CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 5.0 - October 2018

Website: www.survivorshipguidelines.org

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Version 5.0
October 2018

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Abstract

Release date: October 2018

Status: Updated from Version 4.0 incorporating modifications based on recommendations from the Children's Oncology Group's Long- Term Follow-Up Guideline Core Committee and its 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 survivors 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 5.0 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***.

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 5.0*. Monrovia, CA: Children's Oncology Group; October 2018; 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.

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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Preface

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. "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.

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 regard to the screening recommendations outlined for the 155 therapeutic exposures in the COG LTFU Guidelines:

- 108 (70%) are derived primarily from the H&P, of which 91 (59%) rely solely on the H&P and 17 (11%) rely on the H&P plus a baseline diagnostic study (e.g., lab, imaging)
- 42 (27%) include periodic laboratory, diagnostic imaging, or other testing
- 5 (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, a tool to assist in identifying guideline applicability for individual survivors based on therapeutic exposures, and templates for letters appealing denied insurance claims.

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
d. Provides timely intervention for late effects

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***.

Target Population

The recommendations for periodic screening evaluations provided in the COG LTFU Guidelines 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.

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

Preface (cont)

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 survivors 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.

Evidence Collection

Pertinent information from the published medical literature over the past 20 years (updated as of October 2018) was retrieved and reviewed during the development and updating of these guidelines. For each therapeutic exposure, a complete search was performed via MEDLINE (National Library of Medicine, Bethesda, MD). Keywords included "childhood cancer therapy," "complications," and "late effects," combined with keywords for each therapeutic exposure. References from the bibliographies of selected articles were used to broaden the search.

Methods

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

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

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).

Pre-Release Review

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

Revisions

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

In order to keep the guidelines current and clinically meaningful, the COG Late Effects Committee organized 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 COG Outcomes and Survivorship Committee, and recommending revisions to the guidelines and their associated health education materials and references (including the addition of therapeutic exposures) as new

Preface (cont)

information becomes available. 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 relevant to the current release of these guidelines (Version 5.0 – October 2018).

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 Preface). 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 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***.

Scoring Explanation

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 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 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 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.

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Recommendations and Rationale

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

Potential Benefits and Harms

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

Potential harms of guideline implementation include increased patient anxiety related to enhanced awareness of possible complications, as well as the potential for false-positive screening evaluations, leading to unnecessary further workup. In addition, costs of long-term follow-up care may be prohibitive for some survivors, 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 survivors 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 Passport 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***).

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CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Instructions for Use

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.
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***. **Resources:** Books and websites that may provide the clinician with additional relevant information. **Counseling:** Suggested patient counseling regarding measures to prevent/reduce risk or promote early detection of the potential treatment complication. **Potential Considerations for Further Testing and Intervention:** Recommendations for further diagnostic evaluations beyond minimum screening for individuals with positive history and/ or physical examination findings or positive screening tests, recommendations for consultation and/or referral, and recommendations for management of exacerbating or predisposing conditions.
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. See "Scoring Explanation" in the Preface for more information.
Additional Information	Patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors that may increase risk for developing the complication and additional information pertinent to the late effects or its evaluation (previously known as "Info Links")
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.
Cancer Screening Recommendations	Sections 156-164 contain preventive screening recommendations for common adult-onset cancers, organized by column as follows: **Organ:** The organ at risk for developing malignancy. **Standard Risk Parameters and Screening Guidelines:** Screening guidelines provided under the "Standard Risk" category are per the American Cancer Society and the U. S. Preventive Services Task Force recommendations for standard-risk populations and are included here for reference. **Highest Risk Parameters and Screening Guidelines:** High risk populations were those 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. 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.

Instructions for Use (cont)

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

Demographics

- Name
- Sex
- Date of birth

Cancer Diagnosis

- Diagnosis
- Date of diagnosis
- Date cancer therapy was completed

Cancer Treatment: Chemotherapy

- Names of all chemotherapy agents received
  - For a list of chemotherapy agents addressed by these guidelines (Sections 10-42), see the "Chemotherapy" portion of the Patient-Specific Guideline Identification Tool in Appendix I.
  - For 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)
  - See Section 33 of Guidelines for anthracycline isotoxic dose-equivalent conversion.
  - For doses in mg/kg, multiply by 30 to obtain equivalent dosing in mg/m^2 (example: 2 mg/kg = 60 mg/m^2).
- For carboplatin, whether any dose was myeloablative (i.e., given as conditioning for HCT)
- 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)

Cancer Treatment: Radiation

- Names of all radiation field(s) treated
  - For list of radiation fields addressed by these guidelines (Sections 43-97), see "Radiation" portion of the Patient-Specific Guideline Identification Tool in Appendix I
  - For definition of radiation fields, see "Radiation Fields Defined" in Appendix I
- For head/brain, neck, chest, abdomen, spine (whole, cervical, thoracic) radiation and TBI, total dose (in Gy):
  - Total radiation dose to each field (should include boost dose, if given)
  - To convert cGy or rads to Gy, divide dose by 100 (example: 2400 cGy = 2400 rads = 24 Gy)

Cancer Treatment: Hematopoietic Cell Transplant(s)

- Whether or not the survivor underwent a hematopoietic cell transplant (HCT), and if so:
  - Transplant type (autologous vs allogeneic)
  - Chronic graft-versus-host disease (cGVHD) status (no history of chronic GVHD, history of chronic GVHD, currently active chronic GVHD)

Cancer Treatment: Surgery

- Names of all surgical procedures.
  - For list of surgical procedures addressed by these guidelines (Sections 114–149), see "Surgery" portion of the Patient-Specific Guideline Identification Tool in Appendix I

Cancer Treatment: Other Therapeutic Modalities

- Whether or not the survivor received radioiodine therapy (I-131 thyroid ablation) or systemic MIBG (in therapeutic doses)

2. Compile a list of guideline sections relevant to the survivor based off the list generated in step 1.
   - Sections 1 - 6: Applicable to all survivors
   - Section 7: Survivors diagnosed before 1972
   - Section 8: Survivors diagnosed before 1993
   - Section 9: Survivors diagnosed between 1977 and 1985
   - Section 10: All survivors who received chemotherapy
   - Sections 11-42: For survivors who received chemotherapy, include relevant sections
   - Sections 43, 44, 95: All survivors who received radiation

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- Sections 45 - 94, 96- 97: For survivors who received radiation, include relevant sections
- Sections 99 - 104: All survivors who underwent hematopoietic cell transplant
  - Section 99 is for males only
  - Section 100 is for females only
- Section 98: For survivors who underwent autologous hematopoietic cell transplant
- Sections 105 - 113: For survivors who underwent allogeneic hematopoietic cell transplant, include relevant sections
- Sections 114 - 149: For survivors who underwent surgery, include relevant sections
- Sections 150 - 155: For survivors who received other therapeutic modalities, include relevant sections
- Sections 156 - 164: Applicable to all survivors
  - Sections 162, 164 are for males only
  - Sections 156, 157, 159 are for females only
- Section 165: Applicable to all survivors

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 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 Passport 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 5.0

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.

Simplification

An overall goal of Version 5.0 of the COG Long-Term Follow-Up Guidelines is to simplify the format and content of the guidelines in order to focus on clinically-relevant content, reduce the burden of medical record data abstraction necessary to determine tailored recommendations for survivors, reduce the complexity of guideline application to individual survivors, and better align COG's screening recommendations with those of the International Guideline Harmonization Group. Version 5.0 therefore features the following modifications:

- Simplification of design/format with a focus on clinical information that drives screening
- Re-definition/simplification of radiation fields
  - All radiation fields from Version 4.0 are now mapped to body parts
  - In most cases, knowing the general area of the body that received radiation is now all that is necessary in order to generate tailored radiation-related recommendations for survivors
  - It is no longer necessary to know or record specific radiation doses (with a few exceptions)
- Radiation dose cut-offs largely eliminated (with 5 exceptions)
  - Emerging evidence indicates that some late effects (e.g., breast and colorectal cancers) are occurring below the previously determined minimum dose thresholds
  - The dose cut-offs that remain in Version 5.0 are for late effects that require screening beyond the history and physical examination and for which evidence indicates that there is a low risk of developing the late effect below the radiation threshold
- Most InfoLinks have been moved to Additional Information
- All Risk Factors and Highest Risk Factors have been moved to Additional Information

General Updates

- Some History and Physical Exam elements have been reworded for consistency between sections
- Revisions have been made to Counseling and Potential Considerations in most sections
- References have been updated in all sections
- Some column labels have been changed within the Cancer Screening Guidelines Sections (sections 156-164)
- Templates have been added to Appendix I to assist with drafting appeal letters for denied insurance claims

New Sections/Late Effects

The following new sections/late effects have been added:

- Lung cancer related to chest/axillary radiation and TBI (section 75)
- Psychosexual dysfunction (male) related to pelvic surgery/cystectomy (section 143)
- Thyroid nodules related to systemic MIBG in therapeutic doses (section 153)
- Thyroid cancer related to systemic MIBG in therapeutic doses (section 154)
- Melanoma related to HCT (sections 99, 100, 105)

Sections/Late Effects Removed

The following sections or late effects have been removed from Version 5.0 of the COG LTFU Guidelines:

- Clinical leukoencephalopathy related to high-dose cytarabine (section 24 of Version 4.0)
- Lymphoma related to HCT (section 106 of Version 4.0)
- Renal toxicity related to methotrexate (section 28 changed to "No Known Renal Late Effects" in Version 5.0)

Late Effects Renamed

- Gonadal dysfunction (testicular) renamed as: Testicular hormonal dysfunction (sections 11, 89, 138) and Impaired spermatogenesis (sections 12, 90)
- Gonadal dysfunction (ovarian) renamed as: Ovarian hormone deficiencies (sections 13, 91, 135, 137) and Reduced ovarian follicular pool (sections 14, 92, 136)
- Veno-occlusive disease (VOD) of the liver renamed as: Sinusoidal obstruction syndrome (SOS) (section 26)

Newly Divided Sections

The following sections from Version 4.0 have been divided into more than one section in Version 5.0:

New to Version 5.0 (cont)

- Gonadal dysfunction (ovarian) and premature menopause related to alkylating agents, radiation and oophorectomy (unilateral) are now separated into: ovarian hormone deficiencies (sections 13, 91, 135) and reduced ovarian follicular pool (sections 14, 92, 136)
- Gonadal dysfunction (testicular) related to orchiectomy (unilateral/partial) are now separated into: testicular hormonal dysfunction (section 138) and impaired spermatogenesis (section 139)
- Sexual dysfunction (male) related to pelvic surgery/cystectomy are now separated into: psychosexual dysfunction (section 143) and sexual dysfunction (anatomic), infertility (section 144)

Newly Combined Sections

The following sections from Version 4.0 have been combined into one section in Version 5.0:

- Cardiac toxicity related to anthracyclines: Male and female sections combined (now section 33)
- Secondary benign or malignant neoplasms related to radiation: Skin, bone, and soft tissues combined (now section 43)
- Cardiac toxicity related to radiation: Male and female sections combined (now section 76)
- Hyperprolactinemia related to head/brain radiation: Male and female sections combined (now section 55)
- Ototoxicity related to radiation: Conductive and sensorineural hearing loss combined (now section 62)
- Urinary tract toxicity related to radiation: Hemorrhagic cystitis and urinary tract toxicity combined (now section 87)

Late Effects Re-categorized

- Dermatologic toxicity (section 44)
- Hepatic toxicity (section 81)
- Oral toxicity (section 107)

New Potential Late Effects Subcategories Added

- Relationship problems (section 1)
- Sleep problems (section 5)
- Functional deficit in academic fluency (section 46)
- Ectopic molar eruption (sections 10, 64)
- Oral cancer (section 43, 107)
- Luteinizing hormone (LH) and follicle stimulating hormone (FSH) deficiency (sections 57, 58)

Screenings moved from Periodic Evaluations to Considerations for Further Testing (now to be considered based on results of History and Physical Examination)

- Ovarian and testicular hormonal function (sections 11, 13, 14, 53, 54, 57, 58, 89, 91, 92, 135, 136, 138)
- Semen analysis (sections 12, 90, 139)
- Prolactin level (section 55)
- Urinalysis for assessment of radiation-related urinary tract toxicity (section 87)
- Evaluation by subspecialists (gynecologist [section 112], neurologist [sections 124, 125], physiatrist [sections 124], and neurosurgeon [section 126])

Major Screening Changes

Anthracycline and Radiation-Related Cardiac Toxicity (Sections 33, 76)

- Echocardiograms for evaluation of anthracycline and radiation-related cardiac toxicity: Changes in anthracycline and radiation dose cut-offs; changes in frequency of recommended echocardiograms; modification of isotoxic equivalent dose conversion for daunorubicin

Platinum and Radiation-Related Ototoxicity (Sections 21, 62)

- Screening recommendations now based on current age, with recommendations differing for survivors ≤age 5 years, 6-12 years, and ≥13 years; periodic screening now recommended for all at-risk survivors; screening for carboplatin no longer based on age; radiation dose cut-off now ≥30 Gy

Nephrectomy (Sections 121, 122)

- Yearly screening for renal toxicity (BP, serum creatinine, eGFR, urine dipstick for protein) now recommended

Radiation-Related Breast Cancer (Section 72)

- Screening now recommended for radiation to chest, axilla, and TBI without dose threshold

New to Version 5.0 (cont)

Radiation-Related Colorectal Cancer (Section 85)

- Screening now recommended for radiation to abdomen, pelvis, spine (lumbar, sacral, whole), and TBI without dose threshold beginning 5 years after radiation or at age 30, whichever occurs last.
- Colonoscopy every 5 years is the gold standard for screening in high-risk populations; however, multitarget stool DNA test every 3 years and other options may be considered based on informed decision making between patient and provider.

Renal toxicity Related to Chemotherapy, Radiation, and HCT (Sections 20, 23, 86, 104)

- Urinalysis removed

Adrenal Insufficiency Related to Head/Brain Radiation (Section 59)

- 8AM serum cortisol now recommended annually for patients who received ≥30 Gy head/brain radiation (with guidance added for interpretation/referral)

Additional Screening Change Highlights

- Reduced bone mineral density related to methotrexate, steroids, and HCT: Adjustment for height age z-score added for survivors younger than 20 years of age (sections 27, 36, 103)
- Cataracts/ocular toxicity related to head/brain radiation and GVHD: Evaluation by ophthalmologist changed to yearly for all patients; evaluation by optometrist added as an option; all head/brain radiation fields now included regardless of dose (previously ear/infratemporal, nasopharyngeal, and Waldeyer's Ring were excluded and doses <30 Gy were included for cataract monitoring only) (sections 60, 61, 106)
- Neuropsychological testing is now recommended for all head/brain radiation fields (previously, orbital/eye, nasopharyngeal, and Waldeyer's Ring were excluded) (section 46)
- Audiologic evaluation is now recommended for all head/brain fields at doses of ≥30 Gy (previously ocular/eye fields were excluded) (section 62)
- Dental precautions regarding osteoradionecrosis of the jaw are now recommended for all head/brain radiation fields ≥40 Gy (previously, orbital/eye fields were excluded) (section 65)
- Evaluation for febrile illness (PRN T>101° F/38.3° C) is now recommended for all abdominal radiation ≥40 Gy (previously not recommended for abdominal radiation that was limited to the right side, e.g., hepatic) (section 77)
- ALT/AST/Bilirubin (baseline and as clinically indicated) are now recommended for radiation doses <30 Gy to the abdomen (previously recommended only for doses ≥30 Gy) (section 81)

Health Links

- The Health Links have been modified to reflect all Version 5.0 Guideline changes.

General Recommendations Regarding Use of the Simplified COG LTFU Guidelines, Version 5.0

- The COG Long-Term Follow-Up Guidelines are designed to offer general guidance and are not meant to provide or replace the medical advice or judgment of clinicians caring for individual survivors.
- The recommendations in Version 5.0 of these Guidelines rely more extensively on history and physical examination and less on screening evaluations, when compared to prior Guideline versions.
- We recognize that recommendations for over-screening may occur (primarily due to elimination of radiation dose-cutoffs and simplification of radiation fields); however, additional screening will generally result in recommendations for components of the history and physical examination only.
- It is important for clinicians to recognize that not all survivors may be at-risk for all late effects that are associated with the broader exposure categories in Version 5.0; for example, survivors with radiation fields that are known to be limited to a specific targeted area within a broader field. Thus, if clinicians have more detailed information that supports refraining from a specific screening for a particular patient, clinical judgment should be used to guide the individual evaluation.
- Since a number of previously recommended screening evaluations are now to be considered based on findings from the history and physical examination, clinicians need to carefully discern which history and physical examination findings should trigger further evaluations. Additional, more intensive screening and/or diagnostic workup are recommended for any survivors for whom the clinician believes there is reason to suspect the presence of a late effect.
- If clinicians have more detailed information that supports additional screening (or refraining from screening), clinicians are encouraged to modify their recommendations for individual survivors based on their knowledge of that survivor's specific therapeutic exposures during treatment and their current clinical status.

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Guidelines

Version 5.0
October 2018

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

ANY CANCER EXPERIENCE

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
1	**Any Cancer Experience**	**Adverse psychosocial/quality of life effects** Social withdrawal Educational problems Relationship problems Under-employment/ Unemployment Dependent living	**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: A Practical Guide to Your Future,' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 'Educating the Child with Cancer: A Guide for Parents and Teachers' edited by Ruth Hoffman, American Childhood Cancer Organization, 2013 **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Social work consultation. Refer as indicated to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational or vocational resources. Refer as indicated for neuropsychological evaluation. **SYSTEM = Psychosocial** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Female sex, younger age at diagnosis, family history of depression, anxiety, or mental illness, lower household income, lower educational achievement, failure to graduate from high school
- Cancer/Treatment factors: Bone tumor, CNS tumor, CNS-directed therapy, history of hematopoietic cell transplant
- Pre-morbid/Co-morbid medical conditions: Neurocognitive problems, depression, physical limitations, seizures, scarring or disfigurement, vision loss, hearing loss, premorbid learning or emotional difficulties

References

Barrera M, Shaw AK, Speechley KN, et al: Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics. Cancer 104:1751-60, 2005

Bernard F, Auquier P, Herrmann I, et al: Health status of childhood leukemia survivors who received hematopoietic cell transplantation after BU or TBI: an LEA study. Bone Marrow Transplant 49:709-16, 2014

Boman KK, Lindblad F, Hjern A: Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income. Cancer 116:1385-91, 2010

Brinkman TM, Bass JK, Li Z, et al: Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. Cancer 121:4053-61, 2015

Brinkman TM, Krasin MJ, Liu W, et al: Long-term neurocognitive functioning and social attainment in adult survivors of pediatric CNS tumors: results from the St Jude Lifetime Cohort Study. J Clin Oncol 34:1358-67, 2016

Section 1 References (cont)

Brinkman TM, Ullrich NJ, Zhang N, et al: Prevalence and predictors of prescription psychoactive medication use in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Cancer Surviv 7:104-14, 2013

de Blank PM, Fisher MJ, Lu L, et al: Impact of vision loss among survivors of childhood central nervous system astroglial tumors. Cancer 122:730-9, 2016

Font-Gonzalez A, Feijen EL, Sieswerda E, et al: Social outcomes in adult survivors of childhood cancer compared to the general population: linkage of a cohort with population registers. Psycho-Oncol 25:933-41, 2016

Gurney JG, Krull KR, Kadan-Lottick N, et al: Social outcomes in the Childhood Cancer Survivor Study cohort. J Clin Oncol 27:2390-5, 2009

Hornquist L, Rickardsson J, Lannering B, et al: Altered self-perception in adult survivors treated for a CNS tumor in childhood or adolescence: population-based outcomes compared with the general population. Neuro Oncol 17:733-40, 2015

Janson C, Leisenring W, Cox C, et al: Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 18:2626-35, 2009

Kinahan KE, Sharp LK, Seidel K, et al: Scarring, disfigurement, and quality of life in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 30:2466-74, 2012

Kirchhoff AC, Krull KR, Ness KK, et al: Occupational outcomes of adult childhood cancer survivors: A report from the Childhood Cancer Survivor Study. Cancer 117:3033-44, 2011

Kirchhoff AC, Leisenring W, Krull KR, et al: Unemployment among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Med Care 48:1015-25, 2010

Kunin-Batson A, Kadan-Lottick N, Zhu L, et al: Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer 57:1197-203, 2011

Lancashire ER, Frobisher C, Reulen RC, et al: Educational attainment among adult survivors of childhood cancer in Great Britain: a population-based cohort study. J Natl Cancer Inst 102:254-70, 2010

Lown EA, Phillips F, Schwartz LA, et al: Psychosocial follow-up in survivorship as a standard of care in pediatric oncology. Pediatr Blood Cancer 62 Suppl 5:S514-84, 2015

Lund LW, Schmiegelow K, Rechnitzer C, et al: A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may challenge the conclusions. Pediatr Blood Cancer 56:532-43, 2011

Mitby PA, Robison LL, Whitton JA, et al: Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 97:1115-26, 2003

Rueegg CS, Gianinazzi ME, Rischewski J, et al: Health-related quality of life in survivors of childhood cancer: the role of chronic health problems. J Cancer Surviv 7:511-22, 2013

Stokke J, Sung L, Gupta A, et al: Systematic review and meta-analysis of objective and subjective quality of life among pediatric, adolescent, and young adult bone tumor survivors. Pediatr Blood Cancer 62:1616-29, 2015

Wengenroth L, Rueegg CS, Michel G, et al: Life partnerships in childhood cancer survivors, their siblings, and the general population. Pediatr Blood Cancer 61:538-45, 2014

Wong KF, Reulen RC, Winter DL, et al: Risk of adverse health and social outcomes up to 50 years after Wilms tumor: the British Childhood Cancer Survivor Study. J Clin Oncol 34:1772-9, 2016

ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
2	**Any Cancer Experience**	**Mental health disorders** Depression Anxiety Post-traumatic stress Suicidal ideation	**HISTORY** **Psychosocial assessment with attention to:** - **Depression** - **Anxiety** - **Post-traumatic stress** - **Suicidal ideation** Yearly	**HEALTH LINKS** **Emotional Issues** **RESOURCES** 'Childhood Cancer Survivors: A Practical Guide to Your Future,' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Appropriate psychotropic medications. Evaluation of parent for posttraumatic stress. **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Female sex, family history of depression, anxiety, or mental illness, lower household income, lower educational achievement, especially failure to graduate from high school, unemployment, not in a relationship, poor social support, perceived poor physical health, no health insurance or public health insurance
- Cancer/Treatment factors: CNS tumor, CNS-directed therapy, history of hematopoietic cell transplant
- Pre-morbid/Co-morbid medical conditions: Chronic pain, scarring or physical disfigurement, permanent hair loss, premorbid learning or emotional difficulties

References

Brinkman TM, Zhu L, Zeltzer LK, et al: Longitudinal patterns of psychological distress in adult survivors of childhood cancer. Br J Cancer 109:1373-81, 2013

Duran B: Posttraumatic growth as experienced by childhood cancer survivors and their families: a narrative synthesis of qualitative and quantitative research. J Pediatr Oncol Nurs 30:179-97, 2013

Kinahan KE, Sharp LK, Seidel K, et al: Scarring, disfigurement, and quality of life in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 30:2466-74, 2012

Klosky JL, Krull KR, Kawashima T, et al: Relations between posttraumatic stress and posttraumatic growth in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Health Psychol 33:878-82, 2014

Lown EA, Phillips F, Schwartz LA, et al: Psychosocial follow-up in survivorship as a standard of care in pediatric oncology. Pediatr Blood Cancer 62 Suppl 5:S514-84, 2015

Michel G, Rebholz CE, von der Weid NX, et al: Psychological distress in adult survivors of childhood cancer: the Swiss Childhood Cancer Survivor Study. J Clin Oncol 28:1740-8, 2010

Oancea SC, Brinkman TM, Ness KK, et al: Emotional distress among adult survivors of childhood cancer. J Cancer Surviv 8:293-303, 2014

Prasad PK, Hardy KK, Zhang N, et al: Psychosocial and neurocognitive outcomes in adult survivors of adolescent and early young adult cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 33:2545-52, 2015

Recklitis CJ, Diller LR, Li X, et al: Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 28:655-61, 2010

Shah SS, Dellarole A, Peterson EC, et al: Long-term psychiatric outcomes in pediatric brain tumor survivors. Childs Nerv Syst 31:653-63, 2015

Stuber ML, Meeske KA, Krull KR, et al: Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. Pediatrics 125:e1124-34, 2010

Yi J, Zebrack B, Kim MA, et al: Posttraumatic growth outcomes and their correlates among young adult survivors of childhood cancer. J Pediatr Psychol 40:981-91, 2015

Zebrack BJ, Landier W: The perceived impact of cancer on quality of life for post-treatment survivors of childhood cancer. Qual Life Res 20:1595-608, 2011

Zebrack BJ, Stuber ML, Meeske KA, et al: Perceived positive impact of cancer among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Psycho-Oncol 21:630-9, 2012

ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
3	**Any Cancer Experience**	**Risky behaviors** Behaviors known to increase the likelihood of subsequent illness or injury	**HISTORY** **Psychosocial assessment** Yearly	**HEALTH LINKS** **Emotional Issues** **RESOURCES** 'Childhood Cancer Survivors: A Practical Guide to Your Future,' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 www.smokefree.gov www.cancer.org/healthy/stay-away-from-tobacco **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Adolescent/young adult at diagnosis or follow-up, male sex, lower household income, lower educational achievement, psychological distress

References

Buchanan N, Leisenring W, Mitby PA, et al: Behaviors associated with ultraviolet radiation exposure in a cohort of adult survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. Cancer 115:4374-84, 2009

