the Risk of Second Cancers** **Counseling** **Counsel regarding risk/benefits of HPV vaccination.** **Info Link** • Human papillomavirus virus (HPV) is the leading cause of cervical cancer in women. HPV vaccination protects against 70% of cervical cancers and the quadrivalent form the vaccine reduces the incidence of genital warts. • The Centers for Disease Control Advisory Committee on Immunization Practices (CDC/ACIP) and American Cancer Society (ACS) both recommend routine HPV immunization of girls when they are 11–12 years old. • Females as young as 9 years can the receive HPV vaccination at the discretion of their health care provider. HPV vaccination is also recommended for females 13–26 (CDC/ACIP) years to catch up missed vaccines or to complete the series. • For optimal protection, the vaccine should be administered before the onset of sexual activity. Females who are sexually active may still benefit from vaccination through protection against strains to which they have not been exposed. • HPV vaccination does not change recommendations for cervical cancer PAP screening since the vaccine does not protect against all cancer-causing types of HPV. See Markowitz LE et al. (2007) and Centers for Disease Control and Prevention (2010), for further information. **Considerations for Further Testing and Interventions** Gynecology and/or oncology consultation as clinically indicated.

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
159	**Colorectal**	High fat/low fiber diet Age ≥ 50 years Obesity	Radiation with potential impact to the colon/rectum (see Section 90), including ≥ 30 Gy to the following fields: - Spine (thoracic, lumbar, sacral, whole) - Extended Mantle - Hepatic - Renal - Upper quadrant (right, left) - Spleen (partial, entire) - Paraaortic - Flank/Hemiabdomen (right, left) - Whole abdomen - Inverted Y - Pelvic - Vaginal - Prostate - Bladder - Iliac - Inguinal - Femoral - TLI - STLI - TBI* Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps in first degree relative **Info Link** • *Important: Reports of colorectal cancer in cohorts of long-term survivors suggest that radiation likely increases risk; however, the risk related to TBI alone has not been established. • ***Monitoring of patients who received TBI without additional radiation potentially impacting the colon/rectum should be determined on an individual basis***. (See Info Link in next column).	***PATIENTS AT STANDARD RISK (ACS Recommendation)*** **SCREENING** **Option 1** **Fecal occult blood (minimum of 3 cards)** Yearly, beginning at age 50 ***AND/OR*** **Flexible sigmoidoscopy** Every 5 years, beginning at age 50 **Note**: The combination of yearly fecal occult blood testing and every 5 year flexible sigmoidoscopy is preferable to either test done alone. **Option 2** **Double contrast barium enema** Every 5 years, beginning at age 50 **Option 3** **Colonoscopy** Every 10 years, beginning at age 50 ***PATIENTS AT HIGHEST RISK*** **SCREENING** **Colonoscopy** Every 5 years (minimum); more frequently if indicated based on colonoscopy results. Begin monitoring 10 years after radiation or at age 35, whichever occurs last. Monitor more frequently if clinically indicated. Per the ACS, begin screening earlier for the following high-risk groups: HNPCC (at puberty), FAP (at age 21 years), IBD (8 years after diagnosis of IBD). Information from the first colonoscopy will inform frequency of follow-up testing. **Info Link** • Reports of gastrointestinal malignancies in cohorts of long-term survivors suggest that radiation likely increases risk, but the median age of onset is not as well established as that of secondary breast cancer following chest radiation. • The expert panel agreed that early onset of screening likely was beneficial, and that a prudent course would be to initiate screening for colorectal cancer for those at highest risk (abdominal, pelvic, and/or spinal radiation ≥ 30 Gy) at age 35, or 10 years post radiation, whichever occurs last. • Surveillance should be done via colonoscopy as per recommendations for populations at highest risk, with information from the first colonoscopy informing the frequency of follow-up testing. • While the American Cancer Society recently added computed tomographic colonography (CTC) (AKA "Virtual Colonoscopy") as an acceptable option for colorectal cancer screening of average-risk adults, the National Comprehensive Cancer Network and United States Preventive Services Task Force concluded that data was too premature to warrant its use in screening. • Colonoscopy remains the preferred screening modality for survivors at highest risk of colorectal cancer.	**Health Links** **Colorectal Cancer** **Considerations for Further Testing and Interventions** Gastroenterology, surgery and/or oncology consultation as clinically indicated.

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
160 (female)	**Endometrial**	Obesity Older age Unopposed estrogen therapy Tamoxifen Diabetes Hypertension High fat diet Early menopause Late menopause Nulliparity Infertility Failure to ovulate	History of/at risk for hereditary nonpolyposis colon cancer (HNPCC)	***PATIENTS AT STANDARD RISK (ACS Recommendation)*** **SCREENING** **Endometrial biopsy** Yearly, beginning at age 35 for patients at highest risk **Info Link** • Women at highest risk should be informed that the screening recommendation for endometrial biopsy beginning at age 35 is based on expert opinion. • In the absence of definitive scientific evidence, the potential benefits and risks/harms of testing for early endometrial cancer detection should be discussed.	**Health Links** **Reducing the Risk of Second Cancers**

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
161	**Lung**	Chest radiation with potential impact to the lung Smoking Workplace exposures to asbestos, arsenic, radiation Second hand smoke (in non-smokers)	Chest radiation with potential impact to the lung combined with smoking	***PATIENTS AT HIGHEST RISK*** **HISTORY** **Cough** **Wheezing** **SOB** **DOE** Yearly, and as clinically indicated **PHYSICAL** **Pulmonary Exam** Yearly, and as clinically indicated **SCREENING** Clinicians should discuss the benefits and risks/harms of spiral CT scanning for patients at highest risk	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Imaging and surgery and/or oncology consultation as clinically indicated.

