Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 6.0 - October 2023

CHILDREN'S ONCOLOGY GROUP

Website: www.survivorshipguidelines.org

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for editing and typesetting

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Introductory Materials

Version 6.0
October 2023

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Abstract

Release date: October 2023

Status: Updated from Version 5.0 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 6.0 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 6.0*. Monrovia, CA: Children's Oncology Group; October 2023; 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.

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Introduction to Late Effects Guidelines and Health Links: The *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* and accompanying *Health Links* were developed by the Children's Oncology Group as a collaborative effort of the Late Effects Committee and Nursing Discipline 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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CHILDREN'S ONCOLOGY GROUP

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Guideline Development Task Force - Initial Versions

The Children's Oncology Group Nursing Discipline and Late Effects Committee collaboratively developed the initial versions (1.0, 1.1, and 1.2) of the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*. The following individuals comprised the original Guideline Development Task Force:

Development Task Force

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Special Acknowledgment:

Smita Bhatia, MD, MPH, Children's Hospital of Alabama, Birmingham, AL *for her leadership in overseeing the initial development of the COG LTFU Guidelines as Chair of the COG Late Effects Committee, and for her continued oversight of all content in all versions of the COG LTFU Guidelines*
Louis S. "Sandy" Constine, MD, University of Rochester, Rochester, NY *for his in-depth expert review and extensive contributions to all radiation-related sections in all versions of the COG LTFU Guidelines*

CHILDREN'S ONCOLOGY GROUP

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 165 therapeutic exposures in the COG LTFU Guidelines:

- 113 (68%) are derived primarily from the H&P, of which 91 (55%) rely solely on the H&P and 22 (13%) rely on the H&P plus a baseline diagnostic study (e.g., lab, imaging)
- 44 (27%) include periodic laboratory, diagnostic imaging, or other testing
- 8 (5%) 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 45 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

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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 2023) 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

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information becomes available. Task force members are assigned according to their respective areas of expertise and clinical interest and membership is updated every 5 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 6.0 – October 2023).

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 Monica Gramatges, MD, PhD (***gramatge@bcm.edu***) or Susan Krause (***skrause@texaschildrens.org***).

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CHILDREN'S ONCOLOGY GROUP

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.

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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 11-43), 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 34 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 44-98), 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 HCT, and if so:
  - Transplant type (autologous vs allogeneic)
  - Chronic graft-versus-host disease (cGVHD) status (no history of cGVHD, history of cGVHD, currently active cGVHD)

Cancer Treatment: Surgery

- Names of all surgical procedures.
  - For list of surgical procedures addressed by these guidelines (Sections 115–151), 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), systemic MIBG (in therapeutic doses), or other novel agents (Sections 152-163)

2. Compile a list of guideline sections relevant to the survivor based off the list generated in step 1.
   - Sections 1 - 7: Applicable to all survivors
   - Section 8: Survivors diagnosed before 1972
   - Section 9: Survivors diagnosed before 1993
   - Section 10: Survivors diagnosed between 1977 and 1985
   - Section 11: All survivors who received chemotherapy
   - Sections 12-43: For survivors who received chemotherapy, include relevant sections
   - Sections 44, 45, 96: All survivors who received radiation

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- Sections 46 - 95, 97- 98: For survivors who received radiation, include relevant sections
- Sections 100 - 105: All survivors who underwent HCT
  - Section 100 is for males only
  - Section 101 is for females only
- Section 99: For survivors who underwent autologous HCT
- Sections 106 - 114: For survivors who underwent allogeneic HCT, include relevant sections
- Sections 115 - 151: For survivors who underwent surgery, include relevant sections
- Sections 152 - 163: For survivors who received other therapeutic modalities, include relevant sections
- Section 164-165: Applicable to all survivors

1. 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 Monica Gramatges, MD, PhD (***gramatge@bcm.edu***) or Susan Krause (***skrause@texaschildrens.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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CHILDREN'S ONCOLOGY GROUP

New to Version 6.0

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

A continued overall goal of Version 6.0 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 6.0 therefore features the following modifications:

- Guideline navigation has been simplified through the use of hyperlinks. **Hyperlinks** are denoted with **blue text** and assist in moving more easily through the guideline contents. Additionally, there is often a hyperlink at the bottom of most pages to direct the user back to a section or the guideline table of contents.
- Simplification of design/format with a focus on clinical information that drives screening
- Continuation of defined and simplified radiation fields
  - All radiation fields from Version 5.0 are still 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 not necessary to know or record specific radiation doses (with a few exceptions)
- Radiation dose cut-offs largely eliminated
  - 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 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
- 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 applicable sections
- *Secondary* malignancy has been renamed *Subsequent* throughout the guidelines
- References to veno-occlusive disease (VOD) has been removed throughout the guidelines and replaced with the current sinusoidal obstruction syndrome (SOS) term
- Templates remain in 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:

- Subsequent malignancy and/or Risk of malignancy in offspring related to any cancer experience (section 7)
- Hypothyroidism related to (partial) Thyroidectomy (section 151)
- Xerostomia and/or Salivary gland dysfunction and/or Chronic sialadenitis related to radioiodine therapy (I-131 thyroid ablation) (section 154)
- Growth attenuation related to BCR-ABL tyrosine kinase inhibitors (section 159)
- Hypothyroidism related to BCR-ABL tyrosine kinase inhibitors (section 160)
- Insufficient information regarding late effects from Other targeted biologic therapies (section 161)
- Immunologic complications related to B-cell directed antibody-based therapies (section 162)
- Insufficient information regarding late effects from Other antibody-based immune therapies (section 163)
- General health screening regarding vaccinations (section 165)

Sections/Late Effects Removed

The following sections or late effects have been removed from Version 6.0 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)

CHILDREN'S ONCOLOGY GROUP

New to Version 6.0 (cont)

- Renal toxicity related to methotrexate (section 28 changed to "No Known Renal Late Effects" in Version 5.0)
- Reduced bone mineral density related to methotrexate (section 27 changed to "No Known BMD Late Effects" in Version 6.0)
- The Cancer Screening Guidelines Sections (156-164 in Version 5.0) for average risk individuals have been removed due to inconsistencies across cooperative groups and practice standards, as well as timing alignment with suggested changes and publication. Your health care providers will offer guidance based on current recommendations and guidelines.