Frobisher C, Lancashire ER, Reulen RC, et al: Extent of alcohol consumption among adult survivors of childhood cancer: the British Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 19:1174-84, 2010

Gibson TM, Liu W, Armstrong GT, et al: Longitudinal smoking patterns in survivors of childhood cancer: an update from the Childhood Cancer Survivor Study. Cancer 121:4035-43, 2015

Klosky JL, Howell CR, Li Z, et al: Risky health behavior among adolescents in the Childhood Cancer Survivor Study cohort. J Pediatr Psychol 37:634-46, 2012

Krull KR, Annett RD, Pan Z, et al: Neurocognitive functioning and health-related behaviours in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer 47:1380-8, 2011

Lown EA, Goldsby R, Mertens AC, et al: Alcohol consumption patterns and risk factors among childhood cancer survivors compared to siblings and general population peers. Addiction 103:1139-48, 2008

Milam J, Slaughter R, Meeske K, et al: Substance use among adolescent and young adult cancer survivors. Psycho-Oncol 25:1357-1362, 2016

Oancea SC, Gurney JG, Ness KK, et al: Cigarette smoking and pulmonary function in adult survivors of childhood cancer exposed to pulmonary-toxic therapy: results from the St. Jude Lifetime Cohort Study. Cancer Epidemiol Biomarkers Prev 23:1938-43, 2014

Sundberg KK, Lampic C, Arvidson J, et al: Sexual function and experience among long-term survivors of childhood cancer. Eur J Cancer 47:397-403, 2011

Zhang FF, Saltzman E, Must A, et al: Do childhood cancer survivors meet the diet and physical activity guidelines? A review of guidelines and literature. Int J Child Health Nutr 1:44-58, 2012

ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
4	**Any Cancer Experience**	**Psychosocial disability due to pain**	**HISTORY** **Psychosocial assessment** Yearly	**HEALTH LINKS** **Chronic Pain after Childhood Cancer** **RESOURCES** 'Childhood Cancer Survivors: A Practical Guide to Your Future,' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Psychological consultation in patients with chronic pain. Appropriate psychotropic medications. Referral to pain rehabilitation clinic. **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Female sex
- Cancer/Treatment factors: CNS tumor, Hodgkin lymphoma, amputation, limb-sparing surgery, radiation to bone/joint, vincristine exposure
- Pre-morbid/Co-morbid medical conditions: History of osteonecrosis

References

Girard P, Auquier P, Barlogis V, et al: Symptomatic osteonecrosis in childhood leukemia survivors: prevalence, risk factors and impact on quality of life in adulthood. Haematologica 98:1089-97, 2013

Keefe FJ, Rumble ME, Scipio CD, et al: Psychological aspects of persistent pain: current state of the science. J Pain 5:195-211, 2004

Lu Q, Krull KR, Leisenring W, et al: Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. Pain 152:2616-24, 2011

Ness KK, Hudson MM, Jones KE, et al: Effect of temporal changes in therapeutic exposure on self-reported health status in childhood cancer survivors. Ann Intern Med 166:89-98, 2017

Thomas EM, Weiss SM: Nonpharmacological interventions with chronic cancer pain in adults. Cancer Control 7:157-64, 2000

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

ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
5	**Any Cancer Experience**	**Fatigue** **Sleep problems**	**HISTORY** **Psychosocial assessment** Yearly	**RESOURCES** 'Childhood Cancer Survivors: A Practical Guide to Your Future,' by Nancy Keene, Wendy Hobbie & Kathy Ruccione, Childhood Cancer Guides, 2012 **POTENTIAL 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. Referral to specialties such as endocrinology, sleep lab/study, or nutrition as indicated. Referral to psychology for behavioral intervention for emotional difficulties contributing to sleep and fatigue. **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: CNS tumor (e.g., craniopharyngioma), pulmonary radiation
- Pre-morbid/Co-morbid medical conditions: Depression, obesity, history of sleep disturbance

References

Cella D, Davis K, Breitbart W, et al: Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol 19:3385-91, 2001

Gapstur R, Gross CR, Ness K: Factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors: a review. Oncol Nurs Forum 36:723-31, 2009

Jacobsen PB: Assessment of fatigue in cancer patients. J Natl Cancer Inst Monogr:93-7, 2004

Knobel H, Havard Loge J, Lund MB, et al: Late medical complications and fatigue in Hodgkin's disease survivors. J Clin Oncol 19:3226-33, 2001

Lawrence DP, Kupelnick B, Miller K, et al: Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr:40-50, 2004

Mulrooney DA, Ness KK, Neglia JP, et al: Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS). Sleep 31:271-81, 2008

Rosen G, Brand SR: Sleep in children with cancer: case review of 70 children evaluated in a comprehensive pediatric sleep center. Support Care Cancer 19:985-94, 2011

Verberne LM, Maurice-Stam H, Grootenhuis MA, et al: Sleep disorders in children after treatment for a CNS tumour. J Sleep Res 21:461-9, 2012

Zeller B, Loge JH, Kanellopoulos A, et al: Chronic fatigue in long-term survivors of childhood lymphomas and leukemia: persistence and associated clinical factors. J Pediatr Hematol Oncol 36:438-44, 2014

Zhou ES, Vrooman LM, Manley PE, et al: Adapted delivery of cognitive-behavioral treatment for insomnia in adolescent and young adult cancer survivors: a pilot study. Behav Sleep Med 15:288-301, 2017

ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
6	**Any Cancer Experience**	**Limitations in healthcare and insurance access**	**HISTORY** **Psychosocial assessment with attention to healthcare and insurance access** Yearly	**HEALTH LINKS** **Finding and Paying for Healthcare** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Social work consultation. **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Lower household income, lower educational achievement, unemployment
- Cancer/Treatment factors: Testicular cancer, higher cumulative doses of alkylators (especially cyclophosphamide dose ≥20 gm/m^2 or ifosfamide ≥60 gm/m^2), combinations of alkylators, combination with MOPP, cyclophosphamide as conditioning for HCT, in combination with radiation (to abdomen/pelvis, testes [especially dose ≥20 Gy], brain/cranium [neuroendocrine axis], or TBI), unilateral orchiectomy

References

Caplin DA, Smith KR, Ness KK, et al: Effect of population socioeconomic and health system factors on medical care of childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Adolesc Young Adult Oncol 6:74-82, 2017

Langeveld NE, Stam H, Grootenhuis MA, et al: Quality of life in young adult survivors of childhood cancer. Support Care Cancer 10:579-600, 2002

Nathan PC, Greenberg ML, Ness KK, et al: Medical care in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 26:4401-9, 2008

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

Park ER, Kirchhoff AC, Zallen JP, et al: Childhood Cancer Survivor Study participants' perceptions and knowledge of health insurance coverage: implications for the Affordable Care Act. J Cancer Surviv 6:251-9, 2012

Park ER, Li FP, Liu Y, et al: Health insurance coverage in survivors of childhood cancer: the Childhood Cancer Survivor Study. J Clin Oncol 23:9187-97, 2005

BLOOD/SERUM PRODUCTS

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
7	**Diagnosed prior to 1972**	**Chronic hepatitis B**	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Screen for viral hepatitis in patients with persistently abnormal liver function regardless of transfusion history. Gastroenterology or hepatology consultation for patients with chronic hepatitis. Hepatitis A and B immunization in at-risk patients lacking immunity. **SYSTEM = Immune** **SCORE = 1**

Additional Information

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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Living in hyperendemic areas
- Cancer/Treatment factors: Chronic immunosuppression
- Health behaviors: History of IV drug use, unprotected sex, multiple partners, high-risk sexual behavior, sexually transmitted infections, tattoos, body piercing

References

Castellino S, Muir A, Shah A, et al: Hepato-biliary late effects in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group. Pediatr Blood Cancer 54:663-9, 2010
Locasciulli A, Alberti A, Rossetti F, et al: Acute and chronic hepatitis in childhood leukemia: a multicentric study from the Italian Pediatric Cooperative Group for Therapy of Acute Leukemia (AIL-AIEOP). Med Pediatr Oncol 13:203-6, 1985
Willers E, Webber L, Delport R, et al: Hepatitis B--a major threat to childhood survivors of leukaemia/lymphoma. J Trop Pediatr 47:220-5, 2001
Zou S, Stramer SL, Dodd RY: Donor testing and risk: current prevalence, incidence, and residual risk of transfusion-transmissible agents in US allogeneic donations. Transfus Med Rev 26:119-28, 2012

BLOOD/SERUM PRODUCTS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
8	**Diagnosed prior to 1993**	**Chronic hepatitis C**	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Screen for viral hepatitis in patients with persistently abnormal liver function regardless of transfusion history. PCR testing for hepatitis C virus (HCV) in immunosuppressed patients who are negative for antibody. Gastroenterology or hepatology consultation for management of patients with chronic hepatitis. Hepatitis A and B immunization in at-risk patients lacking immunity. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Exposure to blood/serum products prior to initiation of hepatitis C screening of blood supply (1993 in the United States [considering the more reliable EIA-2 screening was released in the U.S. 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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Living in hyperendemic areas
- Cancer/Treatment factors: Chronic immunosuppression, exposure to blood/serum products prior to 1986 (when surrogate screening of blood donors with ALT was initiated and donors with self-reported high-risk behaviors were deferred)
- Health behaviors: History of IV drug use, unprotected sex, multiple partners, high-risk sexual behavior, sexually transmitted infections, tattoos, body piercing

References

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BLOOD/SERUM PRODUCTS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
9	**Diagnosed between 1977 and 1985**	**HIV infection**	**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 safer sex, universal precautions and high-risk behaviors that exacerbate risk. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** HIV/infectious diseases specialist consultation for patients with chronic infection. **SYSTEM = Immune** **SCORE = 1**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Health behaviors: History of IV drug use, unprotected sex, multiple partners, high-risk sexual behavior, sexually transmitted infections, tattoos, body piercing

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
10	**Any Chemotherapy**	**Dental abnormalities** Tooth/root agenesis Root thinning/shortening Enamel dysplasia Microdontia Ectopic molar eruption Dental caries	**PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**HEALTH LINKS** **Dental Health** **POTENTIAL 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** **Ectopic Molar Eruption = 2A** **All Else = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Any patient who had not developed permanent dentition at time of cancer therapy, younger age at treatment, especially age <5 years
- Cancer/Treatment factors: Any radiation treatment involving the oral cavity or salivary glands

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
11 (male)	**Classical Alkylating Agents** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **Heavy Metals** Carboplatin Cisplatin **Non-Classical Alkylators** Dacarbazine (DTIC) Temozolomide	**Testicular hormonal dysfunction** Testosterone deficiency/ insufficiency Delayed/arrested puberty	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Male Health Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Measurement of early morning testosterone concentration and/or endocrinology referral for patients with: - no signs of puberty at age 14 - failure of pubertal progression - 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 percentile on growth chart - testosterone deficiency/insufficiency to weigh risks and benefits of hormonal replacement therapy Periodic re-evaluation of testosterone in males with low normal testosterone as they age or if they become symptomatic. Bone density evaluation in androgen deficient patients. Testosterone insufficiency requiring hormone replacement therapy is rare after treatment with alkylating agents only. **SYSTEM = Reproductive (Male)** **SCORE** **Classical Alkylating Agents = 1** **Heavy Metals = 2A** **Non-Classical Alkylators = 2A**

Additional Information

Testicular volume is not a reliable indicator of pubertal onset/stage in boys treated with alkylating agents and/or direct testicular radiotherapy.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Aging (≥30 years)
- Cancer/Treatment factors: Testicular cancer, higher cumulative doses of alkylators (especially cyclophosphamide dose ≥20 gm/m^2 or ifosfamide ≥60 gm/m^2), combinations of alkylators, combination with MOPP, cyclophosphamide as conditioning for HCT, in combination with radiation (to abdomen/pelvis, testes [especially dose ≥20 Gy], brain/cranium [neuroendocrine axis], or TBI), and unilateral orchiectomy
- Health behaviors: Tobacco/marijuana use

Section 11 References (cont)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
12 (male)	**Classical Alkylating Agents** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **Heavy Metals** Carboplatin Cisplatin **Non-Classical Alkylators** Dacarbazine (DTIC) Temozolomide	**Impaired spermatogenesis** Reduced fertility Oligospermia Azoospermia Infertility	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly	**HEALTH LINKS** **Male Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. Recovery of fertility may occur years after therapy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** For sexually mature patients who desire information about potential future fertility: semen analysis (optimal) and/or FSH and inhibin B (alternative if unable or unwilling to provide semen sample). Reproductive endocrinology/urology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Alkylating agent 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 at treatment does not protect from gonadal injury in males. **SYSTEM = Reproductive (Male)** **SCORE** **Classical Alkylating Agents = 1** **Heavy Metals = 2A** **Non-Classical Alkylators = 2A**

Additional Information

Testicular volume is not a reliable indicator of pubertal onset/stage in boys treated with alkylating agents and/or direct testicular radiotherapy.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents), aging
- Cancer/Treatment factors: Testicular cancer, higher cumulative doses of alkylators (especially busulfan ≥600 mg/m^2, cyclophosphamide ≥4 gm/m^2 or ifosfamide ≥60 gm/m^2), combinations of alkylators, MOPP ≥3 cycles, cyclophosphamide as conditioning for HCT, in combination with radiation to abdomen/pelvis, testes, brain/cranium (neuroendocrine axis), or TBI, genitourinary surgery
- Pre-morbid/Co-morbid medical conditions: Obesity, ejaculatory dysfunction, history of sexually transmitted infections, chronic GVHD
- Health behaviors: Tobacco/marijuana use

Section 12 References (cont)

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da Cunha MF, Meistrich ML, Fuller LM, et al: Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. J Clin Oncol 2:571-7, 1984

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Meistrich ML, Chawla SP, Da Cunha MF, et al: Recovery of sperm production after chemotherapy for osteosarcoma. Cancer 63:2115-23, 1989

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
13 (female)	**Classical Alkylating Agents** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **Heavy Metals** Carboplatin Cisplatin **Non-Classical Alkylators** Dacarbazine (DTIC) Temozolomide	**Ovarian hormone deficiencies** Delayed puberty Arrested puberty Premature ovarian insufficiency/premature menopause	**HISTORY** **Onset and tempo of puberty** **Menstrual history** **Sexual function (vaginal dryness, libido)** **Menopausal symptoms** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Female Health Issues** **COUNSELING** Adverse impact of ovarian hormone deficiencies on growth, bone mineralization, cardiovascular disease and sexual dysfunction. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH and estradiol and/or endocrine/gynecology referral for patients with: - no signs of puberty at age 13 - failure of pubertal progression - abnormal menstrual patterns or menopausal symptoms. - ovarian hormone deficiency/insufficiency to weigh risks and benefits of hormonal replacement therapy Bone density evaluation in patients with ovarian hormone deficiencies. **SYSTEM = Reproductive (Female)** **SCORE** **Classical Alkylating Agents = 1** **Heavy Metals = 2B** **Non-Classical Alkylators = 2A**

Additional Information

Alkylating agent doses that cause gonadal dysfunction show individual variation. Females can typically maintain gonadal function at higher cumulative doses than males.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Older age at treatment
- Cancer/Treatment factors: Higher cumulative doses of alkylators or combinations of alkylators, combination with radiation to abdomen/pelvis, lumbar or sacral spine (from ovarian scatter), or brain/cranium (neuroendocrine axis), any alkylators combined with pelvic radiation or TBI
- Health behaviors: Smoking

References

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Sklar CA, Mertens AC, Mitby P, et al: Premature menopause in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 98:890-6, 2006

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
14 (female)	**Classical Alkylating Agents** Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Procarbazine Thiotepa **Heavy Metals** Carboplatin Cisplatin **Non-Classical Alkylators** Dacarbazine (DTIC) Temozolomide	**Reduced ovarian follicular pool** Infertility	**HISTORY** **Menstrual and pregnancy history** **Hormonal Therapy** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly	**HEALTH LINKS** **Female Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Potential for shorter period of fertility (associated with increased risk of early menopause) in family planning. Need for contraception. Recovery of fertility may occur years after therapy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH and estradiol for patients with menstrual cycle dysfunction suggestive of premature ovarian insufficiency or those who desire information about potential for future fertility. AMH (anti-Mullerian hormone) to assess for diminished ovarian reserve. Reproductive endocrinology referral for antral follicle count, ovarian reserve evaluation and consultation regarding assisted reproductive technologies in at-risk patients who desire information about potential fertility and interventions to preserve future fertility. Alkylating agent doses that cause gonadal dysfunction show individual variation. Females can typically maintain gonadal function at higher cumulative doses than males. **SYSTEM = Reproductive (Female)** **SCORE** **Classical Alkylating Agents = 1** **Heavy Metals = 2B** **Non-Classical Alkylators = 2A**

Additional Information

AMH may be low in the presence of normal FSH.
FSH is lowered and AMH may be lowered by concurrent hormonal contraceptive use.

Section 14 Additional Information (cont)

AMH should be interpreted relative to age-specific reference ranges.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Older age at treatment
- Cancer/Treatment factors: Higher cumulative doses of alkylators or combinations of alkylators, combination with radiation to abdomen/pelvis, lumbar or sacral spine (from ovarian scatter), or brain, cranium (neuroendocrine axis), any alkylators combined with pelvic radiation or TBI
- Health behaviors: Smoking

Section 14 References

Gracia CR, Sammel MD, Freeman E, et al: Impact of cancer therapies on ovarian reserve. Fertil Steril 97:134-40 e1, 2012
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Thomas-Teinturier C, Allodji RS, Svetlova E, et al: Ovarian reserve after treatment with alkylating agents during childhood. Hum Reprod 30:1437-46, 2015

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
15	**Classical 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**	**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** Promptly seek medical attention for fatigue, pallor, petechiae or bone pain. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** CBC and bone marrow exam as clinically indicated. **SYSTEM = SMN** **SCORE** **Classical Alkylating Agents = 1** **Heavy Metals = 2A** **Non-Classical Alkylators = 2A**

Additional Information

There is negligible benefit to obtaining a screening CBC in the absence of clinical signs and symptoms for AML/MDS.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Less than 10 years since exposure to agent, higher cumulative alkylator dose or combination of alkylators, autologous HCT. Note melphalan and mechlorethamine are more potent leukemogens than cyclophosphamide.
- Pre-morbid/Co-morbid medical conditions: Evidence is conflicting that splenectomy modifies risk for AML/MDS

References

Allodji RS, Schwartz B, Veres C, et al: Risk of subsequent leukemia after a solid tumor in childhood: impact of bone marrow radiation therapy and chemotherapy. Int J Radiat Oncol Biol Phys 93:658-67, 2015
Bhatia S: Therapy-related myelodysplasia and acute myeloid leukemia. Semin Oncol 40:666-75, 2013
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 109:46-51, 2007
Eichenauer DA, Thielen I, Haverkamp H, et al: Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood 123:1658-64, 2014
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
16	**Classical Alkylating Agents** Busulfan Carmustine (BCNU) Lomustine (CCNU)	**Pulmonary fibrosis**	**HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** 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** www.smokefree.gov **COUNSELING** Tobacco avoidance/smoking cessation/environmental tobacco smoke. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy). **SYSTEM = Pulmonary** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher cumulative doses, especially BCNU ≥600 mg/m^2 and busulfan ≥500 mg (transplant doses), combination with bleomycin, combination with chest radiation or TBI
- Pre-morbid/Co-morbid medical conditions: Atopic history
- Health behaviors: Smoking, inhaled illicit drug use

References

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Tetrault JM, Crothers K, Moore BA, et al: Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med 167:221-8, 2007
van Hulst RA, Rietbroek RC, Gaastra MT, et al: To dive or not to dive with bleomycin: a practical algorithm. Aviat Space Environ Med 82:814-8, 2011
Wolff AJ, O'Donnell AE: Pulmonary effects of illicit drug use. Clin Chest Med 25:203-16, 2004

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
17	**Classical Alkylating Agents** Busulfan	**Cataracts**	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** Yearly **PHYSICAL** **Visual acuity** **Funduscopic exam** Yearly	**HEALTH LINKS** **Cataracts** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ophthalmology consultation as clinically indicated. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with corticosteroids, combination with TBI, cranial, orbital, or eye radiation, longer interval since treatment

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
18	**Classical Alkylating Agents** Cyclophosphamide Ifosfamide	**Urinary tract toxicity** Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**HEALTH LINKS** **Bladder Health** **COUNSELING** Promptly report dysuria or gross hematuria. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urinalysis, urine culture, spot urine calcium/creatinine ratio for patients with positive history. Ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as >5 RBC/HPF 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, incontinence, or dysfunctional voiding. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher cumulative doses (decreased incidence with Mesna), especially cyclophosphamide dose ≥3 gm/m^2, combination with pelvic radiation, especially pelvic radiation dose ≥30 Gy
- Health behaviors: Alcohol use, smoking

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
19	**Classical Alkylating Agents** Cyclophosphamide	**Bladder malignancy**	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**HEALTH LINKS** **Bladder Health** **COUNSELING** Promptly seek medical attention for dysuria or gross hematuria. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urinalysis, urine culture, spot urine calcium/creatinine ratio for patients with positive history. Ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as >5 RBC/HPF on at least 2 occasions). Nephrology or urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound. Urology referral for patients with culture-negative macroscopic hematuria. **SYSTEM = SMN** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with pelvic radiation
- Health behaviors: Alcohol use, smoking

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
20	**Classical Alkylating Agents** Ifosfamide	**Renal toxicity** Glomerular injury Renal insufficiency Hypertension Tubular injury (renal tubular acidosis, Fanconi syndrome, hypophosphatemic rickets)	**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	**HEALTH LINKS** **Kidney Health** **Cardiovascular Risk Factors** **COUNSELING** In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

Ifosfamide-related renal toxicity typically occurs during the acute treatment phase and improves or progresses over time.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <4 years
- Cancer/Treatment factors: Tumor infiltration of kidney(s), nephrectomy, higher cumulative dose, especially ifosfamide dose ≥60 grams/m^2, combination with other nephrotoxic agents (e.g., cisplatin, carboplatin, aminoglycosides, amphotericin, immunosuppressants, methotrexate, radiation impacting the kidney), renal radiation dose ≥15 Gy
- Pre-morbid/Co-morbid medical conditions: Pre-existing renal impairment, congenital absence of kidney

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
21	**Heavy Metals** Carboplatin (myeloablative doses) Cisplatin	**Ototoxicity** Sensorineural hearing loss Tinnitus Vertigo	**HISTORY** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** Yearly **PHYSICAL** **Otoscopic exam** Yearly **SCREENING** **Complete audiological evaluation by audiologist** Yearly, for patients ages ≤5 years **Pure tone audiometry testing at 1000-8000 Hz** Every 2 years, for patients ages 6-12, then every 5 years beginning at age 13	**HEALTH LINKS** **Hearing Loss** **Educational Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Additional testing with high frequency audiometry at >8000 Hz is recommended if equipment is available. Audiology consultation for any survivor who has symptoms suggestive of hearing loss, tinnitus, or abnormal pure tone audiometry results showing a loss of more than 15 dB absolute threshold level (1000-8000 Hz). Ongoing follow-up with audiology for patients with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Speech and language therapy for patients with hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. Specialized evaluation for specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**

Additional Information

Myeloablative doses of carboplatin are given as conditioning for HCT and are typically ≥1500 mg/m^2.
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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Age <4 years at treatment
- Cancer/Treatment factors: CNS neoplasm, cumulative cisplatin dose ≥360 mg/m^2, high dose cisplatin (i.e., 40 mg/m^2 per day x 5 days per course), carboplatin conditioning for HCT, combination with cranial/ear radiation or ototoxic drugs (e.g., aminoglycosides, loop diuretics), cisplatin administered AFTER cranial/ear radiation, combination with radiation involving ear ≥30 Gy
- Pre-morbid/Co-morbid medical conditions: Chronic otitis, cerumen impaction, renal dysfunction, cerebrospinal fluid shunt

Section 21 References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
22	**Heavy Metals** Carboplatin Cisplatin	**Peripheral sensory neuropathy** Paresthesias Dysesthesias	**HISTORY** **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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Physical therapy referral for patients with symptomatic neuropathy. Physical and occupational therapy assessment of hand function. Treat with effective agent for neuropathic pain (e.g., gabapentin or amitriptyline). **SYSTEM = PNS** **SCORE = 2A**

Additional Information

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.
Studies of adults treated during childhood support higher prevalence of deficits than previously appreciated.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Cumulative cisplatin dose ≥300 mg/m^2, combination with vincristine, taxanes, gemcitabine

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
23	**Heavy Metals** Carboplatin Cisplatin	**Renal toxicity** Glomerular injury Renal insufficiency Hypertension Tubular injury (renal tubular acidosis, Fanconi syndrome, hypophosphatemic rickets)	**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	**HEALTH LINKS** **Kidney Health** **Cardiovascular Risk Factors** **COUNSELING** In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Nephrectomy, combination with other nephrotoxic agents (e.g., aminoglycosides, amphotericin, immunosuppressants, methotrexate, radiation impacting the kidney), cisplatin dose ≥200 mg/m^2, renal radiation dose ≥15 Gy
- Pre-morbid/Co-morbid medical conditions: Diabetes mellitus, hypertension, congenital absence of kidney

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
24	**Antimetabolites** Cytarabine (high dose IV)	**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	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Referral to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Referral to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 2A**

Additional Information

High-dose IV is defined as any single dose ≥1000 mg/m^2.

Formal neuropsychological evaluation includes tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning.

Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., slow processing speed, attention problems). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New and progressive deficits may emerge over time.