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
162	**Oral**	Tobacco use (smoking cigars, cigarettes, or pipes; dipping, chewing) Alcohol abuse Excessive sun exposure (increases risk of cancer of lower lip) HCT (allogeneic > autologous) Human Papillomavirus (HPV) infection	Head/brain radiation Neck radiation TBI Acute/chronic GVHD	***PATIENTS AT STANDARD RISK (ACS Recommendation)*** **PHYSICAL** **Oral cavity exam** Yearly	**Health Links** **Reducing the Risk of Second Cancers** **Dental Health** **Considerations for Further Testing and Intervention** Head and neck/otolaryngology consultation as indicated.

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
163 (male)	**Prostate**	Older age, with steadily increasing risk after age 40 years.	African-American race Family history of prostate cancer in first degree relative	***ALL PATIENTS*** Clinicians should be prepared to discuss prostate cancer testing with patients **Info Link** • The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. • Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cancers that may never have affected a patient's health. • The USPSTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population. ACS concurs with this conclusion.	**Health Links** **Reducing the Risk of Second Cancers** **Considerations for Further Testing and Intervention** Urology and/or oncology consultation as clinically indicated.

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
164	**Skin**	Light skin color Chronic exposure to sun Atypical moles or ≥ 50 moles	Any history of radiation Personal history of melanoma or skin cancer Dysplastic nevi Family history of melanoma or skin cancer History of severe sunburn at young age	***PATIENTS AT STANDARD RISK*** **Info Link** • The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for skin cancer using a total-body skin examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer. • There are no randomized trials or case-control studies that directly examine whether screening by clinicians is associated with improved clinical outcomes such as reduced morbidity or mortality from skin cancer. No studies were found that evaluated whether screening improves the outcomes of these cancers. • The American Cancer Society recommends skin examination as part of a cancer-related checkup, which should occur on the occasion of the patient's periodic health examination. Self-examination of skin is recommended once a month. ***PATIENTS AT HIGHEST RISK*** **PHYSICAL** **Skin self exam** Monthly **Dermatologic exam with attention to skin lesions and pigmented nevi in radiation field** Yearly	**Health Links** **Reducing the Risk of Second Cancers** **Skin Health** **Considerations for Further Testing and Intervention** Surgery, dermatology, and/or oncology consultation as clinically indicated.

SECTION 164 REFERENCES

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Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
165 (male)	**Testicular**	Young males	History of cryptorchidism History of testicular cancer or carcinoma in-situ in contralateral testis History of gonadal dysgenesis Klinefelter's syndrome Family history of testicular cancer	**Info Link** • For standard and high risk populations, the USPSTF recommends against routine screening for testicular cancer in asymptomatic adolescent and adult males. • In 2004, the USPSTF found no new evidence that screening with clinical examination or testicular self-examination is effective in reducing mortality from testicular cancer. Even in the absence of screening, the current treatment interventions provide very favorable health outcomes. • Given the low prevalence of testicular cancer, limited accuracy of screening tests, and no evidence for the incremental benefits of screening, the USPSTF concluded that the harms of screening exceed any potential benefits. • ACS also no longer recommends clinical testicular cancer screening or testicular self-examination.	

SECTION 165 REFERENCES

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GENERAL HEALTH SCREENING

ANY CANCER EXPERIENCE

Sec #	Organ	Population Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
166	**General Health Screening**			**SCREENING** **Refer to United States Preventive Services Task Force recommendations at *www.ahrq.gov/clinic/uspstfix.htm*** Yearly	**Considerations for Further Testing and Intervention** Childhood cancer survivors should receive general health maintenance per standard recommendations for age. Recommended preventive services per the USPSTF include screening for hypertension, obesity, depression, tobacco use, and alcohol misuse. In addition, certain subpopulations require screening for lipid disorders, sexually transmitted diseases, and diabetes mellitus. Others require counseling regarding the prevention of cardiovascular disease, osteoporosis, and other disorders. See ***www.ahrq.gov/clinic/uspstfix.htm*** for specific recommendations. Assess immunization status on all patients; reimmunize as indicated. See ***www.cdc.gov/vaccines/*** for current immunization schedules. For all HCT patients, reimmunization per current recommendations (Ljungman et al, 2009: ***www.nature.com/bmt/journal/v44/n8/full/bmt2009263a.html***).

SECTION 166 REFERENCES

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