Late Effects Renamed

- Reduced ovarian follicular pool renamed as Diminished ovarian reserve (DOR) (15, 93, 137)
- Secondary benign or malignant neoplasm occurring in or near radiation field renamed as Subsequent benign or malignant neoplasm occurring in or near radiation field (44)

Newly Combined Sections

These sections from Version 5.0 have been combined into one section (164) in Version 6.0:

- Breast cancer screening guidelines standard risk (previous section 156)
- Cervical cancer screening guidelines standard risk (previous section 157)
- Colorectal cancer screening guidelines standard risk (previous section 158)
- Endometrial cancer screening guidelines standard risk (previous section 159)
- Lung cancer screening guidelines standard risk (previous section 160)
- Oral cancer screening guidelines standard risk (previous section 161)
- Prostate cancer screening guidelines standard risk (previous section 162)
- Skin cancer screening guidelines standard risk (previous section 163)
- Testicular cancer screening guidelines standard risk (previous section 164)

New Potential Late Effects Subcategories Added

- Subsequent malignancy (section 7)
- Risk of malignancy in offspring (section 7)
- Altered skin pigmentation (section 106)

Major Screening Changes

Guidelines for Genetic Risk Assessment for Cancer Predisposition (7)

Screening for Decreased Bone Mineral Density after Methotrexate (28)

Cardiomyopathy Screening (34, 77)

Cancer Screening for Average Risk Individuals (previously 156-164)

Guidelines for Genetic Risk Assessment for Cancer Predisposition (Section 7)

There is risk for subsequent malignancy and/or malignancy in offspring based on genetic predisposition which warrants further assessment based on the determined risk factors.

Screening for Decreased Bone Mineral Density after Methotrexate (Section 28)

No association has been found concerning decreased BMD and methotrexate; screening is no longer recommended, but the section remains for reference

Cardiomyopathy Screening (Sections 34, 77)

- Echocardiogram screening is not recommended for individuals with both <15Gy radiation dose (with potential impact to heart) and a cumulative doxorubicin equivalent anthracycline dose <100 mg/m^2
- Anthracycline dose conversion of mitoxantrone changed to "multiply total dose x 10" versus the previous recommendation to multiply the total dose x 4

Cancer Screening for Average Risk Individuals

The Average Risk Cancer screening guidelines (Version 5.0 sections 156-164) have been removed and replaced with a combined screening guideline section (164) for average risk individuals. Patients with high risk needs related to their cancer treatment are meticulously addressed in their specific sections. Standard risk patients should consult with their healthcare provider for general health maintenance based on age and gender. High risk patients are those with a history of the following exposure(s):

- Breast cancer: radiation (TBI, chest, axilla) review section 73
- Cervical cancer: HCT review section 100
- Colorectal cancer: radiation (TBI, abdominal, pelvic, spinal [lumbar, sacral, whole]) review section 85
- Lung cancer: radiation (TBI, chest, axilla) review section 75
- Oral cancer: radiation (TBI, head/brain, neck) review section 43 and/or GVHD should review section 107
- Skin cancer: radiation review section 44, with a history of HCT review section 100/101, and/or with a history of cGVHD review section 106

CHILDREN'S ONCOLOGY GROUP

New to Version 6.0 (cont)

Additional Screening Change Highlights

- Testicular hormonal dysfunction related to alkylating agents and/or testicular radiation: Screening with AM testosterone in high-risk patients starting at age 18 years is recommended (12, 90)
- Cyclophosphamide equivalent dose calculator (CED) has been added to assist in determining high risk status (12, 13, 14, 15, 92, 93)
- Cataracts related to corticosteroids, alkylating agents, and/or radiation recommends a yearly evaluation by an ophthalmologist or optometrist (18, 39, 61)
- Reduced bone mineral density related to steroids and HCT: Adjustments for gender and menopause status regarding z-score, as well as the age metric changing from 20 to 50 years old. Guidelines for follow up are indicated with a specific algorithm for ease of implementation. Vitamin D recommendations updated to reflect AAP guidelines with age specific parameters (37, 104)
- Monthly breast "self-exam" is no longer recommended (73)

Health Links

- The Health Links have been modified to reflect all Version 6.0 Guideline changes.
- Five Health Links have been renamed:

  Diet and Physical Activity is now *Staying Healthy through Nutrition and Physical Activity*

  Educational Issues is now *School After Cancer Treatment*

  Emotional Issues is now *Mental Health After Cancer Treatment*

  Female Health Issues after Cancer Treatment is now *Ovarian and Reproductive Health after Cancer Treatment*

  Male Health Issues after Cancer Treatment is now *Testicular and Reproductive Health after Cancer Treatment*

- Two new Health Links for Version 6.0:

  Vaccines after Treatment for Cancer Survivors Treated with Hematopoietic Cell Transplant (HCT)

  Vaccines after Treatment for Cancer Survivors Treated with Chemotherapy and/or Radiation (Non-HCT)

General Recommendations Regarding Use of the Simplified COG LTFU Guidelines, V 6.0

- 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 6.0 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 6.0; 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.

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Abbreviations & Parameters

Abbreviation	Definition
AAP	American Academy of Pediatrics
ABR	Auditory brainstem response
ACIP	Advisory Committee on Immunization Practices
ACS	American Cancer Society
AHA	American Heart Association
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
ATM	Ataxia telangiectasia cancer susceptibility gene (located on chromosome 11)
AVN	Avascular necrosis
BMD	Bone mineral density
BMI	Body mass index
BRCA1	Breast cancer susceptibility gene 1 (located on chromosome 17)
BRCA2	Breast cancer susceptibility gene 2 (located on chromosome 13)
BUN	Blood urea nitrogen
Ca	Calcium
CAD	Coronary artery disease
CBC	Complete blood count
CCG	Children's Cancer Group
CDC	Centers for Disease Control
cGVHD	Chronic graft versus host disease
Cl	Chloride
CNS	Central nervous system
CO_2	Carbon dioxide