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <3 years, female sex, family history of learning or attention problems
- Cancer/Treatment factors: CNS leukemia/lymphoma, relapsed leukemia/lymphoma treated with CNS-directed therapy, longer elapsed time since therapy, combination with corticosteroids, methotrexate (IT, IO, high-dose IV), radiation dose ≥24 Gy, TBI, especially single fraction TBI (10 Gy), cranial radiation
- Pre-morbid/Co-morbid medical conditions: Pre-morbid learning or attention problems

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
25	**Antimetabolites** Cytarabine (low dose IV) Cytarabine IO Cytarabine IT Cytarabine SQ	**No known late effects**	**No known late effects**	**SYSTEM = No Known Late Effects** **SCORE = 1**

Additional Information

Low-dose IV is defined as any single dose <1000 mg/m^2.
Acute toxicities predominate, from which the majority of patients recover without sequelae.

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
26	**Antimetabolites** Mercaptopurine (6MP) Thioguanine (6TG)	**Hepatic dysfunction** **Sinusoidal obstruction syndrome (SOS) [previously known as veno-occlusive disease (VOD)]**	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Platelet count for evaluation of hypersplenism and 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 at-risk patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 2A**

Additional Information

Acute toxicities predominate from which the majority of patients recover without sequelae.

Delayed hepatic dysfunction may occur after a history of acute SOS (previously known as VOD), presenting as portal hypertension with liver biopsy indicating nodular regenerative hyperplasia, fibrosis, or siderosis.

Patients treated on CCG-1952, Regimens B1 and B2, received 6-thioguanine (6TG) in place of 6-mercaptopurine (6MP) during maintenance therapy.

- Acute hepatotoxicity (manifesting as SOS, previously known as VOD) occurred in about 25% of patients.
- Portal hypertension was identified as a late complication of 6TG in a small subset of patients (see Broxson et al., 2005).
- Outcomes are detailed in Stork et al., 2010.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Pre-morbid/Co-morbid medical conditions: Viral hepatitis (especially chronic viral hepatitis), previous SOS (previously known as VOD), siderosis

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
27	**Antimetabolites** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO	**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	**SCREENING** **Bone density evaluation (DXA)** **Adjust for height-age Z-score in survivors <age 20 years*** Baseline at entry into long-term follow-up, repeat as clinically indicated. *Pediatric Z-Score Calculator Adjusted for Height Age: https://zscore.research.chop.edu/bmdCalculator.php	**HEALTH LINKS** **Bone Health** **RESOURCES** National Osteoporosis Foundation: www.nof.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ensure the AAP recommended minimum daily intake of vitamin D (400 IU/day) for children, with consideration 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. 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. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Advocate for regular weight-bearing exercises such as running and jumping. Treat 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**

Additional Information

High-dose IV is defined as any single dose ≥1000 mg/m^2.

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.

Section 27 Additional Information (cont)

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Caucasian race, lower weight/BMI. Both genders are at risk.
- Cancer/Treatment factors: Corticosteroids (especially prolonged therapy, e.g., for chronic GVHD), cyclosporine, tacrolimus, higher cumulative methotrexate dose (especially ≥40 gm/m^2), cranial radiation, craniospinal radiation, HCT/TBI
- Pre-morbid/Co-morbid medical conditions: Growth hormone deficiency, hypogonadism/delayed puberty, hyperthyroidism
- Health behaviors: Intake of calcium and vitamin D, intake of alcohol and carbonated beverages, weight bearing exercise, smoking

Section 27 References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
28	**Antimetabolites** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO	**No known renal late effects**	**No known renal late effects**	**SYSTEM = No Known Renal Late Effects** **SCORE = 2A**

Additional Information

High-dose IV is defined as any single dose ≥1000 mg/m^2.
Acute toxicities predominate, from which the majority of patients recover without sequelae. Renal injury from other events (aminoglycoside exposure, tumor lysis) may make patients more vulnerable.

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
29	**Antimetabolites** Methotrexate (high dose IV) Methotrexate (low dose IV) Methotrexate IM Methotrexate PO	**Hepatic dysfunction**	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Platelet count for evaluation of hypersplenism and 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 at-risk patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 2A**

Additional Information

High-dose IV is defined as any single dose ≥1000 mg/m^2.
Acute toxicities predominate from which the majority of patients recover without sequelae.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Abdominal radiation, treatment before 1970
- Pre-morbid/Co-morbid medical conditions: Viral hepatitis (especially chronic viral hepatitis)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
30	**Antimetabolites** Methotrexate (high dose IV) Methotrexate IO Methotrexate IT	**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	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Referral to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Referral to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

Additional Information

High-dose IV is defined as any single dose ≥1000 mg/m^2.

Formal neuropsychological evaluation includes tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning.

Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., slow processing speed, attention problems). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New and progressive deficits may emerge over time.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <3 years, female sex, family history of learning or attention problems
- Cancer/Treatment factors: CNS leukemia/lymphoma, relapsed leukemia/lymphoma treated with CNS-directed therapy, longer elapsed time since therapy, combination with corticosteroids, cytarabine (high-dose IV), radiation dose ≥24 Gy, TBI, especially single fraction TBI (10 Gy), cranial radiation
- Pre-morbid/Co-morbid medical conditions: Pre-morbid learning or attention problems

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
31	**Antimetabolites** Methotrexate (high dose IV) Methotrexate IO Methotrexate IT	**Clinical leukoencephalopathy** Spasticity Ataxia Dysarthria Dysphagia Hemiparesis Seizures	**HISTORY** **Cognitive, motor and/or sensory deficits** **Seizures** **Other neurologic symptoms** Yearly **PHYSICAL** **Neurologic exam** Yearly	**POTENTIAL 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**

Additional Information

High-dose IV is defined as any single dose ≥1000 mg/m^2.
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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Patient factors: Younger age at treatment
- Cancer/Treatment factors: CNS leukemia/lymphoma, relapsed leukemia/lymphoma treated with CNS-directed therapy, combination with cytarabine (high-dose IV), dexamethasone, cranial radiation, radiation dose ≥24 Gy

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
32	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone	**Acute myeloid leukemia**	**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** Promptly seek medical attention for fatigue, pallor, petechiae or bone pain. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** CBC and bone marrow exam as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family.
There is negligible benefit to obtaining a screening CBC in the absence of clinical signs and symptoms for AML.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Less than 5 years since exposure to agent, autologous HCT
- Pre-morbid/Co-morbid medical conditions: Evidence is conflicting that splenectomy modifies risk for AML

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **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. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** **Recommended Frequency of Echocardiogram** | Anthracycline Dose* | Radiation Dose** | Recommended Frequency | | None | < 15 Gy or none | No screening | | | ≥ 15 - < 35 Gy | Every 5 years | | | ≥ 35 Gy | Every 2 years | | < 250 mg/m² | < 15 Gy or none | Every 5 years | | | ≥ 15 Gy | Every 2 years | | ≥ 250 mg/m² | Any or none | Every 2 years | *Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76. **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** **Diet and Physical Activity** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal LV systolic function. - Survivors with asymptomatic cardiomyopathy should consult cardiology to define limits and precautions for physical activity. - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

Section 33 Additional Information (cont)

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.

Childhood cancer survivors exhibit clinical and subclinical toxicity at lower levels than adults. In patients with abnormal LV systolic function, 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.

Exertional intolerance is an uncommon presentation of left ventricular dysfunction 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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger than age 5 years at time of treatment
- Cancer/Treatment factors: Combined with radiation involving the heart, higher cumulative anthracycline doses (≥550 mg/m^2 in patients 18 years or older at time of treatment, ≥250 mg/m^2 in patients younger than 18 years at time of treatment), chest radiation ≥15 Gy chest radiation combined with ≥100 mg/m^2 anthracycline, longer time since treatment
- Pre-morbid/Co-morbid medical conditions: Obesity, congenital heart disease, hypertension, diabetes mellitus, dyslipidemia. For female patients, pregnancy if systolic function is abnormal pre-pregnancy
- Health behaviors: Smoking, drug use (e.g., cocaine, diet pills, ephedra, mahuang)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
34	**Anti-Tumor Antibiotics** Bleomycin	**Pulmonary toxicity** Pulmonary fibrosis Interstitial pneumonitis Acute respiratory distress syndrome (very rare)	**HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** 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** 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. Tobacco avoidance/smoking cessation/environmental tobacco smoke. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy). **SYSTEM = Pulmonary** **SCORE** **ARDS = 2B** **All Else = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Pulmonary toxicity
- Cancer/Treatment factors: Higher cumulative dose, especially bleomycin dose ≥400 U/m^2 (pulmonary function deficits observed at doses as low as doses 60–100 U/m^2 in children on formal pulmonary function testing), combination with busulfan, carmustine (BCNU), or lomustine (CCNU), combination with chest radiation or TBI
- Pre-morbid/Co-morbid medical conditions: Renal dysfunction, high dose oxygen support such as during general anesthesia
- Health behaviors: Smoking, inhaled illicit drug use

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
35	**Anti-Tumor Antibiotics** Dactinomycin	**No known late effects**	**No known late effects**	**SYSTEM = No Known Late Effects** **SCORE = 1**

Additional Information

Dactinomycin has been associated with acute veno-occlusive disease, from which the majority of patients recover without sequelae.

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
36	**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	**SCREENING** **Bone density evaluation (DXA)** **Adjust for height-age Z-score in survivors <age 20 years*** Baseline at entry into long-term follow-up, repeat as clinically indicated. *Pediatric Z-Score Calculator Adjusted for Height Age: https://zscore.research.chop.edu/bmdCalculator.php	**HEALTH LINKS** **Bone Health** **RESOURCES** National Osteoporosis Foundation: www.nof.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ensure the AAP recommended minimum daily intake of vitamin D (400 IU/day) for children, with consideration 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. 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. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Advocate for regular weight-bearing exercises such as running and jumping. Treat 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**

Additional Information

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.

Section 36 Additional Information (cont)

There are no defined standards for referral or treatment of low BMD in children.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Caucasian race, lower weight/BMI. Both genders are at risk.
- Cancer/Treatment factors: Methotrexate, cyclosporine, tacrolimus, higher cumulative corticosteroid dose (especially ≥9 gm/m^2), cranial radiation, craniospinal radiation, HCT/TBI. Dexamethasone effect is more potent than prednisone.
- Pre-morbid/Co-morbid medical conditions: Growth hormone deficiency, hypogonadism/delayed puberty, hyperthyroidism
- Health behaviors: Intake of calcium and vitamin D, intake of alcohol and carbonated beverages, weight bearing exercise, smoking

Section 36 References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
37	**Corticosteroids** Dexamethasone Prednisone	**Osteonecrosis (avascular necrosis)**	**HISTORY** **Joint pain** **Swelling** **Immobility** **Limited range of motion** Yearly **PHYSICAL** **Musculoskeletal exam** Yearly	**HEALTH LINKS** **Osteonecrosis** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** MRI as clinically indicated. Orthopedic consultation in patients with positive imaging and/or symptoms of osteonecrosis. Physical therapy evaluation (for non-pharmacologic pain management, range of motion, strengthening, stretching, functional mobility). **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Osteonecrosis typically occurs during the acute treatment phase, may progress over time or resolve.
Multifocal osteonecrosis is significantly more common (3:1) than unifocal.
Symptomatic lesions confer the greatest risk for collapse.
Dexamethasone effect is more potent than prednisone.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Being pubertal or post-pubertal at time of treatment, genetic polymorphisms
- Cancer/Treatment factors: High-dose radiation to any bone, orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones, TBI, prolonged immunosuppression (e.g., for chronic GVHD)
- Pre-morbid/Co-morbid medical conditions: Sickle cell disease, chronic GVHD

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
38	**Corticosteroids** Dexamethasone Prednisone	**Cataracts**	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** Yearly **PHYSICAL** **Visual acuity** **Funduscopic exam** Yearly	**HEALTH LINKS** **Cataracts** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ophthalmology consultation as clinically indicated. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with busulfan, combination with TBI, cranial, orbital or eye radiation, longer interval since treatment

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
39	**Enzymes** Asparaginase	**No known late effects**	**No known late effects**	**SYSTEM = No Known Late Effects** **SCORE = 1**

Additional Information

Acute toxicities predominate, from which the majority of patients recover without sequelae.

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
40	**Plant Alkaloids** Vinblastine Vincristine	**Peripheral sensory or motor neuropathy** Areflexia Weakness Foot drop Paresthesias Dysesthesias	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Physical therapy referral for patients with symptomatic neuropathy. Physical and occupational therapy assessment of hand function. Treat with effective agent for neuropathic pain (e.g., gabapentin or amitriptyline). **SYSTEM = PNS** **SCORE = 2A**

Additional Information

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.
Studies of adults treated during childhood support higher prevalence of deficits than previously appreciated.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with platinum chemotherapy, gemcitabine, taxanes
- Pre-morbid/Co-morbid medical conditions: Anorexia, severe weight loss, Charcot-Marie-Tooth disease

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
41	**Plant Alkaloids** Vinblastine Vincristine	**Vasospastic attacks (Raynaud's phenomenon)**	**HISTORY** **Vasospasms of hands, feet, nose, lips, cheeks, or earlobes related to stress or cold temperatures** Yearly **PHYSICAL** **Physical exam of affected area** As clinically indicated	**HEALTH LINKS** **Raynaud's Phenomenon** **COUNSELING** Wear appropriate protective clothing in cold environments. Symptoms may be exacerbated by medications and other chemicals that cause vasoconstriction (e.g., pseudoephedrine, stimulants), illicit drugs (e.g., cocaine), and nicotine in tobacco. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Vasodilating medications (calcium-channel blockers, alpha blockers) for patients with frequent, severe vasospastic attacks unresponsive to behavioral management. **SYSTEM = PNS** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Pre-morbid/Co-morbid medical conditions: Smoking, illicit drug use, use of vasoconstricting medications/substances, exposure to repetitive vibration

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
42	**Epipodophyllotoxins** Etoposide (VP16) Teniposide (VM26)	**Acute myeloid leukemia**	**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** Promptly seek medical attention for fatigue, pallor, petechiae or bone pain. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** CBC and bone marrow exam as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Epipodophyllotoxin administration schedules since approximately 1990 have been modified to reduce the risk of this complication.
There is negligible benefit to obtaining a screening CBC in the absence of clinical signs and symptoms for AML.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Weekly or twice weekly administration, less than 5 years since exposure to agent, autologous HCT
- Pre-morbid/Co-morbid medical conditions: Evidence is conflicting that splenectomy modifies risk for AML

References

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Determining Applicability of Radiation Sections for Specific Patients Based on Exposure

The radiation sections of the COG Long-Term Follow-Up Guidelines (Sections 43-97) are organized by anatomic region from the head downward. In this current version of the COG LTFU Guidelines (V5), the radiation fields have been simplified and categorized by anatomic region, as follows:

- Head/Brain
- Neck
- Chest
- Axilla
- Abdomen
- Pelvis
- Testicular
- Spine (cervical, thoracic, lumbar, sacral, whole)
- Skin/soft tissues/bones/extremities
- Total body irradiation (TBI)

The Guideline sections applicable to each radiation field are listed on the accompanying diagram.

Traditional and combined radiation fields (e.g., mantle, mediastinal, para-aortic, etc.) are defined in Appendix I and mapped to the anatomic fields specified above, as follows:

- Radiation Fields Defined, Table: Appendix I, pages 8-9
- Radiation Fields Defined, Diagram: Appendix I, page 10

Five sections of these Guidelines (Sections 59, 62, 65, 76, 77) include minimum dose specifications. These five Guideline sections are applicable only to patients who received radiation to any of the relevant fields at a total dose higher than the specified minimum dose. Instructions regarding calculating combined radiation doses are available as follows:

- Radiation Dose Calculations: Appendix I, page 11

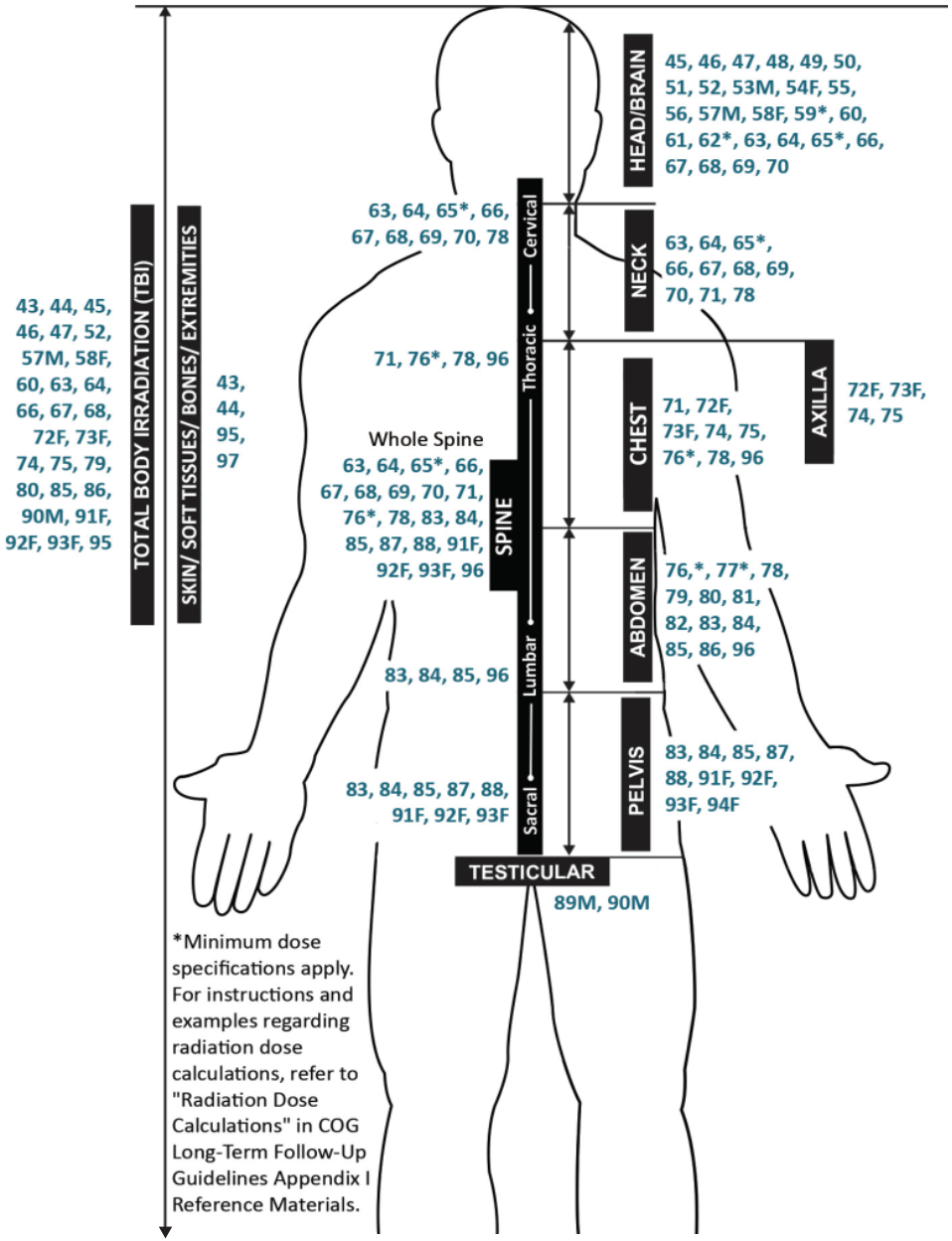
Further details regarding radiation impact by organ systems, with associated potential late effects, are also available in Appendix I, as follows:

- Guideline Radiation Sections by Potential Impact, Table: Appendix I, pages 13-14
- Guideline Radiation Sections by Potential Impact, Diagram: Appendix I, page 15
- Total Body Irradiation (TBI) Related Potential Late Effects: Appendix I, page 16

Use the "Patient-Specific Guideline Identification Tool" in Appendix 1 (pages 37-44) to determine specific screening guidelines by section number for individual patients.

Guideline Radiation Sections by Field

Applicable guideline sections indicated in bold/dark blue; M=Male; F=Female



RADIATION

ALL FIELDS

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
43	**Any Radiation (Including TBI)**	**Secondary benign or malignant neoplasm occurring in or near radiation field** Such as dysplastic nevi, skin cancer (basal cell carcinoma, squamous cell carcinoma), bone malignancies, oral cancer	**HISTORY** **Skin lesions** **Changing moles (asymmetry, bleeding, increasing size, indistinct borders)** **Bone pain (especially in irradiated field)** **Persistent thickening or lump of soft tissue or bone** Yearly **PHYSICAL** **Skin self exam** Monthly **Inspection and palpation of skin and soft tissues in irradiated field(s)** **Dermatologic exam of irradiated fields** **Palpation of bones in irradiated field** Yearly	**HEALTH LINKS** **Reducing the Risk of Second Cancers** **Skin Health** **COUNSELING** Promptly seek medical attention for symptoms (e.g., bone pain, bone mass, persistent fevers). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** See relevant guideline sections to determine screening for specific radiation fields. Dermatology consultation for evaluation and monitoring of atypical nevi. X-ray or other diagnostic imaging in patients as clinically indicated. Surgical and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, adolescent at treatment [bone malignancies]
- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy [bone malignancies], large radiation treatment volumes, alkylating agent exposure, orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones
- Pre-morbid/Co-morbid medical conditions: Predisposing mutation (e.g., p53, NF1), bilateral or familial retinoblastoma (implying RB1 germline mutation), Gorlin syndrome (nevoid basal cell carcinoma syndrome)
- Health behaviors: Sun exposure, tanning booths

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
44	**Any Radiation (Including TBI)**	**Dermatologic toxicity** Permanent alopecia Altered skin pigmentation Telangiectasias Fibrosis	**PHYSICAL** **Dermatologic exam of irradiated fields** Yearly	**HEALTH LINKS** **Skin Health** **SYSTEM = Dermatologic** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: Total radiation dose ≥40 Gy, especially dose ≥50 Gy, large dose fractions (e.g., ≥2 Gy per fraction), orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones

References

Alsner J, Andreassen CN, Overgaard J: Genetic markers for prediction of normal tissue toxicity after radiotherapy. Semin Radiat Oncol 18:126-35, 2008

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
45	**Head/Brain** **TBI**	**Brain tumor (benign or malignant)**	**HISTORY** **Headaches** **Vomiting** **Cognitive, motor or sensory deficits** **Seizures and other neurologic symptoms** Yearly **PHYSICAL** **Neurologic exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Brain MRI as clinically indicated for symptomatic patients. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <6 years
- Cancer/Treatment factors: Higher radiation dose (risk of subsequent CNS tumor after cranial radiation increases in a dose-response relationship)
- Pre-morbid/Co-morbid medical conditions: Neurofibromatosis, ataxia telangiectasia

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
46	**Head/Brain** **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 - Academic fluency Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Referral to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Referral to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

Additional Information

Formal neuropsychological evaluation includes tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning.

Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., slow processing speed, attention problems). 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 or progressive deficits may emerge over time.

Note: academic fluency is defined as the ability to correctly complete multiple simple academic problems (e.g., reading words, simple math equations) within a limited amount of time.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <3 years, female sex, family history of learning or attention problems
- Cancer/Treatment factors: Primary CNS tumor, CNS leukemia/lymphoma, relapsed leukemia/lymphoma treated with CNS-directed therapy, head/neck tumors with brain in radiation field, temporal lobe field, higher radiation dose, larger radiation field, greater cortical volumes, cranial radiation in combination with TBI, combination with corticosteroids, methotrexate (IT, IO, high-dose IV), cytarabine (high-dose IV), longer elapsed time since therapy
- Pre-morbid/Co-morbid medical conditions: Pre-morbid learning or attention problems, sleep disturbance, seizures, hydrocephalus

References

Armstrong GT, Reddick WE, Petersen RC, et al: Evaluation of memory impairment in aging adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiotherapy. J Natl Cancer Inst 105:899-907, 2013

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
47	**Head/Brain** **TBI**	**Clinical leukoencephalopathy** Spasticity Ataxia Dysarthria Dysphagia Hemiparesis Seizures	**HISTORY** **Cognitive, motor and/or sensory deficits** **Seizures** **Other neurologic symptoms** Yearly **PHYSICAL** **Neurologic exam** Yearly	**POTENTIAL 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**

Additional Information

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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: CNS leukemia/lymphoma, relapsed leukemia/lymphoma treated with CNS-directed therapy, longer elapsed time since therapy, higher radiation dose, especially dose ≥24 Gy or fraction dose ≥3 Gy, larger radiation field, greater cortical volumes, combination with dexamethasone, methotrexate (IT, IO, high-dose IV), cytarabine (high-dose IV)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
48	**Head/Brain**	**Cerebrovascular complications** Stroke Moyamoya Occlusive cerebral vasculopathy Cavernomas	**HISTORY** **Hemiparesis** **Hemiplegia** **Weakness** **Aphasia** Yearly **PHYSICAL** **Neurologic exam** Yearly	**COUNSELING** Importance of controlling health conditions known to increase cardiovascular and stroke risk (e.g., hypertension, diabetes, dyslipidemia). **POTENTIAL 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. Revascularization procedures as indicated for moyamoya. **SYSTEM = CNS** **SCORE = 1**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Parasellar tumor, radiation dose ≥18 Gy, especially radiation dose ≥50 Gy, supra-sellar radiation, circle of Willis in radiation field
- Pre-morbid/Co-morbid medical conditions: Down syndrome, sickle cell disease, neurofibromatosis

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
49	**Head/Brain**	**Craniofacial abnormalities**	**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 **POTENTIAL 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <5 years
- Cancer/Treatment factors: Higher radiation dose, especially radiation dose ≥30 Gy

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
50	**Head/Brain**	**Chronic sinusitis**	**HISTORY** **Rhinorrhea, postnasal discharge** **History of URIs** Yearly **PHYSICAL** **Nasal and sinus exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** CT scan of sinuses as clinically indicated. Otolaryngology consultation as clinically indicated. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Radiation dose to sinuses ≥30 Gy, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)
- Pre-morbid/Co-morbid medical conditions: Atopic history, hypogammaglobulinemia, underlying immunodeficiency

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
51	**Head/Brain**	**Overweight** **Obesity**	**PHYSICAL** **Height** **Weight** **BMI** Yearly	**HEALTH LINKS** **Diet and Physical Activity** **Cardiovascular Risk Factors** **COUNSELING** Obesity-related health risks. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluate for other co-morbid conditions, including dyslipidemia, hypertension, and impaired glucose metabolism. Refer to dietician for weight management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Definition of Overweight: Age 2–20 years BMI for age ≥85th to <95th percentile. Age ≥21 years BMI ≥25–29.9.
Definition of 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.
Overweight/obesity may occur in a constellation of conditions known as the metabolic syndrome.
Definitions of the metabolic syndrome 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).
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <4 years, female sex
- Cancer/Treatment factors: Higher cranial radiation dose (especially ≥18 Gy), surgery in supra-sellar region, corticosteroids (especially prolonged therapy, e.g., for chronic GVHD)
- Pre-morbid/Co-morbid medical conditions: Growth hormone deficiency, hypothyroidism, hypogonadism, inability to exercise

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
52	**Head/Brain** **TBI**	**Growth hormone deficiency**	**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** **Hypopituitarism** **RESOURCES** www.magicfoundation.org **POTENTIAL 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 percentile 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**

Additional Information

Growth charts available on-line at www.cdc.gov/growthcharts/.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: Surgery in supra-sellar region, higher radiation dose (especially radiation dose ≥18 Gy), pretransplant radiation (especially pretransplant cranial radiation), TBI ≥10 Gy in single fraction, ≥12 Gy fractionated, TBI given in single fraction

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
53 (male)	**Head/Brain**	**Precocious puberty**	**PHYSICAL** **Height** **Weight** **Tanner staging** **Testicular volume by Prader orchidometer** Yearly until sexually mature	**HEALTH LINKS** **Precocious Puberty** **RESOURCES** www.magicfoundation.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH, LH, testosterone as clinically indicated in patients with signs of accelerated pubertal progression and growth. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: Tumor near hypothalamus and/or optic pathways, radiation doses ≥18 Gy
- Pre-morbid/Co-morbid medical conditions: History of hydrocephalus

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
54 (female)	**Head/Brain**	**Precocious puberty**	**PHYSICAL** **Height** **Weight** **Tanner staging** Yearly until sexually mature	**HEALTH LINKS** **Precocious Puberty** **RESOURCES** www.magicfoundation.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH, LH, estradiol as clinically indicated in patients with signs of accelerated pubertal progression and growth. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: Tumor near hypothalamus and/or optic pathways, radiation doses ≥18 Gy
- Pre-morbid/Co-morbid medical conditions: History of hydrocephalus

References

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Sklar CA, Constine LS: Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113-21, 1995

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
55	**Head/Brain**	**Hyperprolactinemia**	**HISTORY** **Decreased libido** **Galactorrhea** **If female: Menstrual history** Yearly	**HEALTH LINKS** **Hyperprolactinemia** **RESOURCES** www.magicfoundation.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Prolactin level in patients with galactorrhea or decreased libido, or in females with amenorrhea. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose (≥40 Gy, especially ≥50 Gy), surgery or tumor in hypothalamic area

References

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

Sklar CA, Constine LS: Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113-21, 1995

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
56	**Head/Brain**	**Central hypothyroidism**	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**HEALTH LINKS** **Thyroid Problems** **Hypopituitarism** **COUNSELING** For females, thyroid levels prior to attempting pregnancy and periodically throughout pregnancy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** If dose ≥30 Gy and endocrinology care is readily available, refer to endocrinologist for ongoing management, given risk of multiple hormone deficiencies. If endocrinology care is not readily available, screen as indicated, and refer to endocrinologist for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Central hypothyroidism includes thyroid-releasing and thyroid-stimulating hormone deficiency.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy, may occur at lower doses with longer follow-up, surgery or tumor in supra-sellar area.

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
57 (male)	**Head/Brain** **TBI**	**Gonadotropin deficiency** LH and FSH deficiency	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Male Health Issues** **Hypopituitarism** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. Spermatogenesis can be induced with gonadotropins in men with hypogonadotropic hypogonadism. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH, LH, testosterone as clinically indicated in patients with delayed/arrested puberty and/or clinical signs and symptoms of testosterone deficiency. If dose ≥30 Gy and endocrinology care is readily available, refer to endocrinologist for ongoing management, given risk of multiple hormone deficiencies. If endocrinology care is not readily available, screen as indicated, and refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Refer to reproductive endocrinology as clinically indicated for infertility evaluation and consultation regarding assisted reproductive technologies. Bone density testing in patients who are gonadotropin deficient. **SYSTEM = Reproductive (Male)** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy, may occur at lower doses with longer follow-up, surgery or tumor in supra-sellar area

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
58 (female)	**Head/Brain** **TBI**	**Gonadotropin deficiency** LH and FSH deficiency	**HISTORY** **Onset and tempo of puberty** **Menstrual history** **Sexual function (vaginal dryness, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Female Health Issues** **Hypopituitarism** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH, LH, estradiol as clinically indicated in patients with delayed or arrested puberty, irregular menses, primary or secondary amenorrhea, or clinical signs and symptoms of estrogen deficiency. If dose ≥30 Gy and endocrinology care is readily available, refer to endocrinologist for ongoing management, given risk of multiple hormone deficiencies. If endocrinology care is not readily available, screen as indicated, and refer to endocrinologist for delayed puberty or persistently abnormal hormone levels. Hormonal replacement therapy for hypogonadal patients. Refer to reproductive endocrinology as clinically indicated for infertility evaluation and consultation regarding assisted reproductive technologies. Bone density testing in patients who are gonadotropin deficient. **SYSTEM = Reproductive (Female)** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy, may occur at lower doses with longer follow-up, surgery or tumor in supra-sellar area

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
59	**Head/Brain** **TBI** (TBI is included for cumulative dose calculation purposes only; this section is not applicable to patients who received TBI alone.)	**Central adrenal insufficiency**	**HISTORY** **If dose ≥30 Gy:** **Failure to thrive** **Anorexia** **Dehydration** **Hypoglycemia** **Lethargy** **Unexplained hypotension** Yearly **SCREENING** **If dose ≥30 Gy:** **8 AM Cortisol** Yearly, refer to endocrinology for further testing if level <13 mcg/dL or <365 nmol/L	**HEALTH LINKS** **Central Adrenal Insufficiency** **Hypopituitarism** **RESOURCES** www.magicfoundation.org **COUNSELING** Need for corticosteroid replacement therapy and stress dosing. Medical Alert bracelet. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** If dose ≥30 Gy and endocrinology care is readily available, refer to endocrinologist for ongoing management, given risk of multiple hormone deficiencies. If endocrinology care is not readily available, screen as indicated, and refer to endocrinologist if results are abnormal. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Cortisol secretion follows a circadian rhythm. Levels should be drawn as close as possible to 8AM and before 9 AM.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy, may occur at lower doses with longer follow-up, surgery or tumor in supra-sellar area
- Pre-morbid/Co-morbid medical conditions: History of another hypothalamic-pituitary endocrinopathy

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
60	**Head/Brain** **TBI**	**Cataracts**	**HISTORY** **Visual changes (decreased acuity, halos, diplopia)** Yearly **PHYSICAL** **Visual acuity** **Funduscopic exam** Yearly **SCREENING** **Evaluation by ophthalmologist or optometrist** Yearly	**HEALTH LINKS** **Cataracts** **POTENTIAL 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**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Radiation dose ≥10 Gy, especially ≥15 Gy, radiation fraction dose ≥2 Gy, TBI dose ≥2 Gy in single fraction, TBI dose ≥5 Gy fractionated, especially ≥10 Gy, cranial/orbital/eye radiation combined with TBI, radiation combined with corticosteroids or busulfan, longer interval since treatment

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
61	**Head/Brain**	**Ocular toxicity** Orbital hypoplasia Lacrimal duct atrophy Xerophthalmia (keratoconjunctivitis sicca) Keratitis Telangiectasias Retinopathy Optic chiasm neuropathy Enophthalmos Chronic painful eye Maculopathy Papillopathy Glaucoma	**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 or optometrist** Yearly	**HEALTH LINKS** **Eye Health** **RESOURCES** FACES—The National Craniofacial Association: www.faces-cranio.org **POTENTIAL 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**

Additional Information

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.
Reduced visual acuity may be associated with cataracts, retinal damage, and optic nerve damage.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy, higher daily fraction dose, especially fraction dose ≥2 Gy, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) [problems related to tearing]
- Pre-morbid/Co-morbid medical conditions: Chronic GVHD [xerophthalmia only]

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
62	**Head/Brain** **TBI** (TBI is included for cumulative dose calculation purposes only; this section is not applicable to patients who received TBI alone.)	**Ototoxicity** Tympanosclerosis Otosclerosis Eustachian tube dysfunction Conductive hearing loss Sensorineural hearing loss Tinnitus Vertigo	**HISTORY** **If dose ≥30 Gy:** **Hearing difficulties (with/without background noise)** **Tinnitus** **Vertigo** Yearly **PHYSICAL** **If dose ≥30 Gy:** **Otoscopic exam** Yearly **SCREENING** **If dose ≥30 Gy:** **Complete audiological evaluation by audiologist** Yearly, for patients ages ≤5 years **Pure tone audiometry testing at 1000-8000 Hz** Every 2 years, for patients ages 6-12, then every 5 years beginning at age 13	**HEALTH LINKS** **Hearing Loss** **Educational Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Additional testing with high frequency audiometry at >8000 Hz is recommended if equipment is available. Audiology consultation for any survivor who has symptoms suggestive of hearing loss, tinnitus, or abnormal pure tone audiometry results showing a loss of more than 15 dB absolute threshold level (1000-8000 Hz). Ongoing follow-up with audiology for patients with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Speech and language therapy for patients with hearing loss. Refer patients with auditory deficits to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources. Specialized evaluation for specific needs and/or preferential classroom seating, FM amplification system, and other educational assistance as indicated. **SYSTEM = Auditory** **SCORE = 1**

Additional Information

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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: All hearing loss types: higher radiation dose; sensorineural hearing loss/tinnitus: CNS neoplasm, conventional (non-conformal) radiation, combination with other ototoxic agents (cisplatin, carboplatin, aminoglycosides, loop diuretics), radiation administered prior to platinum chemotherapy
- Pre-morbid/Co-morbid medical conditions: All hearing loss types: chronic otitis, chronic cerumen impaction; sensorineural hearing loss/tinnitus: cerebrospinal fluid shunt

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RADIATION

POTENTIAL IMPACT TO ORAL CAVITY

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
63	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Xerostomia** **Salivary gland dysfunction**	**HISTORY** **Xerostomia** Yearly **PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**HEALTH LINKS** **Dental Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Supportive care with saliva substitutes, moistening agents, and sialagogues (pilocarpine). Regular dental care including fluoride applications. **SYSTEM = Dental** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Head and neck radiation involving the parotid gland, higher proportion of one gland or both salivary glands in the radiation field, higher radiation doses, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)
- Pre-morbid/Co-morbid medical conditions: Chronic GVHD

References

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Kaste SC, Goodman P, Leisenring W, et al: Impact of radiation and chemotherapy on risk of dental abnormalities: a report from the Childhood Cancer Survivor Study. Cancer 115:5817-27, 2009

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
64	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Dental abnormalities** Tooth/root agenesis Root thinning/shortening Enamel dysplasia Microdontia Ectopic molar eruption Dental caries Periodontal disease Malocclusion **Temporomandibular joint dysfunction**	**PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**HEALTH LINKS** **Dental Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Regular dental care including fluoride applications. Baseline panorex prior to dental procedures to evaluate root development. Consultation with orthodontist experienced in management of irradiated childhood cancer survivors. **SYSTEM = Dental** **SCORE** **Ectopic Molar Eruption = 2A** **All Else = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <5 years, Gorlin syndrome (nevoid basal cell carcinoma syndrome)
- Cancer/Treatment factors: Higher radiation dose (especially dose ≥10 Gy)

References

Dahllof G, Jonsson A, Ulmner M, et al: Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. Am J Orthod Dentofacial Orthop 120:459-65, 2001

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
65	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI** (TBI is included for cumulative dose calculation purposes only; this section is not applicable to patients who received TBI alone.)	**Osteoradionecrosis of the jaw**	**HISTORY** **If dose ≥40 Gy:** **Impaired or delayed healing following dental work** **Persistent jaw pain or swelling** **Trismus** Yearly **PHYSICAL** **If dose ≥40 Gy:** **Impaired wound healing** **Jaw swelling** **Trismus** As clinically indicated	**HEALTH LINKS** **Osteoradionecrosis** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Imaging studies (x-ray, CT scan and/or MRI) may assist in making diagnosis. Biopsy may be needed to confirm diagnosis. Hyperbaric oxygen treatments pre- or post-mandibular surgery to facilitate healing. **SYSTEM = Dental** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Radiation dose ≥40 Gy (especially dose ≥50 Gy)

References

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Effinger KE, Migliorati CA, Hudson MM, et al: Oral and dental late effects in survivors of childhood cancer: a Children's Oncology Group report. Support Care Cancer 22:2009-19, 2014

Mercado CE, Little SB, Mazewski C, et al: Mandibular condyle erosion and sclerosis in pediatric patients treated with radiotherapy to the head and neck region. Pediatr Blood Cancer 61:1479-80, 2014

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
66	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Thyroid nodules**	**PHYSICAL** **Thyroid exam** Yearly	**HEALTH LINKS** **Thyroid Problems** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ultrasound for evaluation of palpable nodule(s). FNA as clinically indicated. Endocrine and/or surgical consultation for further management. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, female sex
- Cancer/Treatment factors: Thyroid gland directly in radiation field, TBI

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
67	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Thyroid cancer**	**PHYSICAL** **Thyroid exam** Yearly	**HEALTH LINKS** **Thyroid Problems** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ultrasound for evaluation of palpable nodule(s). FNA as clinically indicated. Endocrine and/or surgical consultation for further management. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: >5 years after irradiation, highest risk is between 10-30 Gy, thyroid gland directly in radiation field, TBI, alkylating agents

References

Bhatti P, Veiga LH, Ronckers CM, et al: Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the Childhood Cancer Survivor Study. Radiat Res 174:741-52, 2010
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
68	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Hypothyroidism**	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**HEALTH LINKS** **Thyroid Problems** **COUNSELING** For females, thyroid levels prior to attempting pregnancy and periodically throughout pregnancy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Female sex
- Cancer/Treatment factors: Radiation dose ≥10 Gy (especially radiation dose ≥20 Gy), thyroid gland directly in radiation field, TBI

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
69	**Head/Brain** **Neck** **Spine (cervical, whole)**	**Hyperthyroidism**	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Endocrine consultation for medical management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
70	**Head/Brain** **Neck** **Spine (cervical, whole)**	**Carotid artery disease**	**HISTORY** **Memory impairment** Yearly **PHYSICAL** **Blood pressure** **Diminished carotid pulses** **Carotid bruits** **Abnormal neurologic exam (compromise of blood flow to brain)** Yearly	**HEALTH LINKS** **Cardiovascular Risk Factors** **Diet and Physical Activity** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Optimize cardiovascular risk factors, including blood pressure, lipid profile, and blood glucose. Doppler ultrasound of carotid vessels as clinically indicated. Refer to cardiology if abnormal. MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated. For survivors who received ≥40 Gy radiation to the neck: Color Doppler ultrasound 10 years after completion of radiation therapy as a baseline. Refer to cardiologist if abnormal. **SYSTEM = Cardiovascular** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: ≥40 Gy radiation dose
- Pre-morbid/Co-morbid medical conditions: Hypertension, diabetes mellitus, hypercholesterolemia

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
71	**Neck** **Chest** **Spine (thoracic, whole)**	**Subclavian artery disease**	**PHYSICAL** **Blood pressure in both arms (checking for wide blood pressure variation)** **Diminished brachial and radial pulses** **Pallor of upper extremities** **Coolness of skin** Yearly	**HEALTH LINKS** **Cardiovascular Risk Factors** **Diet and Physical Activity** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Optimize cardiovascular risk factors, including blood pressure, lipid profile, and blood glucose. Doppler ultrasound of carotid vessels as clinically indicated. Refer to cardiology if abnormal. MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated. For survivors who received ≥40 Gy radiation to the neck: Color Doppler ultrasound 10 years after completion of radiation therapy as a baseline. Refer to cardiologist if abnormal. **SYSTEM = Cardiovascular** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: ≥40 Gy radiation dose
- Pre-morbid/Co-morbid medical conditions: Hypertension, diabetes mellitus, hypercholesterolemia

References

Bowers DC, McNeil DE, Liu Y, et al: Stroke as a late treatment effect of Hodgkin's disease: a report from the Childhood Cancer Survivor Study. J Clin Oncol 23:6508-15, 2005

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RADIATION

POTENTIAL IMPACT TO BREAST

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
72 (female)	**Chest** **Axilla** **TBI**	**Breast cancer**	**PHYSICAL** **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	**HEALTH LINKS** **Breast Cancer** **COUNSELING** Teach breast self-exam and counsel to perform monthly beginning at puberty. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

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 mammography and breast MRI should be used for breast cancer surveillance has not been established.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Family history of breast cancer
- Cancer/Treatment factors: Higher radiation dose, especially ≥10 Gy, longer time since radiation (>5 years). Note decreased risk in women treated with alkylating agents of sufficient dose to ablate ovarian function, although annual surveillance is still recommended.
- Pre-morbid/Co-morbid medical conditions: Personal history of BRCA1, BRCA2, ATM or p53 mutation or in absence of personal genetic testing, known BRCA mutation in first degree relative

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
73 (female)	**Chest** **Axilla** **TBI**	**Breast tissue hypoplasia**	**PHYSICAL** **Clinical breast exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgical consultation for breast reconstruction after completion of growth. **SYSTEM = Reproductive (Female)** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Prepubertal at time of treatment
- Cancer/Treatment factors: Radiation dose ≥10 Gy to prepubertal breast bud (especially dose ≥20 Gy)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
74	**Chest** **Axilla** **TBI**	**Pulmonary toxicity** Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	**HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** 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** www.smokefree.gov **COUNSELING** Tobacco avoidance/smoking cessation/environmental tobacco smoke. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy). **SYSTEM = Pulmonary** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at irradiation
- Cancer/Treatment factors: Radiation dose >10 Gy, especially radiation dose ≥15 Gy, TBI ≥6 Gy in single fraction, TBI ≥12 Gy fractionated, chest radiation combined with TBI, radiation combined with bleomycin, busulfan, carmustine (BCNU), or lomustine (CCNU), radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)
- Pre-morbid/Co-morbid medical conditions: Atopic history
- Health behaviors: Smoking, inhaled illicit drug use

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
75	**Chest** **Axilla** **TBI**	**Lung cancer**	**HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** Yearly **PHYSICAL** **Pulmonary Exam** Yearly **SCREENING** **Spiral CT Scan** Discuss the benefits and risks/harms of spiral CT scanning for patients at highest risk (i.e., smokers)	**HEALTH LINKS** **Reducing the Risk of Second Cancers** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Imaging and surgery and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Workplace exposure to asbestos, arsenic, radiation, second hand smoke (in non-smokers)
- Health behaviors: Smoking, especially 30 pack-years or more

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
76	**Chest** **Abdomen** **Spine (thoracic, whole)** **TBI** (TBI is included for cumulative dose calculation purposes only; this section is not applicable to patients who received TBI alone.)	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Pericarditis Pericardial fibrosis Valvular disease Atherosclerotic heart disease Myocardial infarction Arrhythmia	**HISTORY** **If dose ≥15 Gy:** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **If dose ≥15 Gy:** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac anatomy and function)**	**HEALTH LINKS** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **Dental Health** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal LV systolic function. - Survivors with asymptomatic cardiomyopathy should consult cardiology to define limits and precautions for physical activity. - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Optimize cardiovascular risk factors, including blood pressure, lipid profile, and blood glucose. Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Cardiology consultation (5 to 10 years after radiation) may be reasonable to evaluate risk for coronary artery disease in survivors who received ≥35 Gy chest radiation alone or ≥15 Gy chest radiation plus anthracycline. In survivors with valvular disorders: Consult cardiologist to advise regarding need for endocarditis prophylaxis. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Recommended Frequency of Echocardiogram

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.

If dose ≥15 Gy:
EKG (include evaluation of QTc interval)
Baseline at entry into long-term follow-up, repeat as clinically indicated

Section 76 Additional Information

Exertional intolerance is an uncommon presentation of left ventricular dysfunction 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.
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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at irradiation, especially age <5 years, family history of dyslipidemia, coronary artery disease
- Cancer/Treatment factors: Radiation dose ≥20 Gy to chest, TBI, anteriorly-weighted radiation fields, lack of subcarinal shielding, combined with radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin), doses ≥15 Gy in patients who have received ≥100 mg/m^2 of anthracyclines, doses ≥35 Gy in patients who have not received anthracyclines, longer time since treatment
- Pre-morbid/Co-morbid medical conditions: Obesity, congenital heart disease, hypertension, diabetes mellitus, dyslipidemia. For female patients, premature ovarian failure (untreated), pregnancy if systolic function is abnormal pre-pregnancy
- Health behaviors: Smoking, drug use (e.g., cocaine, diet pills, ephedra, mahuang)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
77	**Abdomen** **TBI** (TBI is included for cumulative dose calculation purposes only; this section is not applicable to patients who received TBI alone.)	**Functional asplenia** At risk for life-threatening infection with encapsulated organisms (e.g., Haemophilus influenzae, Streptococcus pneumoniae, meningococcus)	**PHYSICAL** **If dose ≥40 Gy:** **Physical exam at time of febrile illness to evaluate degree of illness and potential source of infection** When febrile T ≥101°F (38.3°C) **SCREENING** **If dose ≥40 Gy:** **Blood culture** When febrile T ≥101°F (38.3°C)	**HEALTH LINKS** **Splenic Precautions** **COUNSELING** Risk of life-threatening infections with encapsulated organisms. Risk associated with malaria and tick-borne diseases if living in or visiting endemic areas. Obtain medical alert bracelet/card noting functional asplenia. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone) in patients with T ≥101°F (38.3°C) or other signs of serious illness and continue close medical monitoring while awaiting blood culture results. Hospitalize and broaden antimicrobial coverage (e.g., addition of vancomycin) under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC, toxic clinical appearance, fever ≥104°F (40°C), meningitis, pneumonia, or other serious focus of infection, signs of septic shock, or previous history of serious infection. Immunize with Pneumococcal, Meningococcal (including serotype B), Influenza and HIB vaccines according to current ACIP recommendations. Discuss with dental provider potential need for antibiotic prophylaxis based on planned procedure. For further details regarding antibiotic prophylaxis and immunizations, see current edition of AAP Red Book. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, larger volume of spleen in treatment field

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
78	**Neck** **Chest** **Abdomen** **Spine (cervical, thoracic, whole)**	**Esophageal stricture**	**HISTORY** **Dysphagia** **Heartburn** Yearly	**HEALTH LINKS** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Radiation dose ≥30 Gy (increased risk with higher radiation dose, particularly dose ≥40 Gy)
- Pre-morbid/Co-morbid medical conditions: Gastroesophageal reflux, history of Candida esophagitis, gut GVHD

References

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Rodriguez ML, Martin MM, Padellano LC, et al: Gastrointestinal toxicity associated to radiation therapy. Clin Transl Oncol 12:554-61, 2010

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
79	**Abdomen** **TBI**	**Impaired glucose metabolism/diabetes mellitus**	**SCREENING** **Fasting blood glucose OR HbA1c** Every 2 years	**HEALTH LINKS** **Diet and Physical Activity** **Cardiovascular Risk Factors** **COUNSELING** Obesity-related health risks. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Endocrine consultation Evaluate for other co-morbid conditions, including dyslipidemia, hypertension, and overweight/obesity. Refer to dietician for blood sugar management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Impaired glucose metabolism may occur in a constellation of conditions known as the metabolic syndrome.
Definitions of the metabolic syndrome 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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Family history of diabetes mellitus
- Cancer/Treatment factors: Prolonged corticosteroid therapy (e.g., for chronic GVHD)
- Pre-morbid/Co-morbid medical conditions: Obesity

References

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Taskinen M, Saarinen-Pihkala UM, Hovi L, et al: Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet 356:993-7, 2000

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
80	**Abdomen** **TBI**	**Dyslipidemia**	**SCREENING** **Fasting lipid profile** Every 2 years	**HEALTH LINKS** **Diet and Physical Activity** **Cardiovascular Risk Factors** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluate for other co-morbid conditions, including hypertension, impaired glucose metabolism, and overweight/obesity. Refer to dietician. **SYSTEM = Endocrine/Metabolic** **SCORE** **Abdominal Radiation = 2A** **TBI = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Family history of dyslipidemia
- Cancer/Treatment factors: Prolonged corticosteroid therapy (e.g., for chronic GVHD)

References

Bajwa R, Skeens M, Garee A, et al: Metabolic syndrome and endocrine dysfunctions after HSCT in children. Pediatr Transplant 16:872-8, 2012

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
81	**Abdomen**	**Hepatic toxicity** Hepatic fibrosis Cirrhosis Focal nodular hyperplasia	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Platelet count for evaluation of hypersplenism and 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 at-risk patients lacking immunity. **SYSTEM = GI/Hepatic** **SCORE = 1**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Higher radiation dose to liver, especially ≥30 Gy, or to larger volume
- Pre-morbid/Co-morbid medical conditions: Chronic hepatitis, history of SOS (previously known as VOD)
- Health behaviors: Alcohol use (in relation to hepatic fibrosis and cirrhosis)

References

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Mulder RL, van Dalen EC, Van den Hof M, et al: Hepatic late adverse effects after antineoplastic treatment for childhood cancer. Cochrane Database Syst Rev:CD008205, 2011
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
82	**Abdomen**	**Cholelithiasis**	**HISTORY** **Colicky abdominal pain related to fatty food intake** **Excessive flatulence** Yearly **PHYSICAL** **RUQ or epigastric tenderness** **Positive Murphy's sign** As clinically indicated	**HEALTH LINKS** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gallbladder ultrasound in patients with chronic abdominal pain. **SYSTEM = GI/Hepatic** **SCORE = 2B**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Family history of cholelithiasis
- Cancer/Treatment factors: Radiation dose ≥30 Gy, abdominal surgery, abdominal radiation, TPN, HCT
- Pre-morbid/Co-morbid medical conditions: Ileal conduit, obesity, pregnancy

References

Castellino S, Muir A, Shah A, et al: Hepato-biliary late effects in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group. Pediatr Blood Cancer 54:663-9, 2010

Hoffmeister PA, Storer BE, McDonald GB, et al: Gallstones in pediatric hematopoietic cell transplant survivors with up to 40 years of follow-up. J Pediatr Hematol Oncol 36:484-90, 2014

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
83	**Abdomen** **Pelvis** **Spine (lumbar, sacral, whole)**	**Bowel obstruction**	**HISTORY** **Abdominal pain** **Distention** **Vomiting** **Constipation** Yearly **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** Yearly	**HEALTH LINKS** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** KUB as clinically indicated for suspected obstruction. Surgical consultation in patients unresponsive to medical management. **SYSTEM = GI/Hepatic** **SCORE = 1**

Additional Information

Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Abdominal surgery, radiation dose ≥20 Gy (particularly radiation dose ≥45 Gy). Obstruction may occur in people who received lower doses of abdominal radiation during childhood.