Abbreviation	Definition
COG	Children's Oncology Group
CRT	Cranial radiation therapy
CT	Computed tomography
CVRF	Cardiovascular risk factors
dB	Decibel
DES	Diethylstilbestrol
DI	Diabetes Insipidus
DLCO	Diffusion capacity of carbon monoxide
DOR	Diminished ovarian reserve
DTI	Diffusion-tensor imaging
DWI	Diffusion-weighted imaging
DXA	Dual energy x-ray absorptiometry
ECHO	Echocardiogram
EKG	Electrocardiogram
EIA	Enzyme immunoassay
FAP	Familial adenomatous polyposis
FM	Frequency modulated
FNA	Fine needle aspiration
FNH	Focal nodular hyperplasia
FSH	Follicle stimulating hormone
G-CSF	Granulocyte colony stimulating factor
GH	Growth hormone
GI	Gastrointestinal
gm	Gram
GVHD	Graft versus host disease
Gy	Gray
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCT	Hematopoietic cell transplant

Abbreviation	Definition
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HIB	Haemophilus influenzae type B
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNPCC	Hereditary nonpolyposis colorectal cancer
HPF	High power field
HPV	Human papillomavirus
ht	Height
Hz	Hertz
IBD	Inflammatory bowel disease
K	Potassium
I-131	Iodine 131 radioisotope
IgA	Immunoglobulin A
IL-2	Interleukin-2
IM	Intramuscular
IMRT	Intensity-modulated radiation therapy
IO	Intra-Ommaya
IQ	Intelligence quotient
IT	Intrathecal
IU	International unit
IV	Intravenous
IVIG	Intravenous immunoglobulin
kg	Kilogram
KUB	Kidneys, ureters, bladder radiograph
LH	Luteinizing hormone
LV	Left ventricular
m^2	Square meter
MDS	Myelodysplastic syndrome
MIBG	Iodine-131-meta-iodobenzylguanidine

CHILDREN'S ONCOLOGY GROUP

Abbreviations & Parameters (cont.)

Abbreviation	Definition
mg	Milligram
Mg	Magnesium
MMF	Mycophenolate mofetil
MOPP	Mechlorethamine, Oncovin, Procarbazine, Prednisone
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
Na	Sodium
NF1	Neurofibromin 1 (neurofibromatosis) cancer susceptibility gene (located on chromosome 17)
NHL	Non-Hodgkin lymphoma
NSAIDs	Non-steroidal anti-inflammatory drugs
p53	Cancer susceptibility gene associated with familial cancers (located on chromosome 17)
PAP	Papanicolaou
PCR	Polymerase chain reaction
PFTs	Pulmonary function tests
PNET	Primitive neuroectodermal tumor
PNS	Peripheral nervous system
PO	By mouth
PO_4	Phosphate
PSA	Prostate specific antigen
PUVA	Psoralen plus ultraviolet-A radiation
QTc	Corrected QT interval
RB1	Retinoblastoma cancer susceptibility gene (located on chromosome 13)
RBC	Red blood cell
RUQ	Right upper quadrant

Abbreviation	Definition
SCUBA	Self-contained underwater breathing apparatus
SD	Standard deviation
SOS	Sinusoidal obstruction syndrome
SQ	Subcutaneous
STLI	Subtotal lymphoid irradiation
T4	Thyroxine
TBI	Total body irradiation
TLI	Total lymphoid irradiation
TPN	Total parenteral nutrition
TSH	Thyroid stimulating hormone
U	Units
USPSTF	United States Preventive Services Task Force
V-A	Ventriculoatrial
VOD	Veno-occlusive disease
V-P	Ventriculoperitoneal
V-V	Ventriculovenus
VZIG	Varicella zoster immunoglobulin
WAGR	Wilms tumor, aniridia, genitourinary anomalies, range of developmental delays
wt	Weight
Parameters commonly referenced in the guidelines	
≥1000 mg/m^2	High dose methotrexate
<1000mg/m^2	Standard dose methotrexate
≥1000 mg/m^2	High dose cytarabine
<1000mg/m^2	Standard dose cytarabine

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Guidelines

Version 6.0
October 2023

CHILDREN'S ONCOLOGY GROUP

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** **Mental Health** **School After Treatment** **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** Preference should be given to self vs. proxy report. 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. Assess social determinants of health including economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (https://health.gov/healthypeople/objectives-and-data/social-determinants-health). **SYSTEM = Psychosocial** **SCORE = 1**

Additional Information

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

- Patient factors: Younger age at diagnosis, family history of depression, anxiety, or mental illness, lower household income, lower educational attainment, school withdrawal, race/ethnicity
- Cancer/Treatment factors: Bone tumor, CNS tumor, CNS-directed therapy, history of HCT
- Pre-morbid/Co-morbid medical conditions: Premorbid learning or emotional difficulties, chronic conditions after cancer treatment (e.g., obesity, endocrine, pulmonary, cardiac conditions) are associated with increased risk for neurocognitive difficulties, and/or increased symptom burden (e.g., pain, fatigue) including neurocognitive problems

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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 behavior	**HISTORY** **Psychosocial assessment with attention to:** • **Depression** • **Anxiety** • **Post-traumatic stress** • **Suicidal ideation** Yearly	**HEALTH LINKS** Mental Health **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** Preference should be given to self vs. proxy report. Psychological consultation in patients with emotional difficulties related to cancer experience, including physical deformities or chronic disabilities. Appropriate psychotropic medications, as clinically indicated. Evaluation of parent for posttraumatic stress. Assess social determinants of health including economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (https://health.gov/healthypeople/objectives-and-data/social-determinants-health). **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

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

- Patient factors: Female sex, family history of depression, anxiety, or mental illness, lower household income, lower educational attainment, especially school withdrawal, 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 HCT
- Pre-morbid/Co-morbid medical conditions: Chronic pain, scarring or physical disfigurement, permanent hair loss, premorbid learning or emotional difficulties, sleep/fatigue issues, substance misuse

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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** **Mental Health** **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 **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Psychological consultation in patients with emotional difficulties related to cancer experience. Assess social determinants of health including economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (https://health.gov/healthypeople/objectives-and-data/social-determinants-health). **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

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

- Patient factors: Adolescent/Young adult at diagnosis or follow-up, male sex, lower household income, lower educational attainment, rural neighborhood, psychological distress

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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, as clinically indicated. 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 that may increase risk.

- Patient factors: Female sex
- Cancer/Treatment factors: CNS tumor, Hodgkin lymphoma, sarcoma/bone diagnosis, radiation to bone/joint, vincristine exposure
- Pre-morbid/Co-morbid medical conditions: History of osteonecrosis, depression, anxiety, sleep/fatigue issues, severe/life threatening chronic medical conditions

References

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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 endocrinopathies. 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/fatigue issues. Refer as indicated for cognitive-behavior therapy for insomnia. Assess social determinants of health including economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (https://health.gov/healthypeople/objectives-and-data/social-determinants-health). **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

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

- Patient factors: Female sex
- Cancer/Treatment factors: CNS tumor (e.g., craniopharyngioma), pulmonary radiation
- Pre-morbid/Co-morbid medical conditions: Depression, anxiety, obesity, sleep/fatigue issues, pain

References

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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

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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. Healthcare and insurance access may differ by country and/or state. Assess social determinants of health including economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (https://health.gov/healthypeople/objectives-and-data/social-determinants-health). **SYSTEM = Psychosocial** **SCORE = 2A**

Additional Information

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

- Patient factors: Lower household income, lower educational attainment, unemployment

References

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ANY CANCER EXPERIENCE (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
7	**Any Cancer Experience**	**Subsequent malignancy** **Risk of malignancy in offspring**	**HISTORY** **Strongly consider assessment for cancer predisposition in the following settings:** • **Any tumor listed in Table 1** • **Any bilateral cancer** • **>1 primary cancer** • **≥1 first degree relative(s) with cancer** • **Other concerning family history including consanguinity** • **Diagnosis of adult-type cancer in a child (basal cell carcinoma, breast, colon, gastrointestinal, ovarian, etc.)** • **Diagnosis of cancer predisposition syndrome in a relative**	**RESOURCES** McGill Interactive Pediatric OncoGenetic Guidelines: www.mipogg.com National Society of Genetic Counselors: www.nsgc.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** For patients who may be at risk for cancer predisposition by history, or with a history of one of the cancer types listed in Table 1, consider: • Referral to genetic counseling or clinical genetics • Referral for preconception/prenatal counseling **SYSTEM = SMN** **SCORE = 1**

Table 1

Solid Tumor	Solid Tumor (cont)	CNS Tumor (cont)
Adrenocortical carcinoma	Pleuropulmonary blastoma	Pineoblastoma
Desmoid tumor	Renal cell carcinoma	Pituitary blastoma
Endolymphatic sac tumor	Rhabdoid tumor	Retinoblastoma
Gastrointestinal stromal tumor	Schwannoma	Sub-ependymomal giant cell astrocytoma
Malignant peripheral nerve sheath tumor	**CNS Tumor**	**Non-Malignant/Other**
Medullary thyroid cancer	Atypical teratoid rhabdoid tumor	Cystic nephroma
Osteosarcoma	Choroid plexus carcinoma	Juvenile myelomonocytic leukemia
Ovarian Sertoli cell or Sertoli-Leydig cell tumor	Ciliary body medullo-ephithelioma	Meningioma
Paraganglioma	Hemangioblastoma	Myelodysplastic syndrome
Pheochromocytoma	Optic pathway glioma	

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors that may increase risk.
Common cancers for which there is increased risk for underlying predisposition under specific clinical scenarios include:

- AML with personal or family history of cytopenias or chronic infections, monosomy 7, short stature, microcephaly, other congenital anomalies, or 3 or more café au lait macules
- B-cell ALL with low hypodiploid cytogenetics (32-39 chromosomes)
- Embryonal rhabdomyosarcoma diagnosed <4 years old, diffuse anaplasia or botryoid subtype, or in genitourinary location
- Medulloblastoma of SHH or WNT subtypes, or diagnosed <3 years old if subtype unknown
- Hepatoblastoma with family history of GI cancer/polyps, or with features of hemihyperplasia/overgrowth syndrome
- Wilms tumor diagnosed <2 years old with GU anomalies (including history of undescended testicle or hypospadias), hemihyperplasia/overgrowth, or other syndromic features

References

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BLOOD/SERUM PRODUCTS

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
8	**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 concentrate, and allogeneic marrow, cord blood, or stem cells.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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

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BLOOD/SERUM PRODUCTS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
9	**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 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 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
10	**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 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

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

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
11	**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 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

Busenhart DM, Erb J, Rigakos G, et al: Adverse effects of chemotherapy on the teeth and surrounding tissues of children with cancer: a systematic review with meta-analysis. Oral Oncol 83:64-72, 2018

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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	**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 **SCREENING** **AM testosterone in high risk patients starting at 18 years**	**HEALTH LINKS** **Testicular and Reproductive Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Testosterone insufficiency or deficiency requiring hormone replacement after alkylating agents only is rare. Endocrine referral for the following: • No signs of puberty by age 14 years • Failure of pubertal progression • Adults with low AM testosterone levels 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. Consider assessment of fertility status prior to initiation of testosterone replacement therapy. **SYSTEM = Reproductive (Male)** **SCORE** **Classical Alkylating Agents = 1** **Heavy Metals = 2A** **Non-Classical Alkylators = 2A**

Commonly used alkylators can be converted to a cyclophosphamide equivalent dose by using: CED (mg/m^2)=

1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) +
0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) +
15 (cumulative BCNU dose (mg/m^2)) + 16 (cumulative CCNU dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) +
50 (cumulative thiotepa dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) +
8.823 (cumulative busulfan dose (mg/m^2))

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 that may increase risk.

- 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

References

Brignardello E, Felicetti F, Castiglione A, et al: Gonadal status in long-term male survivors of childhood cancer. J Cancer Res Clin Oncol 142:1127-32, 2016

Chemaitily W, Liu Q, van Iersel L, et al: Leydig cell function in male survivors of childhood cancer: a report from the St Jude Lifetime cohort study. J Clin Oncol 37:3018-31, 2019

Hamre H, Kiserud CE, Ruud E, et al: Gonadal function and parenthood 20 years after treatment for childhood lymphoma: a cross-sectional study. Pediatr Blood Cancer 59:271-7, 2012

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Kenney LB, Laufer MR, Grant FD, et al: High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 91:613-21, 2001

Lopez R, Plat G, Bertrand Y, et al: Testosterone deficiency in men surviving childhood acute leukemia after treatment with hematopoietic stem cell transplantation or testicular radiation: an L.E.A. study. Bone Marrow Transplant 56(6):1422-1425, 2021

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
13 (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** Testicular and Reproductive Health **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. Fertility recovery can be seen in the early years after completion of therapy and occasionally thereafter. Review previous fertility preservation counseling/interventions. **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.