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
84	**Abdomen** **Pelvis** **Spine (lumbar, sacral, whole)**	**Chronic enterocolitis** **Fistula** **Strictures**	**HISTORY** **Nausea** **Vomiting** **Abdominal pain** **Diarrhea** Yearly	**HEALTH LINKS** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Serum protein and albumin in patients with chronic diarrhea or fistula. Surgical and/or gastroenterology consultation. **SYSTEM = GI/Hepatic** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Abdominal surgery, radiation dose ≥30 Gy (particularly radiation dose ≥45 Gy), higher radiation dose to bowel

References

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Rodriguez ML, Martin MM, Padellano LC, et al: Gastrointestinal toxicity associated to radiation therapy. Clin Transl Oncol 12:554-61, 2010

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
85	**Abdomen** **Pelvis** **Spine (lumbar, sacral, whole)** **TBI**	**Colorectal cancer**	**SCREENING** **Regular screening selected from the options below based on informed decision-making between patient and provider** Beginning 5 years after radiation or at age 30 years (whichever occurs last) **Radiation-Related Colorectal Cancer Screening Options** Test: Multitarget stool DNA test* — Frequency: Every 3 years Test: Colonoscopy — Frequency: Every 5 years *Positive result should be followed up with timely colonoscopy. *Note*: Colonoscopy is considered the gold standard for colorectal cancer screening in high-risk populations; however, recognizing that not all survivors are willing or able to undergo colonoscopy, multitarget stool DNA testing is deemed a reasonable alternative. Alternative stool-based testing (i.e., annual fecal immunochemical testing (FIT) or high-sensitivity guaiac-based fecal occult blood testing) or alternative structural examination (i.e., every 5 year CT colonography or flexible sigmoidoscopy) may also be considered if colonoscopy or multitarget stool DNA testing are not feasible or acceptable to the survivor. All positive results from these alternative testing methods should be followed up with timely colonoscopy.	**HEALTH LINKS** **Colorectal Cancer** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gastroenterology, surgery and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 2A**

Additional Information

Participation in screening remains poor in the cancer survivor population, with >70% of at-risk survivors unscreened (see Daniel et al. 2015); thus it is important for clinicians to engage survivors in informed decision making, weighing risks and benefits of the available options, and to select an option that is acceptable to the survivor and thus likely to result in successful completion of timely periodic screening.

For patients at high risk due to personal or family history or hereditary syndromes predisposing to colorectal cancer, more intensive and earlier screening is recommended (see Giardiello et al. 2014, Kahl et al. 2016, Lieberman et al. 2012, and Syngal et al. 2015).

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Current age≥45 years, family history of colorectal cancer or polyps in first degree relative
- Cancer/Treatment factors: Hepatoblastoma, gastrointestinal malignancy, higher radiation dose, especially ≥20 Gy, combination with chemotherapy (especially alkylators)
- Pre-morbid/Co-morbid medical conditions: Obesity, ulcerative colitis, adenomatous polyps, familial polyposis
- Health behaviors: High fat/low fiber diet

Section 85 References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
86	**Abdomen** **TBI**	**Renal toxicity** Glomerular injury Renal insufficiency Hypertension	**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	**HEALTH LINKS** **Kidney Health** **Cardiovascular Risk Factors** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Nephrology consultation for patients with hypertension or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Bilateral Wilms tumor, nephrectomy, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin), combination with other nephrotoxic agents (e.g., cisplatin, carboplatin, ifosfamide, aminoglycosides, amphotericin, immunosuppressants), radiation dose ≥10 Gy, especially radiation dose ≥15 Gy, TBI ≥6 Gy in single fraction, TBI ≥12 Gy fractionated, TBI combined with radiation to the kidney
- Pre-morbid/Co-morbid medical conditions: Diabetes mellitus, hypertension, congenital absence of kidney

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
87	**Pelvis** **Spine (sacral, whole)**	**Urinary tract toxicity** Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**HEALTH LINKS** **Bladder Health** **COUNSELING** Promptly report dysuria or gross hematuria. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urinalysis, urine culture, spot urine calcium/creatinine ratio for patients with positive history. Ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as >5 RBC/HPF 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, incontinence, or dysfunctional voiding. **SYSTEM = Urinary** **SCORE** **Hemorrhagic cystitis = 2A** **All Else = 1**

Additional Information

The bladder is included in the left and right flank/hemiabdomen treatment fields only if the fields extended below iliac crest.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Higher radiation dose, especially ≥30 Gy to entire bladder, ≥45 Gy to portion of bladder, combination with cyclophosphamide, ifosfamide or vincristine

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
88	**Pelvis** **Spine (sacral, whole)**	**Bladder malignancy**	**HISTORY** **Hematuria** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**HEALTH LINKS** **Bladder Health** **COUNSELING** Promptly seek medical attention for dysuria or gross hematuria. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urinalysis, urine culture, spot urine calcium/creatinine ratio for patients with positive history. Ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as >5 RBC/HPF on at least 2 occasions). Nephrology or urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound. Urology referral for patients with culture-negative macroscopic hematuria. **SYSTEM = SMN** **SCORE = 2A**

Additional Information

The bladder is included in the left and right flank/hemiabdomen treatment fields only if the fields extended below iliac crest.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with cyclophosphamide or ifosfamide
- Health behaviors: Alcohol use, smoking

References

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RADIATION

POTENTIAL IMPACT TO MALE REPRODUCTIVE SYSTEM

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
89 (male)	**Testes**	**Testicular hormonal dysfunction** Testosterone deficiency/ insufficiency Delayed/arrested puberty	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Male Health Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Measurement of early morning testosterone concentration and/or endocrinology referral for patients with: - no signs of puberty at age 14 - failure of pubertal progression - 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 percentile on growth chart - testosterone deficiency/insufficiency to weigh risks and benefits of hormonal replacement therapy Periodic re-evaluation of testosterone in males with low normal testosterone as they age or if they become symptomatic. Bone density evaluation in androgen deficient patients. **SYSTEM = Reproductive (Male)** **SCORE = 1**

Additional Information

Testicular volume is not a reliable indicator of pubertal onset/stage in boys treated with alkylating agents and/or direct testicular radiotherapy.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Aging (≥30 years)
- Cancer/Treatment factors: Testicular cancer, testicular irradiation combined with head/brain irradiation, testicular dose ≥12 Gy, combination with alkylating agents, combination with cyclophosphamide conditioning for HCT, combination with unilateral orchiectomy

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
90 (male)	**Testes** **TBI**	**Impaired spermatogenesis** Reduced fertility Oligospermia Azoospermia Infertility	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly	**HEALTH LINKS** **Male Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. Recovery of fertility may occur years after therapy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** For sexually mature patients who desire information about potential future fertility: semen analysis (optimal) and/or FSH and inhibin B (alternative if unable or unwilling to provide semen sample). Reproductive endocrinology/urology referral for infertility evaluation and consultation regarding assisted reproductive technologies. **SYSTEM = Reproductive (Male)** **SCORE = 1**

Additional Information

Testicular volume is not a reliable indicator of pubertal onset/stage in boys treated with alkylating agents and/or direct testicular radiotherapy.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents), aging
- Cancer/Treatment factors: Testicular cancer, fractionated small doses greater risk than single large doses, radiation dose to testes (up to 6 Gy azoospermia may be transient, ≥6 Gy azoospermia likely permanent and especially testicular dose ≥20 Gy), combination with alkylating agents, genitourinary surgery
- Pre-morbid/Co-morbid medical conditions: Obesity, ejaculatory dysfunction, history of sexually transmitted infections, chronic GVHD
- Health behaviors: Tobacco/marijuana use

References

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RADIATION

POTENTIAL IMPACT TO FEMALE REPRODUCTIVE SYSTEM

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
91 (female)	**Pelvis** **Spine (sacral, whole)** **TBI**	**Ovarian hormone deficiencies** Delayed puberty Arrested puberty Premature ovarian insufficiency/premature menopause	**HISTORY** **Onset and tempo of puberty** **Menstrual history** **Sexual function (vaginal dryness, libido)** **Menopausal symptoms** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Female Health Issues** **COUNSELING** Adverse impact of ovarian hormone deficiencies on growth, bone mineralization, cardiovascular disease and sexual dysfunction. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH and estradiol and/or endocrine/gynecology referral for patients with: - no signs of puberty at age 13 - failure of pubertal progression - abnormal menstrual patterns or menopausal symptoms. - ovarian hormone deficiency/insufficiency to weigh risks and benefits of hormonal replacement therapy Bone density evaluation in patients with ovarian hormone deficiencies. **SYSTEM = Reproductive (Female)** **SCORE = 1**

Additional Information

The ovaries are included in the left and right flank/hemiabdomen treatment fields only if the fields extended below iliac crest.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Older age at irradiation
- Cancer/Treatment factors: Radiation dose ≥5 Gy if pubertal (especially dose ≥10 Gy), radiation dose ≥10 Gy if prepubertal (especially dose ≥15 Gy), combination with alkylating agent chemotherapy, longer time since treatment, combination with cyclophosphamide conditioning for HCT
- Health behaviors: Smoking

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
92 (female)	**Pelvis** **Spine (sacral, whole)** **TBI**	**Reduced ovarian follicular pool** Infertility	**HISTORY** **Menstrual and pregnancy history** **Hormonal Therapy** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly	**HEALTH LINKS** **Female Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Potential for shorter period of fertility (associated with increased risk of early menopause) in family planning. Need for contraception. Recovery of fertility may occur years after therapy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH and estradiol for patients with menstrual cycle dysfunction suggestive of premature ovarian insufficiency or those who desire information about potential for future fertility. AMH (anti-Mullerian hormone) to assess for diminished ovarian reserve. Reproductive endocrinology referral for antral follicle count, ovarian reserve evaluation and consultation regarding assisted reproductive technologies in at-risk patients who desire information about potential fertility and interventions to preserve future fertility. **SYSTEM = Reproductive (Female)** **SCORE = 1**

Additional Information

The ovaries are included in the left and right flank/hemiabdomen treatment fields only if the fields extended below iliac crest.
AMH may be low in the presence of normal FSH.
FSH is lowered and AMH may be lowered by concurrent hormonal contraceptive use.
AMH should be interpreted relative to age-specific reference ranges.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Older age at irradiation
- Cancer/Treatment factors: Radiation dose ≥5 Gy if pubertal (especially dose ≥10 Gy), radiation dose ≥10 Gy if prepubertal (especially dose ≥15 Gy), combination with alkylating agent chemotherapy, longer time since treatment, combination with cyclophosphamide conditioning for HCT
- Health behaviors: Smoking

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
93 (female)	**Pelvis** **Spine (sacral, whole)** **TBI**	**Uterine vascular insufficiency** Resulting in adverse pregnancy outcomes such as: - spontaneous abortion - neonatal death - low-birth weight infant - fetal malposition - premature labor	**HISTORY** **Pregnancy** **Childbirth history** Yearly	**HEALTH LINKS** **Female Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** High-level ultrasound evaluation of genitourinary tract after pubertal development as clinically indicated in patients contemplating pregnancy. High-risk obstetrical care during pregnancy. **SYSTEM = Reproductive (Female)** **SCORE = 2B**

Additional Information

The uterus is included in the left and right flank/hemiabdomen treatment fields only if the fields extended below iliac crest.
10% of girls with Wilms tumor have congenital uterine anomalies.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Patient factors: Wilms tumor and associated Müllerian anomalies, prepubertal at time of treatment
- Cancer/Treatment factors: TBI, higher radiation dose to pelvis, radiation dose ≥30 Gy

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
94 (female)	**Pelvis**	**Vaginal fibrosis/stenosis**	**HISTORY** **Psychosocial assessment** **Dyspareunia** **Post-coital bleeding** **Difficulty with tampon insertion** **Vaginal dryness** **Vulvar pain/tenderness** **Vulvovaginal burning or pruritus** **Dysuria** Yearly **PHYSICAL** **Exam of external genitalia** Yearly	**COUNSELING** Avoid frequent contact with irritants (bubble bath, wet wipes and soaps). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gynecologic consultation for management. Psychological consultation in patients with emotional difficulties. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

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

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Vaginal tumor or pelvic tumor adjacent to vagina, radiation dose ≥50 Gy if postpubertal (especially dose ≥55 Gy), radiation dose ≥25 Gy if prepubertal (especially dose ≥35 Gy)
- Pre-morbid/Co-morbid medical conditions: Chronic GVHD

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
95	**Any Radiation (Including TBI)**	**Musculoskeletal growth problems** Hypoplasia Fibrosis Reduced or uneven growth Shortened trunk height (trunk radiation) Limb length discrepancy (extremity radiation)	**PHYSICAL** **Height** **Weight** Yearly **Sitting height** Yearly for patients who had trunk radiation **Limb lengths** Yearly for patients who had extremity radiation	**COUNSELING** Increased risk of fractures in weight-bearing irradiated bones. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Orthopedic consultation for any deficit noted in growing child. Plastic surgery consult for reconstruction. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially prepubertal at treatment
- Cancer/Treatment factors: Higher cumulative radiation dose, especially dose ≥20 Gy, larger radiation treatment field, higher radiation dose per fraction, orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones, epiphysis in treatment field

References

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Fletcher BD: Effects of pediatric cancer therapy on the musculoskeletal system. Pediatr Radiol 27:623-36, 1997
Gawade PL, Hudson MM, Kaste SC, et al: A systematic review of selected musculoskeletal late effects in survivors of childhood cancer. Curr Pediatr Rev 10:249-62, 2014
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Rohde RS, Puhaindran ME, Morris CD, et al: Complications of radiation therapy to the hand after soft tissue sarcoma surgery. J Hand Surg Am 35:1858-63, 2010

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
96	**Chest** **Abdomen** **Spine (thoracic, lumbar, whole)**	**Scoliosis/Kyphosis**	**PHYSICAL** **Exam of back/spine** Yearly until growth completed, may need more frequent assessment during puberty or if curve detected	**HEALTH LINKS** **Scoliosis and Kyphosis** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on physical and/or radiographic exam. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at irradiation
- Cancer/Treatment factors: Paraspinal malignancies, hemithoracic, abdominal or spinal surgery, hemithoracic or abdominal radiation, radiation of only a portion of (rather than whole) vertebral body, radiation doses ≥20 Gy (lower doses for infants), orthovoltage radiation (commonly used before 1970)
- Pre-morbid/Co-morbid medical conditions: Neurofibromatosis

References

de Jonge T, Slullitel H, Dubousset J, et al: Late-onset spinal deformities in children treated by laminectomy and radiation therapy for malignant tumours. Eur Spine J 14:765-71, 2005
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Marcus RB, Esiashivilli N: Musculoskeletal, Integument, in Schwartz CL, Hobbie WL, Constine LS, et al (eds): Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach. Switzerland, Springer International Publishing, 2015, pp pp. 297-324
Paulino AC, Mayr NA, Simon JH, et al: Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. Int J Radiat Oncol Biol Phys 52:1025-31, 2002
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
97	**Any Radiation (Not Including TBI)**	**Radiation-induced fracture**	**PHYSICAL** **Pain, swelling, deformity of bone** As clinically indicated	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Radiograph of affected bone as clinically indicated. Orthopedic evaluation as clinically indicated. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: History of surgery to cortex of bone, radiation dose ≥40 Gy, radiation dose ≥50 Gy to bone

References

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Hematopoietic Cell Transplant Introductory Information

- Complications after hematopoietic cell transplantation have multifactorial etiologies, including 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, complications of the transplant process (immunosuppression and GVHD), complications in the post-transplant period, underlying disease, host genetic factors, and 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 47:337-41, 2012.
- For the Children's Oncology Group Report regarding late effects surveillance recommendations among survivors of childhood hematopoietic cell transplantation, see: Chow EJ, Anderson L, Baker KS, et al: Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. Biol Blood Marrow Transplant 22:782-95, 2016.

Total Body Irradiation (TBI) Related Potential Late Effects

- The complete list of potential late effects and associated Guideline section numbers are included on the accompanying table 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 the Guidelines.

Total Body Irradiation (TBI) Related Potential Late Effects		
Section Number	**Sex**	**Potential Late Effect**
43	Both	Secondary benign or malignant neoplasm occurring in or near radiation field
44	Both	Dermatologic toxicity
45	Both	Brain tumor (benign or malignant)
46	Both	Neurocognitive deficits
47	Both	Clinical leukoencephalopathy
52	Both	Growth hormone deficiency
57	Male	Gonadotropin deficiency
58	Female	Gonadotropin deficiency
60	Both	Cataracts
63	Both	Xerostomia; Salivary gland dysfunction
64	Both	Dental abnormalities; Temporomandibular joint dysfunction
66	Both	Thyroid nodules
67	Both	Thyroid cancer
68	Both	Hypothyroidism
72	Female	Breast cancer
73	Female	Breast tissue hypoplasia
74	Both	Pulmonary toxicity
75	Both	Lung cancer
79	Both	Impaired glucose metabolism/diabetes mellitus
80	Both	Dyslipidemia
85	Both	Colorectal cancer
86	Both	Renal toxicity
90	Male	Impaired spermatogenesis
91	Female	Ovarian hormone deficiencies
92	Female	Reduced ovarian follicular pool
93	Female	Uterine vascular insufficiency
95	Both	Musculoskeletal growth problems

HEMATOPOIETIC CELL TRANSPLANT

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
98	**Autologous Hematopoietic Cell Transplant (HCT)**	**Acute myeloid leukemia** **Myelodysplasia**	**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** Promptly seek medical attention for fatigue, pallor, petechiae or bone pain. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** CBC and bone marrow exam as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

There is negligible benefit to obtaining a screening CBC in the absence of clinical signs and symptoms for AML/MDS.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Older age at transplant
- Cancer/Treatment factors: Radiation therapy, alkylating agent chemotherapy, epipodophyllotoxins, anthracyclines, history of Non-Hodgkin and Hodgkin lymphoma, peripheral blood stem cells as the stem cell source
- Pre-morbid/Co-morbid medical conditions: Evidence is conflicting that splenectomy modifies risk for AML/MDS

References

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
99 (male)	**Hematopoietic Cell Transplant (HCT)**	**Solid tumors** Such as basal cell carcinoma, melanoma, liver cancer	**PHYSICAL** **Skin self exam** Monthly **Dermatologic exam** **Abdominal exam** Yearly	**HEALTH LINKS** **Reducing the Risk of Second Cancers** **COUNSELING** Importance of sun protection measures. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Dermatology and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at transplant
- Cancer/Treatment factors: Radiation therapy (especially TBI), second HCT, umbilical cord blood HCT, haploidentical HCT, unrelated donor transplant, HLA mismatch, T-cell depletion, anti-thymocyte globulin (ATG)
- Pre-morbid/Co-morbid medical conditions: Hepatitis C infection, chronic GVHD, Fanconi anemia, primary immune deficiency

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
100 (female)	**Hematopoietic Cell Transplant (HCT)**	**Solid tumors** Such as basal cell carcinoma, melanoma, liver cancer, cervical cancer	**PHYSICAL** **Skin self exam** Monthly **Dermatologic exam** **Abdominal exam** Yearly **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. Women ages 21 to 29: PAP test every 3 years. Women ages 30 to 65: HPV and PAP test every 5 years (optimal), or PAP test alone every 3 years (alternative). Women over age 65: No testing for cervical cancer if normal cervical cancer screening results in past 10 years.	**HEALTH LINKS** **Reducing the Risk of Second Cancers** **COUNSELING** Importance of sun protection measures. Safer sexual practices to reduce HPV transmission. Importance of HPV vaccination. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Dermatology, gynecology and/or oncology consultation as clinically indicated. HPV vaccination per current recommendations. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at transplant
- Cancer/Treatment factors: Radiation therapy (especially TBI), second HCT, umbilical cord blood HCT, haploidentical HCT, unrelated donor transplant, HLA mismatch, T-cell depletion, anti-thymocyte globulin (ATG)
- Pre-morbid/Co-morbid medical conditions: Hepatitis C infection, human papillomavirus (HPV) infection, chronic GVHD, Fanconi anemia, primary immune deficiency

References

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
101	**Hematopoietic Cell Transplant (HCT)**	**Hepatic toxicity** Chronic hepatitis Cirrhosis Iron overload Cholelithiasis Focal nodular hyperplasia	**PHYSICAL** **Scleral icterus** **Jaundice** **Ascites** **Hepatomegaly** **Splenomegaly** Yearly **SCREENING** **ALT** **AST** **Bilirubin** **Ferritin** Baseline at entry into long-term follow-up, repeat as clinically indicated	**HEALTH LINKS** **Liver Health** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Platelet count for evaluation of hypersplenism and 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. PCR testing for hepatitis C virus (HCV) in immunosuppressed patients who are negative for antibody. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction or known hepatitis. Hepatitis A and B immunization in at-risk patients lacking immunity. T2* MRI for evaluation of liver iron content. Liver biopsy in patients with evidence of excessive liver iron content (based on clinical context and magnitude of elevation). Phlebotomy or chelation therapy for treatment of iron overload. **SYSTEM = GI/Hepatic** **SCORE = 1**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: History of multiple transfusions, radiation to the liver, antimetabolite therapy
- Pre-morbid/Co-morbid medical conditions: Chronic GVHD, viral hepatitis, history of SOS (previously known as VOD), chronic hepatitis C with siderosis, steatosis, cholelithiasis
- Health behaviors: Alcohol use (in relation to hepatic fibrosis and cirrhosis)

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
102	**Hematopoietic Cell Transplant (HCT)**	**Osteonecrosis (avascular necrosis)**	**HISTORY** **Joint pain** **Swelling** **Immobility** **Limited range of motion** Yearly **PHYSICAL** **Musculoskeletal exam** Yearly	**HEALTH LINKS** **Osteonecrosis** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** MRI as clinically indicated. Orthopedic consultation in patients with positive imaging and/or symptoms of osteonecrosis. Physical therapy evaluation (for non-pharmacologic pain management, range of motion, strengthening, stretching, functional mobility). **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Osteonecrosis typically occurs during the acute treatment phase, may progress over time or resolve.
Multifocal osteonecrosis is significantly more common (3:1) than unifocal.
Symptomatic lesions confer the greatest risk for collapse.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Being pubertal or post-pubertal at time of transplant
- Cancer/Treatment factors: Corticosteroids (dexamethasone effect is more potent than prednisone), other immunosuppressants, prolonged immunosuppressive therapy (e.g., for chronic GVHD), TBI, high-dose radiation to any bone, allogeneic HCT >autologous HCT
- Pre-morbid/Co-morbid medical conditions: Sickle cell disease, chronic GVHD

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
103	**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	**SCREENING** **Bone density evaluation (DXA)** **Adjust for height-age Z-score in survivors <age 20 years*** Baseline at entry into long-term follow-up, repeat as clinically indicated. *Pediatric Z-Score Calculator Adjusted for Height Age: https://zscore.research.chop.edu/bmdCalculator.php	**HEALTH LINKS** **Bone Health** **RESOURCES** National Osteoporosis Foundation: www.nof.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ensure the AAP recommended minimum daily intake of vitamin D (400 IU/day) for children, with consideration 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. 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. Use caution regarding calcium supplementation in patients with history of renal lithiasis. Advocate for regular weight-bearing exercises such as running and jumping. Treat 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**

Additional Information

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.