Commonly used alkylators can be converted to a cyclophosphamide equivalent dose by using: CED (mg/m^2)=

1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15 (cumulative BCNU dose (mg/m^2)) + 16 (cumulative CCNU dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative thiotepa dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2))

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 that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents)
- Cancer/Treatment factors: Testicular cancer, higher cumulative doses of alkylators (especially busulfan ≥600 mg/m^2, cyclophosphamide ≥4 gm/m^2, CED >4 gm/m^2, ifosfamide ≥50 gm/m^2), and cisplatin >488 mg/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, cGVHD
- Health behaviors: Tobacco/Marijuana use

References

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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	**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** Ovarian and Reproductive Health **COUNSELING** Higher cumulative doses of alkylating agents with or without radiation may increase risk. Dose can be estimated using CED dose calculation. 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 by age 13 years • 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.

Commonly used alkylators can be converted to a cyclophosphamide equivalent dose by using: CED (mg/m^2)=

1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) +
0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) +
15 (cumulative BCNU dose (mg/m^2)) + 16 (cumulative CCNU dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) +
50 (cumulative thiotepa dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) +
8.823 (cumulative busulfan dose (mg/m^2))

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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
15 (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	**Diminished Ovarian Reserve (DOR)** Infertility	**HISTORY** **Menstrual and pregnancy history** **Hormonal therapy** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly	**HEALTH LINKS** **Ovarian and Reproductive Health** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org Livestrong Foundation: www.livestrong.org/what-we-do/program/fertility Oncofertility Consortium: https://oncofertility.msu.edu **COUNSELING** Need for contraception. Review previous fertility preservation counseling/interventions. Fertility recovery can be seen in the early years after the completion of therapy and occasionally thereafter. Potential for shorter period of fertility in family planning. Those with DOR should consider discussing reproductive health options with a reproductive endocrinologist or fertility specialist. Higher cumulative doses of alkylating agents with or without radiation may increase risk. Dose can be estimated using CED dose calculation. **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 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.

Commonly used alkylators can be converted to a cyclophosphamide equivalent dose by using: CED (mg/m^2)=

1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) +
0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) +
15 (cumulative BCNU dose (mg/m^2)) + 16 (cumulative CCNU dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) +
50 (cumulative thiotepa dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) +
8.823 (cumulative busulfan dose (mg/m^2))

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. AMH should be interpreted relative to age-specific reference ranges. FSH is lowered and AMH may be lowered by concurrent hormonal contraceptive use.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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 15 References (cont)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
16	**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 (AML)** **Myelodysplasia (MDS)**	**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 Subsequent 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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
17	**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. Influenza and Pneumococcal vaccinations. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. 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 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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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
18	**Classical Alkylating Agents** Busulfan	**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** 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 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
19	**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 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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Kooijmans EC, Bökenkamp A, Tjahjadi NS, et al: Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev 11;3(3), 2019

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
20	**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 that may increase risk.

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

References

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Kersun LS, Wimmer RS, Hoot AC, et al: Secondary malignant neoplasms of the bladder after cyclophosphamide treatment for childhood acute lymphocytic leukemia. Pediatr Blood Cancer 42:289-91, 2004

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
21	**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 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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
22	**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 years, then every 5 years beginning at age 13 years	**HEALTH LINKS** Hearing Loss School After Treatment **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 can be performed if the above is inconclusive.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
23	**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 entry to 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 that may increase risk.

- Cancer/Treatment factors: Cumulative cisplatin dose ≥300 mg/m^2, combination with vincristine, taxanes, gemcitabine

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
24	**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 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
25	**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** School After Treatment **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

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 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

Ehrhardt MJ, Mulrooney DA, Li C, et al: Neurocognitive, psychosocial, and quality-of-life outcomes in adult survivors of childhood non-Hodgkin lymphoma. Cancer 124(2):417-25, 2018

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
26	**Antimetabolites** Cytarabine (low dose IV) Cytarabine IO Cytarabine IT Cytarabine SQ	**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.

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
27	**Antimetabolites** Mercaptopurine (6MP) Thioguanine (6TG)	**Hepatic dysfunction** **Sinusoidal obstruction syndrome (SOS)**	**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, presenting as portal hypertension with liver biopsy indicating nodular regenerative hyperplasia, fibrosis, or siderosis.
Patients treated on CCG-1952, Regimens B1 and B2, received 6TG in place of 6MP during maintenance therapy.
Acute hepatotoxicity (manifesting as SOS) 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 that may increase risk.
- Pre-morbid/Co-morbid medical conditions: Viral hepatitis (especially chronic viral hepatitis), previous SOS, siderosis

References

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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

Green DM, Wang M, Krasin MJ, et al. Serum alanine aminotransferase elevations in survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Hepatol 69(1):94-106, 2019

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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 bone mineral density (BMD) late effects**		**SYSTEM = No Known BMD Late Effects** **SCORE = 2B**

References

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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	**No known renal late effects**		**SYSTEM = No Known Renal Late Effects** **SCORE = 2A**

Additional Information

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.

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
30	**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

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 that may increase risk.

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

References

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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	**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** School After Treatment **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 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). 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 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), TBI, especially single fraction TBI (10 Gy), or CRT especially ≥24 Gy
- Pre-morbid/Co-morbid medical conditions: Pre-morbid learning or attention problems

References

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Ehrhardt MJ, Mulrooney DA, Li C, et al: Neurocognitive, psychosocial, and quality-of-life outcomes in adult survivors of childhood non-Hodgkin lymphoma. Cancer 124(2):417-25, 2018

Hardy KK, Embry L, Kairalla JA, et al: Neurocognitive functioning of children treated for high-risk B-acute lymphoblastic leukemia randomly assigned to different methotrexate and corticosteroid treatment strategies: a report from the children's oncology group. J Clin Oncol 35(23):2700-7, 2017

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
32	**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 or Brain MRI with MRA as clinically indicated with preferred study based on intracranial lesion to be evaluated: • Calcifications: CT • White matter: MRI with DTI • Microvascular injury: Gadolinium-enhanced MRI with 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 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, CRT especially ≥24 Gy