Section 103 Additional Information (cont)

There are no defined standards for referral or treatment of low BMD in children.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Caucasian race, lower weight/BMI. Both genders are at risk.
- Cancer/Treatment factors: Corticosteroids (especially prolonged therapy, e.g., for chronic GVHD), methotrexate, cyclosporine, tacrolimus, cranial radiation, craniospinal radiation, HCT/TBI
- Pre-morbid/Co-morbid medical conditions: Growth hormone deficiency, hypogonadism/delayed puberty, hyperthyroidism
- Health behaviors: Intake of calcium and vitamin D, intake of alcohol and carbonated beverages, weight bearing exercise, smoking

Section 103 References

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
104	**Hematopoietic Cell Transplant (HCT)**	**Renal toxicity** Glomerular injury Renal insufficiency Hypertension Tubular injury (renal tubular acidosis, Fanconi syndrome, hypophosphatemic rickets)	**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	**HEALTH LINKS** **Kidney Health** **Cardiovascular Risk Factors** **COUNSELING** In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Older age
- Cancer/Treatment factors: Chronic cyclosporine use, TBI
- Pre-morbid/Co-morbid medical conditions: Acute kidney injury within 6 months of HCT, history of chronic GVHD

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
105	**HCT with any history of Chronic GVHD**	**Dermatologic toxicity** Permanent alopecia Nail dystrophy Vitiligo Sclerodermatous changes Squamous cell carcinoma of the skin Melanoma	**PHYSICAL** **Skin self exam** Monthly **Hair (alopecia)** **Nails (hypoplasia)** **Skin (vitiligo, sclerodermatous changes)** Yearly	**HEALTH LINKS** **Skin Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery, dermatology, and/or oncology consultation as clinically indicated. **SYSTEM = Dermatologic** **SCORE = 1**

Additional Information

Dermatologic toxicity is more common in presence of active chronic GVHD; effects may persist after chronic GVHD resolves.

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
106	**HCT with any history of Chronic GVHD**	**Xerophthalmia (keratoconjunctivitis sicca)**	**HISTORY** **Dry eyes (burning, itching, foreign body sensation, inflammation)** Yearly **PHYSICAL** **Eye exam** Yearly **SCREENING** **Evaluation by ophthalmologist or optometrist** Yearly	**HEALTH LINKS** **Eye Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Supportive care with artificial tears. **SYSTEM = Ocular** **SCORE = 1**

Additional Information

Xerophthalmia is more common in presence of active chronic GVHD; effects may persist after chronic GVHD resolves.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Cranial radiation, higher radiation dose, especially ≥30 Gy, radiation fraction ≥2 Gy, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
107	**HCT with any history of Chronic GVHD**	**Oral toxicity** Xerostomia Salivary gland dysfunction Dental caries Periodontal disease Oral cancer (squamous cell carcinoma)	**HISTORY** **Xerostomia** Yearly **PHYSICAL** **Oral exam** Yearly **SCREENING** **Dental exam and cleaning** Every 6 months	**HEALTH LINKS** **Dental Health** **COUNSELING** Safer sexual practices to reduce HPV transmission. Importance of HPV vaccination. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Supportive care with saliva substitutes, moistening agents, and sialagogues (pilocarpine). Regular dental care including fluoride applications and screening for intraoral malignancy. Head and neck/otolaryngology consultation as indicated. HPV vaccination per current recommendations. **SYSTEM = Dental** **SCORE = 1**

Additional Information

Oral-dental late effects are more common in presence of active chronic GVHD; effects may persist after chronic GVHD resolves.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Use of azathioprine for chronic GVHD management, head and neck radiation involving the parotid gland, higher radiation dose, especially ≥30 Gy, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)
- Pre-morbid/Co-morbid medical conditions: High grade of chronic GVHD, Fanconi anemia, dyskeratosis congenita, human papillomavirus (HPV) infection

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
108	**HCT with any history of Chronic GVHD**	**Pulmonary toxicity** Bronchiolitis obliterans Chronic bronchitis Bronchiectasis	**HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** 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** www.smokefree.gov **COUNSELING** Tobacco avoidance/smoking cessation/environmental tobacco smoke. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy). **SYSTEM = Pulmonary** **SCORE = 1**

Additional Information

Pulmonary late effects are more common in presence of active chronic GVHD; effects may persist after chronic GVHD resolves.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Prolonged immunosuppression related to chronic GVHD, chest radiation, TBI, pulmonary toxic chemotherapy (e.g., busulfan, bleomycin, carmustine [BCNU], lomustine [CCNU])
- Health behaviors: Smoking, inhaled illicit drug use

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
109	**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)	**HISTORY** **Chronic conjunctivitis** **Chronic sinusitis** **Chronic bronchitis** **Recurrent or unusual infections** **Sepsis** Yearly **PHYSICAL** **Eye exam** **Nasal exam** **Pulmonary exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Administer pneumocystis jirovecii (previously pneumocystis carinii) pneumonia prophylaxis and consider anti-viral and anti-fungal prophylaxis in patients with active chronic GVHD for duration of immunosuppressive therapy. Immunize with inactivated vaccines for all patients according to published guidelines; postponing vaccination in patients with GVHD is not recommended with the exception of live vaccines. Immunology or infectious diseases consultation for assistance with management of infections. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Immunologic complications related to chronic GVHD may persist or resolve over time. Immunologic abnormalities may persist for up to 20 years post transplant.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Pre-morbid/Co-morbid medical conditions: Active chronic GVHD, prolonged immunosuppression related to chronic GVHD and its treatment

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
110	**HCT with CURRENTLY ACTIVE Chronic GVHD**	**Functional 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 ≥101°F (38.3°C) as indicated for patients with active chronic GVHD **SCREENING** **Blood culture** When febrile T ≥101°F (38.3°C) as indicated for patients with active chronic GVHD	**HEALTH LINKS** **Splenic Precautions** **COUNSELING** Risk of life-threatening infections with encapsulated organisms. Risk associated with malaria and tick-borne diseases if living in or visiting endemic areas. Obtain medical alert bracelet/card noting functional asplenia. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** 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). Administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone) in patients with T ≥101°F (38.3°C) or other signs of serious illness and continue close medical monitoring while awaiting blood culture results. Hospitalize and broaden antimicrobial coverage (e.g., addition of vancomycin) under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC, toxic clinical appearance, fever ≥104°F (40°C), meningitis, pneumonia, or other serious focus of infection, signs of septic shock, or previous history of serious infection. Immunize with Pneumococcal, Meningococcal (including serotype B), Influenza and HIB vaccines according to current ACIP recommendations. For further details regarding antibiotic prophylaxis and immunizations, see current edition of AAP Red Book. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Splenic radiation, ongoing immunosuppression
- Pre-morbid/Co-morbid medical conditions: Hypogammaglobulinemia

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
111	**HCT with any history of Chronic GVHD**	**Esophageal stricture**	**HISTORY** **Dysphagia** **Heartburn** Yearly	**HEALTH LINKS** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery and/or gastroenterology consultation for symptomatic patients. **SYSTEM = GI/Hepatic** **SCORE = 1**

Additional Information

Esophageal stricture related to chronic GVHD is generally not reversible over time.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Radiation involving the esophagus, radiation dose ≥30 Gy (increased risk with higher radiation dose, particularly dose ≥40 Gy)
- Pre-morbid/Co-morbid medical conditions: Gastroesophageal reflux, candida esophagitis, gut GVHD

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
112 (female)	**HCT with any history of Chronic GVHD**	**Vulvar scarring** **Vaginal fibrosis/stenosis**	**HISTORY** **Psychosocial assessment** **Dyspareunia** **Post-coital bleeding** **Difficulty with tampon insertion** **Vaginal dryness** **Vulvar pain/tenderness** **Vulvovaginal burning or pruritus** **Dysuria** Yearly **PHYSICAL** **Exam of genitalia for lichen planus-like features, erosions, fissures, ulcers** Yearly	**COUNSELING** Avoid frequent contact with irritants (bubble bath, wet wipes and soaps). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gynecologic consultation for management. Psychological consultation in patients with emotional difficulties. **SYSTEM = Reproductive (Female)** **SCORE = 1**

Additional Information

Vulvovaginal chronic GVHD is rare before the onset of puberty, but should be considered beyond thelarche.
Estrogen deficiency and infection (HPV/HSV, yeast, bacteria and other recognized gynecological pathogens) should be ruled out before a diagnosis of genital chronic GVHD is made.
Vaginal fibrosis/stenosis related to chronic GVHD is generally not reversible over time.
Physical examination should be done with each assessment for chronic GVHD to detect vulvar lesions before vaginal stenosis develops.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Pelvic radiation

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
113	**HCT with any history of Chronic GVHD**	**Joint contractures**	**PHYSICAL** **Musculoskeletal exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Consultation with physical therapy, rehabilitation medicine/physiatrist. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Joint contractures related to chronic GVHD are generally not reversible over time.

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
114	**Amputation**	**Amputation-related complications** Impaired cosmesis Functional and activity limitations Residual limb integrity problems Pain Increased energy expenditure Impaired quality of life Psychological maladjustment	**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** Skin checks Signs of poor prosthetic fit Residual limb and prosthetic hygiene Physical fitness Importance of maintaining a healthy weight and lifestyle. **POTENTIAL 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, depression or sexual health. Vocational counseling/training to identify vocations that will not produce/ exacerbate functional limitations. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Skeletally immature/growing children
- Cancer/Treatment factors: Hemipelvectomy site of amputation (trans-femur amputation, trans-tibia amputation)
- Pre-morbid/Co-morbid medical conditions: Obesity, diabetes, poor residual limb healing

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
115	**Central venous catheter**	**Thrombosis** **Vascular insufficiency** **Infection of retained cuff or line tract** **Post-thrombotic syndrome**	**HISTORY** **Tenderness or swelling at previous catheter site** Yearly **PHYSICAL** **Venous stasis** **Swelling** **Tenderness at previous catheter site** Yearly	**SYSTEM = Cardiovascular** **SCORE = 2A**

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
116	**Cystectomy**	**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 enterocystoplasty only)	**SCREENING** **Vitamin B12 level** Yearly, starting 5 years after cystectomy (patients with ileal enterocystoplasty only) **Evaluation by urologist** Yearly	**HEALTH LINKS** **Cystectomy** **Kidney Health** **SYSTEM = Urinary** **SCORE** **Reservoir calculi = 2A** **Vitamin B12/folate/carotene deficiency = 2B** **All Else = 1**

Additional Information

All potential late effects for pelvic surgery apply to cystectomy (see also sections 141–145).
Reservoir calculi are stones in the neobladder (a reservoir for urine usually constructed of ileum/colon).

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
117	**Enucleation**	**Impaired cosmesis** **Poor prosthetic fit** **Orbital hypoplasia**	**SCREENING** **Evaluation by ocularist** Yearly **Evaluation by ophthalmologist** Yearly	**HEALTH LINKS** **Eye Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Psychological consultation in patients with emotional difficulties related to cosmetic and visual impairment. Vocational rehabilitation referral as clinically indicated. **SYSTEM = Ocular** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at enucleation
- Cancer/Treatment factors: Combination with radiation

References

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Kaste SC, Chen G, Fontanesi J, et al: Orbital development in long-term survivors of retinoblastoma. J Clin Oncol 15:1183-9, 1997

Shildkrot Y, Kirzhner M, Haik BG, et al: The effect of cancer therapies on pediatric anophthalmic sockets. Ophthalmology 118:2480-6, 2011

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
118 (female)	**Hysterectomy**	**Pelvic floor dysfunction** **Urinary incontinence** **Sexual dysfunction**	**HISTORY** **Psychosocial assessment** **Urinary leakage** **Abdominal pain** **Dyspareunia** Yearly	**HEALTH LINKS** **Female Health Issues** **COUNSELING** Potential for biologic parenthood using gestational surrogate. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Reproductive endocrinology consultation for patients wishing to pursue pregnancy via gestational surrogate. Female pelvic medicine and reconstructive surgery consultation for patients with urinary complaints after hysterectomy. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

For patients who also underwent oophorectomy, see also: sections 135-136 (unilateral oophorectomy) or section 137 (bilateral oophorectomy).
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Pelvic radiation

References

Benedetti-Panici P, Zullo MA, Plotti F, et al: Long-term bladder function in patients with locally advanced cervical carcinoma treated with neoadjuvant chemotherapy and type 3-4 radical hysterectomy. Cancer 100:2110-7, 2004
Jensen PT, Groenvold M, Klee MC, et al: Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study. Cancer 100:97-106, 2004
Laterza RM, Sievert KD, de Ridder D, et al: Bladder function after radical hysterectomy for cervical cancer. Neurourol Urodyn 34:309-15, 2015
Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013
Skjeldestad FE, Hagen B: Long-term consequences of gynecological cancer treatment on urinary incontinence: a population-based cross-sectional study. Acta Obstet Gynecol Scand 87:469-75, 2008

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
119	**Laparotomy**	**Adhesions** **Bowel obstruction**	**HISTORY** **Abdominal pain** **Distention** **Vomiting** **Constipation** Yearly **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** Yearly	**HEALTH LINKS** **Gastrointestinal Health** **POTENTIAL 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combined with radiation

References

Jockovich M, Mendenhall NP, Sombeck MD, et al: Long-term complications of laparotomy in Hodgkin's disease. Ann Surg 219:615-21; discussion 621-4, 1994

Madenci AL, Fisher S, Diller LR, et al: Intestinal obstruction in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 33:2893-900, 2015

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

Ritchey ML, Shamberger RC, Haase G, et al: Surgical complications after primary nephrectomy for Wilms' tumor: report from the National Wilms' Tumor Study Group. J Am Coll Surg 192:63-8; quiz 146, 2001

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
120	**Limb sparing procedure**	**Complications related to limb sparing procedure** Functional and activity limitations Contractures Chronic infection Chronic pain Limb length discrepancy Increased energy expenditure Fibrosis Prosthetic malfunction (loosening, non-union, fracture) requiring revision, replacement or amputation Impaired quality of life Complications with pregnancy/ delivery (in female patients with internal hemipelvectomy)	**HISTORY** **Functional and activity limitations** Yearly **PHYSICAL** **Residual limb integrity** Yearly **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** Potential need to discuss antibiotic prophylaxis prior to dental and invasive procedures with their treating dentist/orthopedic surgeon. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** 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. Psychological consultation as needed to assist with emotional difficulties related to body image, marriage, pregnancy, parenting, employment, insurance, depression or sexual health. Vocational counseling/training to identify vocations that will not produce/ exacerbate functional limitations. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at surgery, being skeletally immature, rapid growth spurt
- Cancer/Treatment factors: Tibial endoprosthesis, use of biologic material (allograft or autograft) for reconstruction, radiation to extremity
- Pre-morbid/Co-morbid medical conditions: Obesity, endoprosthetic infection, history of poor healing, infection of reconstruction
- 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)

References

American Academy of Orthopedic Surgeons, American Dental Association: Prevention of orthopaedic implant infection in patients undergoing dental procedures. Rosemont, IL, American Academy of Orthopedic Surgeons, 2012
Eiser C, Darlington AS, Stride CB, et al: Quality of life implications as a consequence of surgery: limb salvage, primary and secondary amputation. Sarcoma 5:189-95, 2001
Henderson ER, Pepper AM, Marulanda G, et al: Outcome of lower-limb preservation with an expandable endoprosthesis after bone tumor resection in children. J Bone Joint Surg Am 94:537-47, 2012
Nagarajan R, Mogil R, Neglia JP, et al: Self-reported global function among adult survivors of childhood lower-extremity bone tumors: a report from the Childhood Cancer Survivor Study (CCSS). J Cancer Surviv 3:59-65, 2009
Nagarajan R, Neglia JP, Clohisy DR, et al: Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? J Clin Oncol 20:4493-501, 2002
Ottaviani G, Robert RS, Huh WW, et al: Socioоccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: limb salvage versus amputation. Cancer 119:3727-36, 2013
Shehadeh A, Noveau J, Malawer M, et al: Late complications and survival of endoprosthetic reconstruction after resection of bone tumors. Clin Orthop Relat Res 468:2885-95, 2010
Stokke J, Sung L, Gupta A, et al: Systematic review and meta-analysis of objective and subjective quality of life among pediatric, adolescent, and young adult bone tumor survivors. Pediatr Blood Cancer 62:1616-29, 2015
Tunn PU, Schmidt-Peter P, Pomraenke D, et al: Osteosarcoma in children: long-term functional analysis. Clin Orthop Relat Res:212-7, 2004
Wright EH, Gwilym S, Gibbons CL, et al: Functional and oncological outcomes after limb-salvage surgery for primary sarcomas of the upper limb. J Plast Reconstr Aesthet Surg 61:382-7, 2008

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
121 (male)	**Nephrectomy**	**Hydrocele** **Renal toxicity** Proteinuria Hyperfiltration Renal insufficiency Hypertension	**PHYSICAL** **Height** **Weight** **BMI** **Blood pressure** Yearly **Testicular exam to evaluate for hydrocele** Yearly **SCREENING** **BUN** **Na, K, Cl, CO_2, Ca, Mg, PO_4** Baseline at entry into long-term follow-up, repeat as clinically indicated **Urine dipstick for protein** **Creatinine with calculated eGFR*** Yearly *eGFR Calculator available at: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators	**HEALTH LINKS** **Single Kidney Health** **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 lap belts around hips, not waist). Consideration should be given to survivor health status, current kidney health (position, size, function), and acceptability of unlikely risk of sports-related renal injury to the survivor and/or family. Use NSAIDs with caution. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Bilateral Wilms tumor, combination with other nephrotoxic therapy (e.g., cisplatin, carboplatin, ifosfamide, aminoglycosides, amphotericin, immunosuppressants, methotrexate, radiation impacting the kidneys)
- Pre-morbid/Co-morbid medical conditions: Denys-Drash syndrome, WAGR syndrome, hypospadias, cryptorchidism

References

Bailey S, Roberts A, Brock C, et al: Nephrotoxicity in survivors of Wilms' tumours in the North of England. Br J Cancer 87:1092-8, 2002

Breslow NE, Collins AJ, Ritchey ML, et al: End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 174:1972-5, 2005

Cozzi DA, Ceccanti S, Frediani S, et al: Renal function adaptation up to the fifth decade after treatment of children with unilateral renal tumor: a cross-sectional and longitudinal study. Pediatr Blood Cancer 60:1534-8, 2013

Section 121 References (cont)

Finklestein JZ, Norkool P, Green DM, et al: Diastolic hypertension in Wilms' tumor survivors: a late effect of treatment? A report from the National Wilms' Tumor Study Group. Am J Clin Oncol 16:201-5, 1993
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Grinsell MM, Showalter S, Gordon KA, et al: Single kidney and sports participation: perception versus reality. Pediatrics 118:1019-27, 2006
Hubertus J, Gunther B, Becker K, et al: Development of hypertension is less frequent after bilateral nephron sparing surgery for bilateral Wilms tumor in a long-term survey. J Urol 193:262-6, 2015
Johnson B, Christensen C, Dirusso S, et al: A need for reevaluation of sports participation recommendations for children with a solitary kidney. J Urol 174:686-9; discussion 689, 2005
Mitus A, Tefft M, Fellers FX: Long-term follow-up of renal functions of 108 children who underwent nephrectomy for malignant disease. Pediatrics 44:912-21, 1969
Paulino AC, Wen BC, Brown CK, et al: Late effects in children treated with radiation therapy for Wilms' tumor. Int J Radiat Oncol Biol Phys 46:1239-46, 2000
Ritchey ML, Green DM, Thomas PR, et al: Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 26:75-80, 1996
Sharp DS, Ross JH, Kay R: Attitudes of pediatric urologists regarding sports participation by children with a solitary kidney. J Urol 168:1811-4; discussion 1815, 2002
Srinivas M, Agarwala S, Padhy AK, et al: Somatic growth and renal function after unilateral nephrectomy for Wilms' tumor. Pediatr Surg Int 14:185-8, 1998

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
122 (female)	**Nephrectomy**	**Renal toxicity** Proteinuria Hyperfiltration Renal insufficiency Hypertension	**PHYSICAL** **Height** **Weight** **BMI** **Blood pressure** Yearly **SCREENING** **BUN** **Na, K, Cl, CO_2, Ca, Mg, PO_4** Baseline at entry into long-term follow-up, repeat as clinically indicated **Urine dipstick for protein** **Creatinine with calculated eGFR*** Yearly *eGFR Calculator available at: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators	**HEALTH LINKS** **Single Kidney Health** **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 lap belts around hips, not waist). Consideration should be given to survivor health status, current kidney health (position, size, function), and acceptability of unlikely risk of sports-related renal injury to the survivor and/or family. Use NSAIDs with caution. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

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.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Bilateral Wilms tumor, combination with other nephrotoxic therapy (e.g., cisplatin, carboplatin, ifosfamide, aminoglycosides, amphotericin, immunosuppressants, methotrexate, radiation impacting the kidneys)
- Pre-morbid/Co-morbid medical conditions: Denys-Drash syndrome, WAGR syndrome

References

Bailey S, Roberts A, Brock C, et al: Nephrotoxicity in survivors of Wilms' tumours in the North of England. Br J Cancer 87:1092-8, 2002

Breslow NE, Collins AJ, Ritchey ML, et al: End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 174:1972-5, 2005

Cozzi DA, Ceccanti S, Frediani S, et al: Renal function adaptation up to the fifth decade after treatment of children with unilateral renal tumor: a cross-sectional and longitudinal study. Pediatr Blood Cancer 60:1534-8, 2013

Finklestein JZ, Norkool P, Green DM, et al: Diastolic hypertension in Wilms' tumor survivors: a late effect of treatment? A report from the National Wilms' Tumor Study Group. Am J Clin Oncol 16:201-5, 1993

Grinsell MM, Showalter S, Gordon KA, et al: Single kidney and sports participation: perception versus reality. Pediatrics 118:1019-27, 2006

Section 122 References (cont)

Hubertus J, Gunther B, Becker K, et al: Development of hypertension is less frequent after bilateral nephron sparing surgery for bilateral Wilms tumor in a long-term survey. J Urol 193:262-6, 2015
Johnson B, Christensen C, Dirusso S, et al: A need for reevaluation of sports participation recommendations for children with a solitary kidney. J Urol 174:686-9; discussion 689, 2005
Mitus A, Tefft M, Fellers FX: Long-term follow-up of renal functions of 108 children who underwent nephrectomy for malignant disease. Pediatrics 44:912-21, 1969
Paulino AC, Wen BC, Brown CK, et al: Late effects in children treated with radiation therapy for Wilms' tumor. Int J Radiat Oncol Biol Phys 46:1239-46, 2000
Ritchey ML, Green DM, Thomas PR, et al: Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 26:75-80, 1996
Sharp DS, Ross JH, Kay R: Attitudes of pediatric urologists regarding sports participation by children with a solitary kidney. J Urol 168:1811-4; discussion 1815, 2002
Srinivas M, Agarwala S, Padhy AK, et al: Somatic growth and renal function after unilateral nephrectomy for Wilms' tumor. Pediatr Surg Int 14:185-8, 1998

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
123	**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	**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** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Referral to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Referral to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

Additional Information

Formal neuropsychological evaluation includes tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning.

Neurocognitive deficits vary with extent of surgery, postoperative complications and location. Neurosensory deficits (i.e., vision, hearing) due to tumor or its therapy may complicate neurocognitive outcomes. Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New and progressive deficits may emerge over time.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger age at treatment, especially age <3 years, family history of learning or attention problems
- Cancer/Treatment factors: Primary CNS tumor, extent and location of resection, longer elapsed time since therapy, combination with methotrexate (IT, IO, high-dose IV), cytarabine (high-dose IV), radiation dose ≥24 Gy to whole brain, radiation dose ≥40 Gy to local fields, TBI, cranial radiation
- Pre-morbid/Co-morbid medical conditions: Pre-morbid learning or attention problems, hydrocephalus/history of shunt placement, seizures, posterior fossa syndrome, CNS infection

References

Aarsen FK, Paquier PF, Arts WF, et al: Cognitive deficits and predictors 3 years after diagnosis of a pilocytic astrocytoma in childhood. J Clin Oncol 27:3526-32, 2009

Armstrong GT, Conklin HM, Huang S, et al: Survival and long-term health and cognitive outcomes after low-grade glioma. Neuro Oncol 13:223-34, 2011

Carpentieri SC, Waber DP, Pomeroy SL, et al: Neuropsychological functioning after surgery in children treated for brain tumor. Neurosurgery 52:1348-56; discussion 1356-7, 2003

Catsman-Berrevoets CE, Aarsen FK: The spectrum of neurobehavioural deficits in the posterior fossa syndrome in children after cerebellar tumour surgery. Cortex 46:933-46, 2010

Mulhern RK, Merchant TE, Gajjar A, et al: Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 5:399-408, 2004

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

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
124	**Neurosurgery-Brain**	**Motor and/or sensory deficits** Paralysis Movement disorders Ataxia Eye problems (ocular nerve palsy, gaze paresis, nystagmus, papilledema, optic atrophy)	**HISTORY** **Paralysis** **Movement problems** **Ataxia** **Eye problems** Yearly **PHYSICAL** **Neurologic exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluation by neurologist for persistent neurologic symptoms. Speech, physical, and occupational therapy in patients with persistent deficits. Evaluation by physiatrist/rehabilitation medicine specialist in patients with motor dysfunction. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Primary CNS tumor, skull base tumors, optic pathway tumor, hypothalamic tumor, supra-sellar tumor (eye problems)
- Pre-morbid/Co-morbid medical conditions: Hydrocephalus

References

Elliott RE, Hsieh K, Hochm T, et al: Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. J Neurosurg Pediatr 5:30-48, 2010

Jane JA, Jr., Prevedello DM, Alden TD, et al: The transsphenoidal resection of pediatric craniopharyngiomas: a case series. J Neurosurg Pediatr 5:49-60, 2010

Kotecha RS, Jacoby P, Cole CH, et al: Morbidity in survivors of child and adolescent meningioma. Cancer 119:4350-7, 2013

Lo AC, Howard AF, Nichol A, et al: Long-term outcomes and complications in patients with craniopharyngioma: the British Columbia Cancer Agency experience. Int J Radiat Oncol Biol Phys 88:1011-8, 2014

Pietila S, Korpela R, Lenko HL, et al: Neurological outcome of childhood brain tumor survivors. J Neurooncol 108:153-61, 2012

Robertson PL, Muraszko KM, Holmes EJ, et al: Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg 105:444-51, 2006

Sonderkaer S, Schmiegelow M, Carstensen H, et al: Long-term neurological outcome of childhood brain tumors treated by surgery only. J Clin Oncol 21:1347-51, 2003

Ullrich NJ, Pomeroy SL, Kapur K, et al: Incidence, risk factors, and longitudinal outcome of seizures in long-term survivors of pediatric brain tumors. Epilepsia 56:1599-604, 2015

Wibroe M, Cappelen J, Castor C, et al: Cerebellar mutism syndrome in children with brain tumours of the posterior fossa. BMC Cancer 17:439, 2017

Yano S, Kudo M, Hide T, et al: Quality of life and clinical features of long-term survivors surgically treated for pediatric craniopharyngioma. World Neurosurg 85:153-62, 2016

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
125	**Neurosurgery-Brain**	**Seizures**	**HISTORY** **Seizures** Yearly **PHYSICAL** **Neurologic exam** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluation by neurologist as clinically indicated. **SYSTEM = CNS** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Primary CNS tumor, methotrexate (IV, IT, IO)

References

Kotecha RS, Jacoby P, Cole CH, et al: Morbidity in survivors of child and adolescent meningioma. Cancer 119:4350-7, 2013

Lo AC, Howard AF, Nichol A, et al: Long-term outcomes and complications in patients with craniopharyngioma: the British Columbia Cancer Agency experience. Int J Radiat Oncol Biol Phys 88:1011-8, 2014

Pietila S, Korpela R, Lenko HL, et al: Neurological outcome of childhood brain tumor survivors. J Neurooncol 108:153-61, 2012

Sonderkaer S, Schmiegelow M, Carstensen H, et al: Long-term neurological outcome of childhood brain tumors treated by surgery only. J Clin Oncol 21:1347-51, 2003

Ullrich NJ, Pomeroy SL, Kapur K, et al: Incidence, risk factors, and longitudinal outcome of seizures in long-term survivors of pediatric brain tumors. Epilepsia 56:1599-604, 2015

Yano S, Kudo M, Hide T, et al: Quality of life and clinical features of long-term survivors surgically treated for pediatric craniopharyngioma. World Neurosurg 85:153-62, 2016

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
126	**Neurosurgery-Brain**	**Hydrocephalus** **Shunt malfunction**	**HISTORY** **Headaches** **Nausea/Vomiting** **Ataxia** **Irritability** **Drowsiness** Yearly **PHYSICAL** **Neurologic exam** Yearly **SCREENING** **Abdominal x-ray** After pubertal growth spurt for patients with shunts to assure distal shunt tubing in peritoneum	**COUNSELING** Educate patient/family regarding potential symptoms of shunt malfunction. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluation by neurosurgeon for patients with shunts. Per the American Academy of Pediatric Dentistry endocarditis prophylaxis guidelines, antibiotic prophylaxis prior to dental work is indicated for survivors with V-A and V-V shunts. Antibiotic prophylaxis prior to dental work is not indicated for survivors with V-P shunts. **SYSTEM = CNS** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Primary CNS tumor

References

American Academy of Pediatric Dentistry Clinical Affairs Committee, American Academy of Pediatric Dentistry Council on Clinical Affairs: Guideline on antibiotic prophylaxis for dental patients at risk for infection. Chicago, IL, American Academy of Pediatric Dentistry, 2011

Kotecha RS, Jacoby P, Cole CH, et al: Morbidity in survivors of child and adolescent meningioma. Cancer 119:4350-7, 2013

Lo AC, Howard AF, Nichol A, et al: Long-term outcomes and complications in patients with craniopharyngioma: the British Columbia Cancer Agency experience. Int J Radiat Oncol Biol Phys 88:1011-8, 2014

Pietila S, Korpela R, Lenko HL, et al: Neurological outcome of childhood brain tumor survivors. J Neurooncol 108:153-61, 2012

Ullrich NJ, Pomeroy SL, Kapur K, et al: Incidence, risk factors, and longitudinal outcome of seizures in long-term survivors of pediatric brain tumors. Epilepsia 56:1599-604, 2015

Yano S, Kudo M, Hide T, et al: Quality of life and clinical features of long-term survivors surgically treated for pediatric craniopharyngioma. World Neurosurg 85:153-62, 2016

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
127	**Neurosurgery-Brain** (applies only to neurosurgery with potential to affect the hypothalamic-pituitary axis)	**Overweight** **Obesity**	**PHYSICAL** **Height** **Weight** **BMI** Yearly	**HEALTH LINKS** **Diet and Physical Activity** **Cardiovascular Risk Factors** **COUNSELING** Obesity-related health risks. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluate for central endocrinopathies, including growth hormone deficiency, central hypothyroidism, central adrenal insufficiency, precocious puberty, and gonadotropin deficiency. Refer to endocrine for management of hormonal dysfunction. Evaluate for other co-morbid conditions, including dyslipidemia, hypertension, and impaired glucose metabolism. Refer to dietician for weight management. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

Additional Information

Definition of Overweight: Age 2–20 years BMI for age ≥85th to <95th percentile. Age ≥21 years BMI ≥25–29.9.
Definition of 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.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Craniopharyngioma, tumor extension to hypothalamus, surgery in supra-sellar region
- Pre-morbid/Co-morbid medical conditions: Pre-treatment obesity

References

De Vile CJ, Grant DB, Kendall BE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? J Neurosurg 85:73-81, 1996
Elliott RE, Hsieh K, Hochm T, et al: Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. J Neurosurg Pediatr 5:30-48, 2010
Elliott RE, Wisoff JH: Surgical management of giant pediatric craniopharyngiomas. J Neurosurg Pediatr 6:403-16, 2010
Jane JA, Jr., Prevedello DM, Alden TD, et al: The transsphenoidal resection of pediatric craniopharyngiomas: a case series. J Neurosurg Pediatr 5:49-60, 2010
Lustig RH, Post SR, Srivannaboon K, et al: Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 88:611-6, 2003
Muller HL, Emser A, Faldum A, et al: Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. J Clin Endocrinol Metab 89:3298-305, 2004
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Sainte-Rose C, Puget S, Wray A, et al: Craniopharyngioma: the pendulum of surgical management. Childs Nerv Syst 21:691-5, 2005

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
128	**Neurosurgery-Brain** (applies only to neurosurgery with potential to affect the hypothalamic-pituitary axis)	**Diabetes insipidus**	**HISTORY** **Assessment of excessive thirst/polyuria** Yearly	**HEALTH LINKS** **Hypopituitarism** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Na, K, Cl, CO_2, serum osmolality, and urine osmolality as clinically indicated if history consistent with excessive thirst and/or polyuria. 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Craniopharyngioma, extension of tumor into hypothalamus, surgery in supra-sellar region, reoperation for recurrent tumor

References

Elliott RE, Hsieh K, Hochm T, et al: Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. J Neurosurg Pediatr 5:30-48, 2010

Jane JA, Jr., Prevedello DM, Alden TD, et al: The transsphenoidal resection of pediatric craniopharyngiomas: a case series. J Neurosurg Pediatr 5:49-60, 2010

Lo AC, Howard AF, Nichol A, et al: Long-term outcomes and complications in patients with craniopharyngioma: the British Columbia Cancer Agency experience. Int J Radiat Oncol Biol Phys 88:1011-8, 2014

Olsson DS, Andersson E, Bryngelsson IL, et al: Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab 100:467-74, 2015

Puget S, Garnett M, Wray A, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. J Neurosurg 106:3-12, 2007

Sainte-Rose C, Puget S, Wray A, et al: Craniopharyngioma: the pendulum of surgical management. Childs Nerv Syst 21:691-5, 2005

Vinchon M, Baroncini M, Leblond P, et al: Morbidity and tumor-related mortality among adult survivors of pediatric brain tumors: a review. Childs Nerv Syst 27:697-704, 2011

Yano S, Kudo M, Hide T, et al: Quality of life and clinical features of long-term survivors surgically treated for pediatric craniopharyngioma. World Neurosurg 85:153-62, 2016

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
129	**Neurosurgery-Spinal cord**	**Neurogenic bladder** **Urinary incontinence**	**HISTORY** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**HEALTH LINKS** **Neurogenic Bladder** **COUNSELING** Importance of adequate fluid intake, regular voiding, and seeking medical attention for symptoms of voiding dysfunction or urinary tract infection. Importance of compliance with recommended bladder catheterization regimen. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections. **SYSTEM = CNS** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to or compressing spinal cord or cauda equina, injury above the level of the sacrum, radiation dose ≥45 Gy to lumbar and/or sacral spine and/or cauda equina, especially radiation dose ≥50 Gy

References

Fowler CJ, Sakakibara R, Frohman EM, et al: Neurologic bladder, bowel and sexual dysfunction, in Munsat TL (ed): World Federation of Neurology Seminars in Clinical Neurology. The Netherlands, Elsevier Science B.V., 2001

Hoover M, Bowman LC, Crawford SE, et al: Long-term outcome of patients with intraspinal neuroblastoma. Med Pediatr Oncol 32:353-9, 1999

McGirt MJ, Chaichana KL, Atiba A, et al: Resection of intramedullary spinal cord tumors in children: assessment of long-term motor and sensory deficits. J Neurosurg Pediatr 1:63-7, 2008

Poretti A, Zehnder D, Boltshauser E, et al: Long-term complications and quality of life in children with intraspinal tumors. Pediatr Blood Cancer 50:844-8, 2008

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
130	**Neurosurgery-Spinal cord**	**Neurogenic bowel** **Fecal incontinence**	**HISTORY** **Chronic constipation** **Fecal soiling** Yearly **PHYSICAL** **Rectal exam** As clinically indicated	**COUNSELING** Benefits of adherence to bowel regimen, including adequate hydration, fiber, laxatives/enemas as clinically indicated. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** GI consultation to establish bowel regimen for patients with chronic impaction or fecal soiling. **SYSTEM = CNS** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to or compressing spinal cord or cauda equina, injury above the level of the sacrum, radiation dose ≥50 Gy to bladder, pelvis, or spine

References

Fowler CJ, Sakakibara R, Frohman EM, et al: Neurologic bladder, bowel and sexual dysfunction, in Munsat TL (ed): World Federation of Neurology Seminars in Clinical Neurology. The Netherlands, Elsevier Science B.V., 2001

Hoover M, Bowman LC, Crawford SE, et al: Long-term outcome of patients with intraspinal neuroblastoma. Med Pediatr Oncol 32:353-9, 1999

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
131 (male)	**Neurosurgery-Spinal cord**	**Psychosexual dysfunction** Erectile dysfunction Ejaculatory dysfunction	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly	**HEALTH LINKS** **Male Health Issues** **RESOURCES** www.urologychannel.com **COUNSELING** Use of assisted reproductive technology for sperm retrieval. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urologic consultation in patients with positive history. **SYSTEM = Reproductive (Male)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to or compressing spinal cord or cauda equina, radiation to bladder, pelvis, or spine, radiation dose ≥55 Gy to penile bulb in adult, ≥45 Gy in prepubertal child
- Pre-morbid/Co-morbid medical conditions: Testosterone deficiency/insufficiency, injury above the level of the sacrum

References

Albright TH, Grabel Z, DePasse JM, et al: Sexual and reproductive function in spinal cord injury and spinal surgery patients. Orthop Rev (Pavia) 7:5842, 2015

Fowler CJ, Sakakibara R, Frohman EM, et al: Neurologic bladder, bowel and sexual dysfunction, in Munsat TL (ed): World Federation of Neurology Seminars in Clinical Neurology. The Netherlands, Elsevier Science B.V., 2001

Kenney LB, Cohen LE, Shnorhavorian M, et al: Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol 30:3408-16, 2012

Kubota M, Yagi M, Kanada S, et al: Long-term follow-up status of patients with neuroblastoma after undergoing either aggressive surgery or chemotherapy--a single institutional study. J Pediatr Surg 39:1328-32, 2004

Ritenour CW, Seidel KD, Leisenring W, et al: Erectile dysfunction in male survivors of childhood cancer-a report from the Childhood Cancer Survivor Study. J Sex Med 13:945-54, 2016

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
132 (female)	**Neurosurgery-Spinal cord**	**Psychosexual dysfunction**	**HISTORY** **Altered or diminished sensation, loss of sensation** **Dyspareunia** **Medication use** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gynecologic consultation in patients with positive history. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to or compressing spinal cord or cauda equina, radiation to bladder, pelvis, or spine
- Pre-morbid/Co-morbid medical conditions: Hypogonadism, vaginal fibrosis/stenosis, chronic GVHD, injury above the level of the sacrum

References

Fowler CJ, Sakakibara R, Frohman EM, et al: Neurologic bladder, bowel and sexual dysfunction, in Munsat TL (ed): World Federation of Neurology Seminars in Clinical Neurology. The Netherlands, Elsevier Science B.V., 2001

Hoover M, Bowman LC, Crawford SE, et al: Long-term outcome of patients with intraspinal neuroblastoma. Med Pediatr Oncol 32:353-9, 1999

Korse NS, Nicolai MP, Both S, et al: Discussing sexual health in spinal care. Eur Spine J 25:766-73, 2016

Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013

Piotrowski K, Snell L: Health needs of women with disabilities across the lifespan. J Obstet Gynecol Neonatal Nurs 36:79-87, 2007

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
133	**Neurosurgery-Spinal cord** Laminectomy Laminoplasty	**Scoliosis/Kyphosis**	**PHYSICAL** **Exam of back/spine** Yearly until growth completed, may need more frequent assessment during puberty or if curve detected	**HEALTH LINKS** **Scoliosis and Kyphosis** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on physical and/or radiographic exam. **SYSTEM = Musculoskeletal** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Young age (deformity can still develop even if skeletally mature at time of surgery)
- Cancer/Treatment factors: Radiation to the spine, increasing number of laminae removed, especially > 3 laminae removed, facetectomy, laminectomy (versus laminotomy), laminectomy without fusion, increasing number of resections, surgery of thoracolumbar junction
- Pre-morbid/Co-morbid medical conditions: Preoperative deformity

References

Anakwenze OA, Auerbach JD, Buck DW, et al: The role of concurrent fusion to prevent spinal deformity after intramedullary spinal cord tumor excision in children. J Pediatr Orthop 31:475-9, 2011
de Jonge T, Slullitel H, Dubousset J, et al: Late-onset spinal deformities in children treated by laminectomy and radiation therapy for malignant tumours. Eur Spine J 14:765-71, 2005
Gawade PL, Hudson MM, Kaste SC, et al: A systematic review of selected musculoskeletal late effects in survivors of childhood cancer. Curr Pediatr Rev 10:249-62, 2014
Laverdiere C, Liu Q, Yasui Y, et al: Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 101:1131-40, 2009
McGirt MJ, Chaichana KL, Atiba A, et al: Incidence of spinal deformity after resection of intramedullary spinal cord tumors in children who underwent laminectomy compared with laminoplasty. J Neurosurg Pediatr 1:57-62, 2008
Papagelopoulos PJ, Peterson HA, Ebersold MJ, et al: Spinal column deformity and instability after lumbar or thoracolumbar laminectomy for intraspinal tumors in children and young adults. Spine 22:442-451, 1997
Paulino AC, Fowler BZ: Risk factors for scoliosis in children with neuroblastoma. Int J Radiat Oncol Biol Phys 61:865-869, 2005
Yao KC, Mcgirt MJ, Chaichana KL, et al: Risk factors for progressive spinal deformity following resection of intramedullary spinal cord tumors in children: an analysis of 161 consecutive cases. J Neurosurg 107:463-468, 2007

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
134 (female)	**Oophoropexy**	**Oophoropexy-related complications** Inability to conceive despite normal ovarian function Dyspareunia Symptomatic ovarian cysts Bowel obstruction Pelvic adhesions	**HISTORY** **Inability to conceive** **Dyspareunia** **Abdominal pain** **Pelvic pain** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gynecologic consultation for patients with positive history. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Ovarian radiation, tubo-ovarian dislocation (especially with lateral ovarian transposition)

References

Chambers SK, Chambers JT, Kier R, et al: Sequelae of lateral ovarian transposition in irradiated cervical cancer patients. Int J Radiat Oncol Biol Phys 20:1305-8, 1991

Damewood MD, Hesla HS, Lowen M, et al: Induction of ovulation and pregnancy following lateral oophoropexy for Hodgkin's disease. Int J Gynaecol Obstet 33:369-71, 1990

Hadar H, Loven D, Herskovitz P, et al: An evaluation of lateral and medial transposition of the ovaries out of radiation fields. Cancer 74:774-9, 1994

Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013

Terenziani M, Piva L, Meazza C, et al: Oophoropexy: a relevant role in preservation of ovarian function after pelvic irradiation. Fertil Steril 91:935 e15-6, 2009

Thibaud E, Ramirez M, Brauner R, et al: Preservation of ovarian function by ovarian transposition performed before pelvic irradiation during childhood. J Pediatr 121:880-4, 1992

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
135 (female)	**Oophorectomy** unilateral	**Ovarian hormone deficiencies** Delayed puberty Arrested puberty Premature ovarian insufficiency/premature menopause	**HISTORY** **Onset and tempo of puberty** **Menstrual history** **Sexual function (vaginal dryness, libido)** **Menopausal symptoms** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Female Health Issues** **COUNSELING** Adverse impact of ovarian hormone deficiencies on growth, bone mineralization, cardiovascular disease and sexual dysfunction. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH and estradiol and/or endocrine/gynecology referral for patients with: - no signs of puberty at age 13 - failure of pubertal progression - abnormal menstrual patterns or menopausal symptoms. - ovarian hormone deficiency/insufficiency to weigh risks and benefits of hormonal replacement therapy Bone density evaluation in patients with ovarian hormone deficiencies. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Combination with pelvic radiation, TBI, or alkylating agents
- Health behaviors: Smoking

References

Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013

Thomas-Teinturier C, El Fayech C, Oberlin O, et al: Age at menopause and its influencing factors in a cohort of survivors of childhood cancer: earlier but rarely premature. Hum Reprod 28:488-95, 2013

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
136 (female)	**Oophorectomy** unilateral	**Reduced ovarian follicular pool** Infertility	**HISTORY** **Menstrual and pregnancy history** **Hormonal therapy** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly	**HEALTH LINKS** **Female Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Potential for shorter period of fertility (associated with increased risk of early menopause) in family planning. Need for contraception. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** FSH and estradiol for patients with menstrual cycle dysfunction suggestive of premature ovarian insufficiency or those who desire information about potential for future fertility. AMH (anti-Mullerian hormone) to assess for diminished ovarian reserve. Reproductive endocrinology referral for antral follicle count, ovarian reserve evaluation and consultation regarding assisted reproductive technologies in at-risk patients who desire information about potential fertility and interventions to preserve future fertility. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

AMH may be low in the presence of normal FSH.
FSH is lowered and AMH may be lowered by concurrent hormonal contraceptive use.
AMH should be interpreted relative to age-specific reference ranges.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with pelvic radiation, TBI, or alkylating agents
- Health behaviors: Smoking

References

Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013

Thomas-Teinturier C, El Fayech C, Oberlin O, et al: Age at menopause and its influencing factors in a cohort of survivors of childhood cancer: earlier but rarely premature. Hum Reprod 28:488-95, 2013

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
137 (female)	**Oophorectomy** bilateral	**Ovarian hormone deficiencies** Absence of puberty **Loss of ovarian follicular pool** Infertility	**SCREENING** **Endocrinologic or gynecologic 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 Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Benefits of hormone replacement therapy in promoting pubertal progression, bone and cardiovascular health. Counsel women regarding pregnancy potential with donor eggs (if uterus is intact). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Reproductive endocrinology referral regarding assisted reproductive technologies. Bone density evaluation. **SYSTEM = Reproductive (Female)** **SCORE = 1**

References

Candy B, Jones L, Vickerstaff V, et al: Interventions for sexual dysfunction following treatments for cancer in women. Cochrane Database of Systematic Reviews, 2016

Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013

Rivera CM, Grossardt BR, Rhodes DJ, et al: Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 16:15-23, 2009

Schover LR: Sexuality and fertility after cancer. Hematology Am Soc Hematol Educ Program:523-7, 2005

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
138 (male)	**Orchiectomy** unilateral partial	**Testicular hormonal dysfunction** Testosterone deficiency/ insufficiency Delayed/arrested puberty	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly **Monitor growth until mature** Yearly	**HEALTH LINKS** **Male Health Issues** **COUNSELING** Wear athletic supporter with protective cup during athletic activities. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Measurement of early morning testosterone concentration and/or endocrinology referral for patients with: - no signs of puberty at age 14 - failure of pubertal progression - 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 percentile on growth chart - testosterone deficiency/insufficiency to weigh risks and benefits of hormonal replacement therapy Periodic re-evaluation of testosterone in males with low normal testosterone as they age or if they become symptomatic. Bone density evaluation in androgen deficient patients. Surgical placement of testicular prosthesis and ongoing monitoring for surgical complications after prosthesis placement. Psychology referral (because orchiectomy can be associated with psychological distress related to altered body image). **SYSTEM = Reproductive (Male)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents), aging
- Cancer/Treatment factors: Testicular cancer, unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents, higher cumulative dose platinum chemotherapy, infradiaphragmatic radiation
- Pre-morbid/Co-morbid medical conditions: Obesity, ejaculatory dysfunction, history of sexually transmitted infections
- Health behaviors: Tobacco/marijuana use

Section 138 References

Bandak M, Aksglaede L, Juul A, et al: The pituitary-Leydig cell axis before and after orchiectomy in patients with stage I testicular cancer. Eur J Cancer 47:2585-2591, 2011

Eberhard J, Stahl O, Cwikiel M, et al: Risk factors for post-treatment hypogonadism in testicular cancer patients. Eur J Endocrinol 158:561-570, 2008

Huddart RA, Norman A, Moynihan C, et al: Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer 93:200-207, 2005

Jacobsen KD, Fossa SD, Bjoro TP, et al: Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. Eur Urol 42:229-237, 2002

Sprauten M, Brydoy M, Haugnes HS, et al: Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. J Clin Oncol 32:571-8, 2014

Woo LL, Ross JH: The role of testis-sparing surgery in children and adolescents with testicular tumors. Urol Oncol 34:76-83, 2016

Yossepowitch O, Aviv D, Wainchwaig L, et al: Testicular prostheses for testis cancer survivors: patient perspectives and predictors of long-term satisfaction. J Urol 186:2249-2252, 2011

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
139 (male)	**Orchiectomy** unilateral partial	**Impaired spermatogenesis** Reduced fertility Oligospermia Azoospermia Infertility	**HISTORY** **Onset and tempo of puberty** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly **PHYSICAL** **Tanner staging until sexually mature** **Testicular volume by Prader orchidometer** Yearly	**HEALTH LINKS** **Male Health Issues** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Wear athletic supporter with protective cup during athletic activities. Need for contraception. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** For sexually mature patients who desire information about potential future fertility: semen analysis (optimal) and/or FSH and inhibin B (alternative if unable or unwilling to provide semen sample). Reproductive endocrinology/urology referral for infertility evaluation and consultation regarding assisted reproductive technologies. Surgical placement of testicular prosthesis and ongoing monitoring for surgical complications after prosthesis placement. Psychology referral (because orchiectomy can be associated with psychological distress related to altered body image). **SYSTEM = Reproductive (Male)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents), aging
- Cancer/Treatment factors: Testicular cancer, unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents, higher cumulative dose platinum chemotherapy, infradiaphragmatic radiation
- Pre-morbid/Co-morbid medical conditions: Obesity, ejaculatory dysfunction, history of sexually transmitted infections
- Health behaviors: Tobacco/marijuana use

References

Eskenazi B, Wyrobek AJ, Sloter E, et al: The association of age and semen quality in healthy men. Hum Reprod 18:447-454, 2003

Green DM, Zhu L, Zhang N, et al: Lack of specificity of plasma concentrations of inhibin B and follicle-stimulating hormone for identification of azoospermic survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 31:1324-8, 2013

Section 139 References (cont)

Huddart RA, Norman A, Moynihan C, et al: Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer 93:200-207, 2005

Jacobsen KD, Fossa SD, Bjoro TP, et al: Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. Eur Urol 42:229-237, 2002

Meistrich ML, Chawla SP, Da Cunha MF, et al: Recovery of sperm production after chemotherapy for osteosarcoma. Cancer 63:2115-23, 1989

Nudell DM, Monoski MM, Lipshultz LI: Common medications and drugs: how they affect male fertility. Urol Clin N Am 29:965-+, 2002

Romerius P, Stahl O, Moell C, et al: High risk of azoospermia in men treated for childhood cancer. Int J Androl 34:69-76, 2011

Sprauten M, Brydoy M, Haugnes HS, et al: Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. J Clin Oncol 32:571-8, 2014

Woo LL, Ross JH: The role of testis-sparing surgery in children and adolescents with testicular tumors. Urol Oncol 34:76-83, 2016

Yossepowitch O, Aviv D, Wainchwaig L, et al: Testicular prostheses for testis cancer survivors: patient perspectives and predictors of long-term satisfaction. J Urol 186:2249-2252, 2011