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**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 Subsequent 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 anthraquinone 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 of AML.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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
34	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** Use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. **To estimate cumulative anthracycline dose in doxorubicin isotoxic equivalents** 1.0 x (doxorubicin total dose) + 0.5 x (daunorubicin total dose) + 0.67 x (epirubicin total dose) + 5.0 x (idarubicin total dose) + 10.0 x (mitoxantrone total dose)	**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: nausea, vomiting** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **Echo (or comparable imaging to evaluate cardiac function)** **RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM** (see table below) **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 Nutrition and Physical Activity **COUNSELING** Traditional CVRFs significantly increase survivors' risk of cardiomyopathy. Counsel regarding the importance of maintaining blood pressure, BMI, lipids, and glucose levels within goal ranges per general population guidelines. Regarding exercise: • Exercise is generally safe and encouraged for patients with normal LV systolic function • Consult cardiology for survivors with asymptomatic cardiomyopathy to define physical activity limits and precautions. • Consider cardiology consultation to define physical activity limits and precautions 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 use of QTc prolonging medications (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echo images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, LV dysfunction, dysrhythmia, or prolonged QTc interval. For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: • ≥250 mg/m^2 anthracyclines • ≥30 Gy chest radiation, or • Anthracycline (any dose) combined with chest radiation (≥15 Gy) • Evaluation should include a baseline echo (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echos, follow-up echos 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, and should be monitored periodically during pregnancy, labor and delivery due to increased risk for heart failure. **SYSTEM = Cardiovascular** **SCORE = 1**

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None to <100mg/m^2	None to <15Gy	No screening
None to <100mg/m^2 ≥100 to <250mg/m^2	15Gy to <30Gy None to <15Gy	Every 5 years
≥100 to <250mg/m^2 None to Any ≥ 250mg/m^2	≥15Gy ≥30Gy None to Any	Every 2 years

*Based on doxorubicin isotonic equivalent dose.
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 77.

Additional Information

Although mitoxantrone is an anthraquinone, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

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.

Abdominal symptoms (nausea, emesis) may be seen more frequently than exertional dyspnea or chest pain in younger patients.

Exertional intolerance is an uncommon presentation of left ventricular dysfunction in patients <25 years old.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors that may increase risk.

- Patient factors: Age <5 years at time of treatment, genetic variants associated with increased anthracycline-induced cardiotoxicity
- Cancer/Treatment factors: Combined with radiation involving the heart, higher cumulative anthracycline doses (≥550 mg/m^2 in patients ≥18 years at time of treatment, ≥250 mg/m^2 in patients <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
35	**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. Influenza and Pneumococcal vaccinations. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. 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 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 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

References

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

Additional Information

Dactinomycin has been associated with acute SOS, 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
37	**Corticosteroids** Dexamethasone Prednisone	**Reduced bone mineral density (BMD)** Defined as Z-score >2 SD below the mean in male survivors <50 years old and premenopausal women or T-score >1 SD below the mean in male survivors >50 years old and postmenopausal women	**SCREENING** **Bone density evaluation (DXA)** **Adjust for height-age Z-score in survivors <age 20 years*** Baseline BMD at entry into long-term follow-up (2 to 5 years after completion of therapy) with the following recommended actions: • If Z-score >1 SD above the mean (normal), repeat at 25 years of age when peak bone mass should be achieved • Between these two measurements and thereafter, screen as clinically indicated based on BMD and ongoing risk assessment • If Z-score >2 SD below the mean, referral to (or consultation of) a bone health specialist • If Z-score >1 and <2 SD below the mean, evaluation for endocrine defects (e.g., hypogonadism or GH deficiency) and consultation with a bone health specialist for further evaluation and interpretation of findings as clinically indicated. Repeat DXA after 2 years and thereafter as clinically indicated based on BMD change (i.e., BMD decline is greater than the DXA least significant change) and ongoing risk assessment *Pediatric Z-score calculator adjusted for height age: https://zscore.research.chop.edu/calcpedbonedens.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 infants <12 months, 600 IU/day for those age 12 months through age 70 years, 800 IU/day for those >70 years 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, GH 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 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 BMD 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 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 cGVHD), higher cumulative corticosteroid dose (especially ≥9 gm/m^2), cranial/craniospinal radiation, HCT, or TBI.
- Pre-morbid/Co-morbid medical conditions: GH deficiency, hypogonadism/delayed puberty, hyperthyroidism
- Health behaviors: Intake of calcium and vitamin D, intake of alcohol and carbonated beverages, weight bearing exercise, smoking

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
38	**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 is associated with a greater risk than prednisone, especially for patients with ALL ≥10 years of age at time of exposure.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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 cGVHD)
- Pre-morbid/Co-morbid medical conditions: Sickle cell disease, cGVHD

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
39	**Corticosteroids** Dexamethasone Prednisone	**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** 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 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
40	**Enzymes** Asparaginase	**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
41	**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 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
42	**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/chemicals that cause vasoconstriction (e.g., pseudoephedrine, stimulants), illicit drugs (e.g., cocaine), and nicotine. **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 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
43	**Epipodophyllotoxins** Etoposide (VP16) Teniposide (VM26)	**Acute myeloid leukemia (AML)**	**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 Subsequent 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 have been modified since approximately 1990 to reduce the risk of AML.
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 that may increase risk.

- Cancer/Treatment factors: Weekly or twice weekly administration, <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 44-98) are organized by anatomic region from the head downward. In this current version of the COG LTFU Guidelines, the radiation fields are still 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
- 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 6-7
- Radiation Fields Defined, Diagram: Appendix I, page 8

Five sections of these Guidelines (Sections 60, 63, 66, 77, 78) 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 9

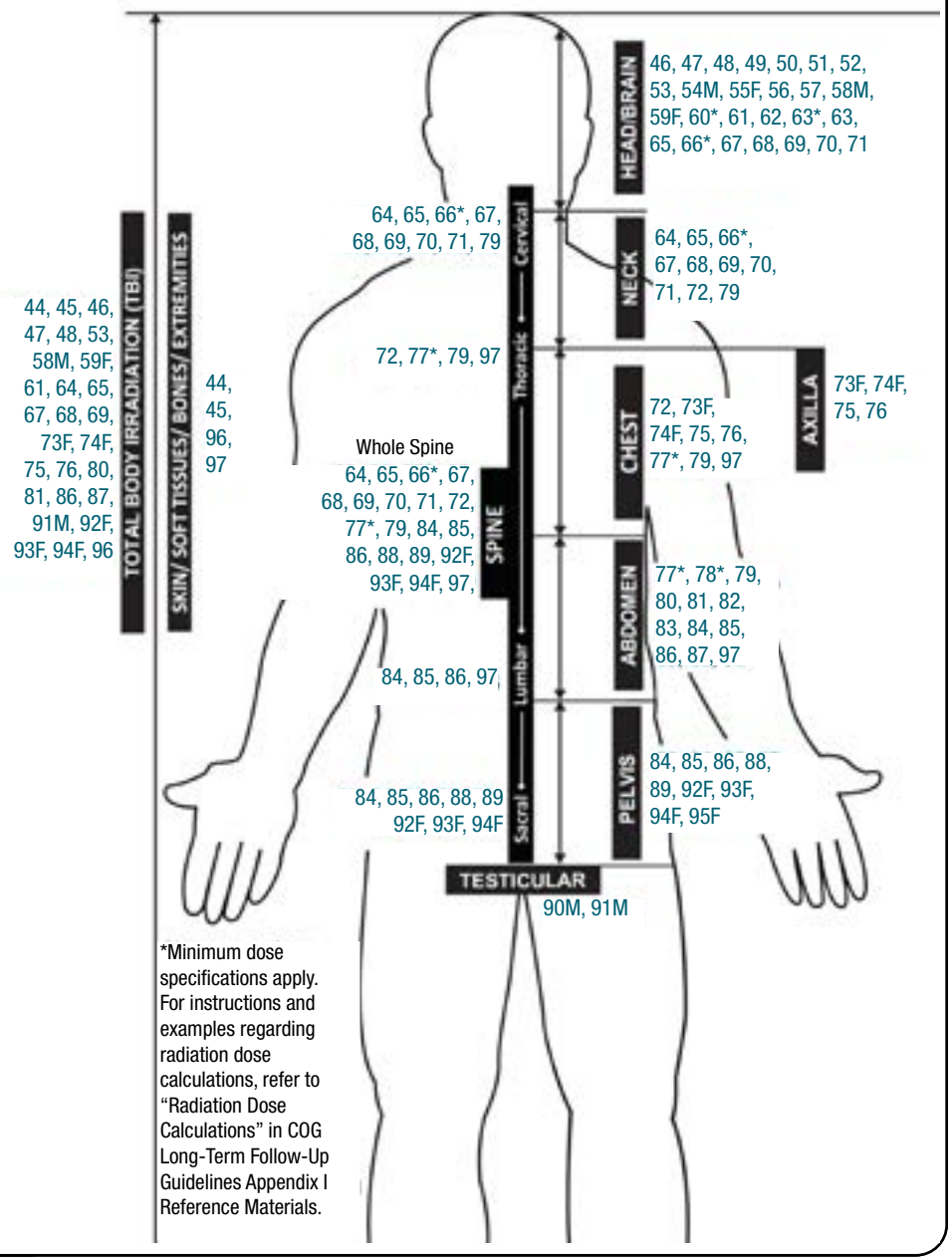
Further details regarding radiation impact by organ systems, with associated potential late effects, are also available in Appendix I, as follows:

- Guideline Radiation Sections by Potential Impact, Table: Appendix I, pages 11-12
- Guideline Radiation Sections by Potential Impact, Diagram: Appendix I, page 13
- Total Body Irradiation (TBI) Related Potential Late Effects: Appendix I, page 14

Use the "Patient-Specific Guideline Identification Tool" in Appendix I (pages 32-37) 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



Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
44	**Any Radiation (Including TBI)**	**Subsequent 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 Subsequent 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. 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 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* likely pathogenic variant), 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
45	**Any Radiation (Including TBI)**	**Dermatologic toxicity other than neoplasms** 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 that may increase risk.

- Patient factors: Younger age at treatment
- Cancer/Treatment factors: Total radiation dose ≥40 Gy, especially ≥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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
46	**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 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-dependent fashion)
- 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
47	**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** School After Treatment **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 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 including hippocampus (without hippocampal sparing), higher radiation dose, larger radiation field, greater cortical volumes, cranial radiation in combination with TBI, lack of volume-sparing radiation techniques (e.g., proton beam therapy), 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, CRT-induced ototoxicity, chronic conditions (e.g., endocrine, cardiopulmonary, frailty)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
48	**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 or Brain MRI with MRA as clinically indicated with preferred study based on intracranial lesion to be evaluated: • Calcifications: CT • White matter: MRI with DTI • Microvascular injury: Gadolinium-enhanced MRI with 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 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 ≥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)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
49	**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 DWI with MRA 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 ≥1 of the three major cerebral vessels with the development of small, immature collateral vessels, and 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 that may increase risk.

- Cancer/Treatment factors: Parasellar tumor, radiation dose ≥18 Gy, especially ≥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
50	**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 that may increase risk.

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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
51	**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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
52	**Head/Brain**	**Overweight** **Obesity**	**PHYSICAL** **Height** **Weight** **BMI** Yearly	**HEALTH LINKS** Nutrition 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 dietitian for nutrition education and 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 metabolic syndrome.
Definitions of metabolic syndrome generally include a combination of central (abdominal) obesity with at least 2 or more of the following: elevated blood pressure, atherogenic dyslipidemia (elevated triglycerides, reduced HDL cholesterol), and abnormal glucose metabolism.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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 cGVHD)
- Pre-morbid/Co-morbid medical conditions: GH deficiency, hypothyroidism, hypogonadism, inability to exercise

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
53	**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** Magic Foundation for Children's Growth: www.magicfoundation.org **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Growth velocity can be assessed using dedicated charts or electronic medical record tools if available. Consider bone density testing in patients who are GH deficient. Evaluate thyroid function in any poorly growing child. Endocrine consultation for: • Dose ≥30 Gy • Poor growth for age or stage of puberty as evidenced by persistent decline in growth velocity and change in percentile rankings on growth chart, weight <3rd percentile on growth chart • Discuss risks/benefits of adult GH replacement **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Growth charts available on-line at www.cdc.gov/growthcharts/ and www.who.int/tools/child-growth-standards/standards