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
140 (male)	**Orchiectomy** bilateral	**Testosterone deficiency** Absence of puberty **Azoospermia** Infertility	**PHYSICAL** **Exam of testicular prostheses** Yearly **SCREENING** **Endocrinologic consultation for initiation of hormonal replacement therapy** At age 11 or immediately for post-pubertal patients	**HEALTH LINKS** **Male Health Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgical placement of testicular prostheses and ongoing monitoring for surgical complications after prostheses placement. Psychology referral (because orchiectomy can be associated with psychological distress related to altered body image). Bone density evaluation. **SYSTEM = Reproductive (Male)** **SCORE = 1**

References

Herman-Giddens ME, Steffes J, Harris D, et al: Secondary sexual characteristics in boys: data from the pediatric research in office settings network. Pediatrics 130:E1058-E1068, 2012

Jacobsen KD, Fossa SD, Bjoro TP, et al: Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. Eur Urol 42:229-237, 2002

Modh RA, Mulhall JP, Gilbert SM: Sexual dysfunction after cystectomy and urinary diversion. Nat Rev Urol 11:445-53, 2014

Yossepowitch O, Aviv D, Wainchwaig L, et al: Testicular prostheses for testis cancer survivors: patient perspectives and predictors of long-term satisfaction. J Urol 186:2249-2252, 2011

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
141	**Pelvic surgery** **Cystectomy**	**Urinary incontinence** **Urinary tract obstruction**	**HISTORY** **Urinary urgency/frequency** **Urinary incontinence/retention** **Dysuria** **Nocturia** **Abnormal urinary stream** Yearly	**COUNSELING** Importance of adequate fluid intake, regular voiding, and seeking medical attention for symptoms of voiding dysfunction or urinary tract infection. Importance of compliance with recommended bladder catheterization regimen. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections. **SYSTEM = Urinary** **SCORE = 1**

Additional Information

For patients with cystectomy, see also section 116.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Pre-morbid/Co-morbid medical conditions: Tumor adjacent to or compressing spinal cord or cauda equina, 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

References

Derikx JPM, De Backer A, van de Schoot L, et al: Long-term functional sequelae of sacrococcygeal teratoma: a national study in the Netherlands. J Pediatr Surg 42:1122-1126, 2007

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 21:115-22, 1999

Heyn R, Raney RB, Jr., Hays DM, et al: Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. J Clin Oncol 10:614-23, 1992

Koyle MA, Hatch DA, Furness PD, et al: Long-term urological complications in survivors younger than 15 months of advanced stage abdominal neuroblastoma. J Urol 166:1455-1458, 2001

Kremer ME, Derikx JP, van Baren R, et al: Patient-reported defecation and micturition problems among adults treated for sacrococcygeal teratoma during childhood--the need for new surveillance strategies. Pediatr Blood Cancer 63:690-4, 2016

Ozkan KU, Bauer SB, Khoshbin S, et al: Neurogenic bladder dysfunction after sacrococcygeal teratoma resection. J Urol 175:292-296, 2006

Raney B, Anderson J, Jenney M, et al: Late effects in 164 patients with rhabdomyosarcoma of the bladder/prostate region: A report from the international workshop. J Urol 176:2190-2194, 2006

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
142	**Pelvic surgery** **Cystectomy**	**Fecal incontinence**	**HISTORY** **Chronic constipation** **Fecal soiling** Yearly **PHYSICAL** **Rectal exam** As clinically indicated	**COUNSELING** Benefits of adherence to bowel regimen, including adequate hydration, fiber, laxatives/enemas as clinically indicated. **POTENTIAL 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to or compressing spinal cord or cauda equina, radiation to bladder, pelvis, or spine

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
143 (male)	**Pelvic surgery** **Cystectomy**	**Psychosexual dysfunction** Erectile dysfunction	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly	**HEALTH LINKS** **Male Health Issues** **RESOURCES** www.urologychannel.com **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urologic consultation in patients with positive history. **SYSTEM = Reproductive (Male)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to spine, retroperitoneal node dissection, retroperitoneal tumor resection, extensive presacral tumor resection, cystectomy, radical prostatectomy, radiation to bladder, pelvis, or spine, or dissection, radiation dose ≥55 Gy to penile bulb in adult, ≥45 Gy in prepubertal child
- Pre-morbid/Co-morbid medical conditions: Hypogonadism

References

Brydoy M, Fossa SD, Klepp O, et al: Paternity following treatment for testicular cancer. J Natl Cancer Inst 97:1580-1588, 2005

Jacobsen KD, Ous S, Waehre H, et al: Ejaculation in testicular cancer patients after post-chemotherapy retroperitoneal lymph node dissection. Br J Cancer 80:249-55, 1999

Macedo A, Jr., Ferreira PV, Barroso U, Jr., et al: Sexual function in teenagers after multimodal treatment of pelvic rhabdomyosarcoma: A preliminary report. J Pediatr Urol 6:605-8, 2010

Modh RA, Mulhall JP, Gilbert SM: Sexual dysfunction after cystectomy and urinary diversion. Nat Rev Urol 11:445-53, 2014

Ritenour CW, Seidel KD, Leisenring W, et al: Erectile dysfunction in male survivors of childhood cancer-a report from the Childhood Cancer Survivor Study. J Sex Med 13:945-54, 2016

Zippe C, Nandipati K, Agarwal A, et al: Sexual dysfunction after pelvic surgery. Int J Impot Res 18:1-18, 2006

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
144 (male)	**Pelvic surgery** **Cystectomy**	**Sexual dysfunction (anatomic)** Retrograde ejaculation Anejaculation Obstructive azoospermia **Infertility**	**HISTORY** **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** Use of assisted reproductive technology for sperm retrieval. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urologic consultation in patients with positive history. **SYSTEM = Reproductive (Male)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to spine, retroperitoneal node dissection, retroperitoneal tumor resection, extensive presacral tumor resection, cystectomy, radical prostatectomy, radiation to bladder, pelvis, or spine, or dissection, radiation dose ≥55 Gy to penile bulb in adult, ≥45 Gy in prepubertal child
- Pre-morbid/Co-morbid medical conditions: Hypogonadism

References

Brydoy M, Fossa SD, Klepp O, et al: Paternity following treatment for testicular cancer. J Natl Cancer Inst 97:1580-1588, 2005

Jacobsen KD, Ous S, Waehre H, et al: Ejaculation in testicular cancer patients after post-chemotherapy retroperitoneal lymph node dissection. Br J Cancer 80:249-55, 1999

Macedo A, Jr., Ferreira PV, Barroso U, Jr., et al: Sexual function in teenagers after multimodal treatment of pelvic rhabdomyosarcoma: A preliminary report. J Pediatr Urol 6:605-8, 2010

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Zippe C, Nandipati K, Agarwal A, et al: Sexual dysfunction after pelvic surgery. Int J Impot Res 18:1-18, 2006

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
145 (female)	**Pelvic surgery** **Cystectomy**	**Sexual dysfunction**	**HISTORY** **Altered or diminished sensation, loss of sensation** **Dyspareunia** **Medication use** Yearly	**HEALTH LINKS** **Female Health Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gynecologic consultation for patients with positive history. **SYSTEM = Reproductive (Female)** **SCORE = 2A**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Tumor adjacent to spine, radiation to bladder, pelvis or spine
- Pre-morbid/Co-morbid medical conditions: Chronic GVHD, hypogonadism

References

Aerts L, Enzlin P, Verhaeghe J, et al: Sexual and psychological functioning in women after pelvic surgery for gynaecological cancer. Eur J Gynaecol Oncol 30:652-6, 2009

Metzger ML, Meacham LR, Patterson B, et al: Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol 31:1239-47, 2013

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
146	**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 ≥101°F (38.3°C) **SCREENING** **Blood culture** When febrile T ≥101°F (38.3°C)	**HEALTH LINKS** **Splenic Precautions** **COUNSELING** Risk of life-threatening infections with encapsulated organisms. Risk associated with malaria and tick-borne diseases if living in or visiting endemic areas. Obtain medical alert bracelet/card noting asplenia. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone) in patients with T ≥101°F (38.3°C) or other signs of serious illness and continue close medical monitoring while awaiting blood culture results. Hospitalize and broaden antimicrobial coverage (e.g., addition of vancomycin) under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC, toxic clinical appearance, fever ≥104°F (40°C), meningitis, pneumonia, or other serious focus of infection, signs of septic shock, or previous history of serious infection. Immunize with Pneumococcal, Meningococcal (including serotype B), Influenza and HIB vaccines according to current ACIP recommendations. Discuss with dental provider potential need for antibiotic prophylaxis based on planned procedure. For further details regarding antibiotic prophylaxis and immunizations, see current edition of AAP Red Book. **SYSTEM = Immune** **SCORE = 2A**

References

Castagnola E, Fioredda F: Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenia or asplenia: a brief review of current recommendations for practical purposes. Eur J Haematol 71:319-26, 2003

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Omlin AG, Muhlemann K, Fey MF, et al: Pneumococcal vaccination in splenectomised cancer patients. Eur J Cancer 41:1731-1734, 2005

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
147	**Thoracic surgery**	**Pulmonary dysfunction**	**HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** 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** www.smokefree.gov **COUNSELING** Tobacco avoidance/smoking cessation/environmental tobacco smoke. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy). **SYSTEM = Pulmonary** **SCORE = 2A**

Additional Information

Thoracic surgery includes thoractomy, chest wall surgery, rib resection, pulmonary lobectomy, pulmonary metastasectomy and pulmonary wedge resection.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Cancer/Treatment factors: Combination with pulmonary toxic therapy (e.g., bleomycin, busulfan, carmustine [BCNU], lomustine [CCNU]), combination with chest radiation and TBI
- Pre-morbid/Co-morbid medical conditions: Atopic history
- Health behaviors: Smoking, inhaled illicit drug use

References

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Wolff AJ, O'Donnell AE: Pulmonary effects of illicit drug use. Clin Chest Med 25:203-16, 2004

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
148	**Thoracic surgery**	**Scoliosis/Kyphosis**	**PHYSICAL** **Exam of back/spine** Yearly until growth completed, may need more frequent assessment during puberty or if curve detected	**HEALTH LINKS** **Scoliosis and Kyphosis** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Spine films in patients with clinically apparent curve. Orthopedic consultation as indicated based on physical and/or radiographic exam. **SYSTEM = Musculoskeletal** **SCORE = 2A**

Additional Information

Thoracic surgery includes thoractomy, chest wall surgery, rib resection, pulmonary lobectomy, pulmonary metastasectomy and pulmonary wedge resection.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Young age (deformity can still develop even if skeletally mature at time of surgery)
- Cancer/Treatment factors: Radiation to the spine, greater number of ribs resected
- Pre-morbid/Co-morbid medical conditions: Preoperative deformity

References

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Deschamps C, Tirnaksiz BM, Darbandi R, et al: Early and long-term results of prosthetic chest wall reconstruction. J Thorac Cardiovasc Surg 117:588-91; discussion 591-2, 1999
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Laverdiere C, Liu Q, Yasui Y, et al: Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 101:1131-40, 2009
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
149	**Thyroidectomy**	**Hypothyroidism**	**SCREENING** **Endocrinologic consultation for initiation of thyroid hormone replacement** Immediately	**HEALTH LINKS** **Thyroid Problems** **COUNSELING** For females, thyroid levels prior to attempting pregnancy and periodically throughout pregnancy. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Total thyroidectomy 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).

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
150	**Radioiodine therapy (I-131 thyroid ablation)**	**Lacrimal duct atrophy**	**HISTORY** **Excessive tearing** Yearly	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ophthalmology consultation as clinically indicated. **SYSTEM = Ocular** **SCORE = 2A**

References

Burns JA, Morgenstern KE, Cahill KV, et al: Nasolacrimal obstruction secondary to I-131 therapy. Ophthal Plast Recons 20:126-129, 2004

Morgenstern KE, Vadysirisack DD, Zhang ZX, et al: Expression of sodium iodide symporter in the lacrimal drainage system: Implication for the mechanism underlying nasolacrimal duct obstruction in I-131-treated patients. Ophthal Plast Recons 21:337-344, 2005

Zettinig G, Hanselmayer G, Fueger BJ, et al: Long-term impairment of the lacrimal glands after radioiodine therapy: a cross-sectional study. Eur J Nucl Med Mol Imaging 29:1428-32, 2002

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
151	**Radioiodine therapy (I-131 thyroid ablation)**	**Hypothyroidism**	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**HEALTH LINKS** **Thyroid Problems** **COUNSELING** For females, thyroid levels prior to attempting pregnancy and periodically throughout pregnancy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

References

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Safa AM, Skillern PG: Treatment of hyperthyroidism with a large initial dose of sodium iodide I 131. Arch Intern Med 135:673-5, 1975

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
152	**Systemic MIBG (in therapeutic doses)**	**Hypothyroidism**	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**HEALTH LINKS** **Thyroid Problems** **COUNSELING** For females, thyroid levels prior to attempting pregnancy and periodically throughout pregnancy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

MIBG used for diagnostic purposes (i.e., MIBG scanning) does NOT put patients at risk for hypothyroidism.

References

Bhandari S, Cheung NK, Kushner BH, et al: Hypothyroidism after 131I-monoclonal antibody treatment of neuroblastoma. Pediatr Blood Cancer 55:76-80, 2010

Brans B, Monsieurs M, Laureys G, et al: Thyroidal uptake and radiation dose after repetitive I-131-MIBG treatments: influence of potassium iodide for thyroid blocking. Med Pediatr Oncol 38:41-6, 2002

Picco P, Garaventa A, Claudiani F, et al: Primary hypothyroidism as a consequence of 131-I-metaiodobenzylguanidine treatment for children with neuroblastoma. Cancer 76:1662-4, 1995

van Santen HM, de Kraker J, van Eck BL, et al: High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during (131)I-meta-iodobenzylguanidine treatment in children with neuroblastoma. Cancer 94:2081-9, 2002

van Santen HM, de Kraker J, van Eck BLF, et al: Improved radiation protection of the thyroid gland with thyroxine, methimazole, and potassium iodide during diagnostic and therapeutic use of radiolabeled metaiodobenzylguanidine in children with neuroblastoma. Cancer 98:389-396, 2003

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
153	**Systemic MIBG (in therapeutic doses)**	**Thyroid nodules**	**PHYSICAL** **Thyroid exam** Yearly	**HEALTH LINKS** **Thyroid Problems** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ultrasound for evaluation of palpable nodule(s). FNA as clinically indicated. Endocrine and/or surgical consultation for further management. **SYSTEM = SMN** **SCORE = 2A**

References

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Clement SC, van Rijn RR, van Eck-Smit BL, et al: Long-term efficacy of current thyroid prophylaxis and future perspectives on thyroid protection during 131I-metaiodobenzylguanidine treatment in children with neuroblastoma. Eur J Nucl Med Mol Imaging 42:706-15, 2015

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
154	**Systemic MIBG (in therapeutic doses)**	**Thyroid cancer**	**PHYSICAL** **Thyroid exam** Yearly	**HEALTH LINKS** **Thyroid Problems** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Ultrasound for evaluation of palpable nodule(s). FNA as clinically indicated. Endocrine and/or surgical consultation for further management. **SYSTEM = SMN** **SCORE = 2A**

References

Clement SC, van Eck-Smit BL, van Trotsenburg AS, et al: Long-term follow-up of the thyroid gland after treatment with 131I-Metaiodobenzylguanidine in children with neuroblastoma: importance of continuous surveillance. Pediatr Blood Cancer 60:1833-8, 2013

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

Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
156 (female)	**Breast**	**STANDARD RISK PARAMETERS** **≥ Age 40** **PHYSICAL** **Clinical breast exam is NOT recommended for women of any age at standard risk** **SCREENING** **Mammogram** Women ages 40 to 44: May initiate yearly screening based on shared decision-making between patient and provider Women ages 45 to 54: Yearly screening Women ages 55 and older: May transition to biennial screening or continue yearly screening (based on shared decision-making between patient and provider). Women should continue screening mammography as long as overall health is good and life expectancy is ≥10 years	**HIGHEST RISK PARAMETERS** **History of radiation (TBI, chest, axilla), see section 72** **Personal history of BRCA1, BRCA2, ATM or p53 mutation** **In absence of personal genetic testing, known BRCA mutation in first degree relative** **PHYSICAL** **For patients with history of radiation (TBI, chest, axilla), see section 72** **SCREENING** **For patients with history of radiation (TBI, chest, axilla), see section 72** **For patients at high risk due to personal or family history of hereditary syndromes predisposing to breast cancer, see current ACS high risk screening recommendations (Smith et al. 2018)**	**COUNSELING** For standard risk patients, general guidance regarding routine screening beginning at age 40 per current ACS guidelines. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery and/or oncology consultation as clinically indicated.

Additional Information

Mammography is currently limited in its ability to evaluate the premenopausal breast.

Standard population risk factors include 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, and hormone replacement therapy.

References

Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-37, 2004

National Comprehensive Cancer Network: Breast cancer screening and diagnosis guidelines version 1.2015. Plymouth Meeting, PA, National Comprehensive Cancer Network, 2015

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Saslow D, Boetes C, Burke W, et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75-89, 2007

Siu AL, U. S. Preventive Services Task Force: Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 164:279-96, 2016

Smith RA, Andrews KS, Brooks D, et al: Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin, 2018

Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
157 (female)	**Cervical**	**STANDARD RISK PARAMETERS** **≥ Age 21** **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. Women ages 21 to 29: PAP test every 3 years. Women ages 30 to 65: HPV and PAP test every 5 years (optimal), or PAP test alone every 3 years (alternative). Women over age 65: No testing for cervical cancer if normal cervical cancer screening results in past 10 years.	**HIGHEST RISK PARAMETERS** **History of HCT, see section 100** **Personal history of cervical dysplasia** **Prenatal DES exposure** **HPV infection** **Immunosuppression** **Chronic steroid use** **HIV positive** **History of Hodgkin lymphoma** **Chronic GVHD** **SCREENING** **Same as standard risk**	**COUNSELING** Safer sexual practices to reduce HPV transmission. Importance of HPV vaccination. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gynecology and/or oncology consultation as clinically indicated. HPV vaccination per current recommendations.

Additional Information

Human papillomavirus virus (HPV) is the leading cause of cervical cancer in women.
HPV vaccination protects against 90% of cervical cancers and 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 receive HPV vaccination at the discretion of their health care provider.
- HPV vaccination is also recommended (CDC/ACIP) for females 13–26 years to catch up on 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 Petrosky E et al. (2015) and Centers for Disease Control and Prevention (2010), for further information.
Standard population risk factors include early age at first intercourse, multiple lifetime sex partners, smoking, sexually transmitted infections.

References

Joura EA, Giuliano AR, Iversen OE, et al: A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 372:711-23, 2015
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Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
158	**Colorectal**	**STANDARD RISK PARAMETERS** **≥ Age 45** **SCREENING** **Regular screening with either stool-based testing or structural examination based on patient preference and test availability, selected from the options below** Beginning at age 45	**HIGHEST RISK PARAMETERS** **History of radiation (TBI, abdominal, pelvic, spinal [lumbar, sacral, whole]), see section 85** **Familial adenomatous polyposis (FAP)** **Hereditary Nonpolyposis Colon Cancer (HNPCC)** **Lynch syndrome** **Inflammatory bowel disease (IBD)** **Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps or hepatoblastoma** **Family history of colorectal cancer or polyps in first degree relative** **SCREENING** **For patients with history of radiation (TBI, abdominal, pelvic, spinal [lumbar, sacral, whole]), see section 85** **For patients at high risk due to personal or family history or hereditary syndromes predisposing to colorectal cancer, more intensive and earlier screening is recommended (see Giardiello et al. 2014, Kahl et al. 2016, Lieberman et al. 2012, and Syngal et al. 2015)**	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Gastroenterology, surgery and/or oncology consultation as clinically indicated.

Colorectal Cancer Screening Options

Type	Test	Frequency
Stool-Based Tests	Fecal immunochemical test*	Yearly
	High-sensitivity, guaiac-based fecal occult blood test*	Yearly
	Multitarget stool DNA test*	Every 3 years
Structural Examinations	Colonoscopy	Every 10 years
	CT colonography*	Every 5 years
	Flexible sigmoidoscopy*	Every 5 years

*All positive results on non-colonoscopy screening tests should be followed up with timely colonoscopy.

Additional Information

Standard population risk factors include high fat/low fiber diet and obesity.

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Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
159 (female)	**Endometrial**	**SCREENING** **No screening for standard risk patients**	**HIGHEST RISK PARAMETERS** **History of/at risk for hereditary nonpolyposis colon cancer (HNPCC)** **SCREENING** **Endometrial biopsy** Yearly, beginning at age 35, based on shared decision-making between patient and provider	**COUNSELING** Risks and symptoms of endometrial cancer. Promptly seek medical attention for unexpected vaginal bleeding or spotting.

Additional Information

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.
Standard population risk factors include obesity, older age, unopposed estrogen therapy, tamoxifen, diabetes, hypertension, high fat diet, early menopause, late menopause, nulliparity, infertility, and failure to ovulate.

References

Smith RA, Andrews KS, Brooks D, et al: Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin, 2018

Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
160	**Lung**	**SCREENING** **No screening for standard risk patients**	**HIGHEST RISK PARAMETERS** **History of radiation (TBI, chest, axilla), see section 75** **History of heavy smoking (30 pack years or more), AND smoke now or have quit within the past 15 years, AND current age 55-80** **HISTORY** **Cough** **Wheezing** **Shortness of breath** **Dyspnea on exertion** Yearly **PHYSICAL** **Pulmonary Exam** Yearly **SCREENING** **Spiral CT Scan** Discuss the benefits and risks/harms of spiral CT scanning for patients at highest risk	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Imaging and surgery and/or oncology consultation as clinically indicated.

Additional Information

A pack year is smoking an average of one pack of cigarettes per day for one year. For example, a person could have a 30 pack-year history by smoking one pack a day for 30 years or two packs a day for 15 years.
Standard population risk factors include smoking, workplace exposures to asbestos, arsenic, radiation, and second hand smoke (in non-smokers).

References

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Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
161	**Oral**	**STANDARD RISK PARAMETERS** **Tobacco use (smoking cigars, cigarettes, or pipes, dipping, chewing)** **Alcohol abuse** **Excessive sun exposure (increases risk of cancer of lower lip)** **Human Papillomavirus (HPV) infection** **PHYSICAL** **Oral exam** Yearly	**HIGHEST RISK PARAMETERS** **History of radiation (TBI, head/brain, neck), see section 43** **Acute/chronic GVHD, see section 107** **Fanconi anemia** **Dyskeratosis congenita** **SCREENING** **Same as standard risk**	**COUNSELING** Importance of HPV vaccination. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Head and neck/otolaryngology consultation as indicated. HPV vaccination per current recommendations.

Additional Information

HPV vaccination is associated with reduction in vaccine-type oral HPV prevalence among young adults in the United States.
Although HPV vaccine is not currently licensed for prevention of oral cancers (efficacy studies not yet available), it is recommended for the prevention of anogenital cancers in males and females 9-26 years of age.
Survivors should be encouraged to receive the HPV vaccine, due to their increased risk (compared with age- and sex-matched general population) for development of HPV-related cancers.

References

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Ojha RP, Tota JE, Offutt-Powell TN, et al: Human papillomavirus-associated subsequent malignancies among long-term survivors of pediatric and young adult cancers. PLoS One 8:e70349, 2013
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Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
162 (male)	**Prostate**	**STANDARD RISK PARAMETERS** **Older age, with steadily increasing risk after age 40 years** **SCREENING** **Clinicians should be prepared to discuss prostate cancer screening with patients.**	**HIGHEST RISK PARAMETERS** **African-American race** **Family history of prostate cancer in first degree relative** **SCREENING** **Same as standard risk**	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Urology and/or oncology consultation as clinically indicated.

Additional Information

The U.S. Preventive Services Task Force (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.

References

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Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
163	**Skin**	**SCREENING** **No screening for standard risk patients**	**HIGHEST RISK PARAMETERS** **History of any radiation, see section 43** **History of HCT, see section 99 (male) or section 100 (female)** **Chronic GVHD, see section 105** **Personal history of melanoma or skin cancer** **Dysplastic nevi** **Family history of melanoma or skin cancer** **History of severe sunburn at young age** **Light skin and age 65 and older** **Atypical moles or ≥50 moles** **PHYSICAL** **Skin self exam** Monthly **Dermatologic exam** Yearly in the context of physical examinations performed for other purposes	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery, dermatology, and/or oncology consultation as clinically indicated.

Additional Information

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 for patients at highest risk.

Standard population factors include light skin color and chronic exposure to sun.

References

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Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
164 (male)	**Testicular**	**SCREENING** **No screening for standard risk patients**	**HIGHEST RISK PARAMETERS** **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** **SCREENING** **No screening for high risk patients**	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Self examination techniques or increased awareness about the signs and symptoms of testicular cancer can be discussed based on the patient's interests.

Additional Information

For standard and high risk populations, the USPSTF recommends against routine screening for testicular cancer in asymptomatic adolescent and adult males, due to lack of 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.
Standard population risk factors include young males.

References

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GENERAL HEALTH SCREENING

Sec #	Screening	Health Counseling/ Further Considerations
165	**SCREENING** **Refer to United Stated Preventive Services Task Force recommendations at www.ahrq.gov/clinic** Yearly	**COUNSELING** Importance of general health maintenance based on age and gender, including all recommended immunizations. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** General health maintenance and screening per standard recommendations for age. Screening for hypertension, obesity, depression, tobacco use, alcohol misuse. Certain subpopulations require screening for lipid disorders, sexually transmitted infections, 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 and screen for HPV vaccination in males and females. 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).

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