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

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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
54 (male)	**Head/Brain**	**Precocious puberty**	**PHYSICAL** **Height** **Weight** **Tanner staging** **Testicular volume by Prader orchidometer** Yearly until sexually mature	**HEALTH LINKS** **Precocious Puberty** **RESOURCES** Magic Foundation for Children's Growth: 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. Growth velocity can be assessed using dedicated charts or electronic medical record tools if available. Endocrine consultation for suspected precocious puberty (males <9 years). **SYSTEM = Endocrine/Metabolic** **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.
Affected children may present with accelerated linear growth but this could mask co-existing GH deficiency.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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
55 (female)	**Head/Brain**	**Precocious puberty**	**PHYSICAL** **Height** **Weight** **Tanner staging** Yearly until sexually mature	**HEALTH LINKS** Precocious Puberty **RESOURCES** Magic Foundation for Children's Growth: 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. Growth velocity can be assessed using dedicated charts or electronic medical record tools if available. Endocrine consultation for suspected precocious puberty (females <8 years). **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Affected children may present with accelerated linear growth but this could mask co-existing GH deficiency.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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
56	**Head/Brain**	**Hyperprolactinemia**	**HISTORY** **Decreased libido** **Galactorrhea** **Menstrual history** Yearly	**HEALTH LINKS** Hyperprolactinemia **RESOURCES** Magic Foundation for Children's Growth: 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 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
57	**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 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 TSH deficiency.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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 (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** Testicular and Reproductive Health 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 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. Hormonal replacement therapy for hypogonadal patients. Refer to reproductive endocrinology as clinically indicated for infertility evaluation and consultation regarding assisted reproductive technologies. BMD 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 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

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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
59 (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** Ovarian and Reproductive Health 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 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. Hormonal replacement therapy for hypogonadal patients. Refer to reproductive endocrinology as clinically indicated for infertility evaluation and consultation regarding assisted reproductive technologies. BMD 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 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

Chemaitilly W, Li Z, Huang S, et al: Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 33:492-500, 2015

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
60	**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** Magic Foundation for Children's Growth: www.magicfoundation.org **COUNSELING** Need for corticosteroid replacement therapy and stress dosing. Obtain medical alert bracelet or card. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** If dose ≥30 Gy 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

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 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
61	**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 CRT.

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 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
62	**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 CRT.
Patients with a history of an ocular tumor (e.g., retinoblastoma) are at higher risk for late-onset ocular complications and should receive ongoing opthalmology follow-up 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 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: cGVHD (xerophthalmia only)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
63	**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 years	**HEALTH LINKS** Hearing Loss School After Treatment **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 can be performed if the above is inconclusive.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
64	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Xerostomia** **Salivary gland dysfunction**	**HISTORY** **Xerostomia (dry mouth)** 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 (e.g., 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 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: cGVHD

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
65	**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 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 ≥10 Gy)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
66	**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 that may increase risk.

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

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 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 that may increase risk.

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

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**	**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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
69	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Hypothyroidism**	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** **Menstrual Irregularity** 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 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
70	**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 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
71	**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 Nutrition and Physical Activity **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Optimize CVRFs, including blood pressure, lipid profile, and blood glucose. Doppler ultrasound of carotid vessels as clinically indicated. Refer to cardiology if abnormal. MRI with DWI with MRA 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 that may increase risk.

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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
72	**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 Nutrition and Physical Activity **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Optimize CVRFs, including blood pressure, lipid profile, and blood glucose. Doppler ultrasound of carotid vessels as clinically indicated. Refer to cardiology if abnormal. MRI with DWI with MRA 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 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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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
73 (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 **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Surgery and/or oncology consultation as clinically indicated. **SYSTEM = SMN** **SCORE = 1**

Additional Information

Mammography is 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 pathogenic or likely pathogenic variant 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 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
74 (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 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)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
75	**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 and environmental tobacco smoke avoidance/Smoking cessation. Influenza and Pneumococcal vaccinations. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. 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 that may increase risk.

- Patient factors: Younger age at irradiation
- Cancer/Treatment factors: Radiation dose >10 Gy, especially ≥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
76	**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 Subsequent 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 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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
77	**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 <15 Gy 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)** **RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM** **Anthracycline Dose*** / **Radiation Dose**** / **Recommended Frequency** None to <100mg/m² / None to <15Gy / No screening None to <100mg/m² ≥100 to <250mg/m² / 15Gy to <30Gy None to <15Gy / Every 5 years ≥100 to <250mg/m² None to Any ≥ 250mg/m² / ≥15Gy ≥30Gy None to Any / Every 2 years *Based on doxorubicin isotonic equivalent dose. See dose conversion instructions in section 34. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). **If dose ≥15 Gy:** **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 Nutrition and Physical Activity Dental Health **COUNSELING** Traditional CVRFs significantly increase survivors' risk of cardiomyopathy. Counsel regarding the importance of maintaining blood pressure, BMI, lipids, and glucose levels within goal ranges per general population guidelines. Regarding exercise: • Exercise is generally safe and encouraged for patients with normal LV systolic function • Consult cardiology for survivors with asymptomatic cardiomyopathy to define physical activity limits and precautions. • Consider cardiology consultation to define physical activity limits and precautions 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 use of QTc prolonging medications (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echo images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, LV 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 ≥30 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 • ≥30 Gy chest radiation, or • Anthracycline (any dose) combined with chest radiation (≥15 Gy) • Evaluation should include a baseline echo (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echos, follow-up echos 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, and should be monitored periodically during pregnancy and during labor and delivery due to increased risk for heart failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Additional Information

Exertional intolerance is an uncommon presentation of LV dysfunction in patients <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 that may increase risk.

- Patient factors: Younger age at irradiation, especially age <5 years, family history of dyslipidemia, CAD
- 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 ≥30 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)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
78	**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 radiation 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 of malaria and tick-borne diseases if living in or visiting endemic areas. Obtain medical alert bracelet/card noting functional asplenia. Discuss importance of immunization 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. **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. Discuss with dental provider potential need for antibiotic prophylaxis based on planned procedure. **SYSTEM = Immune** **SCORE = 1**

Additional Information

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

- Cancer/Treatment factors: Higher radiation dose, larger volume of spleen in treatment field, include documentation of splenic radiation dose exposure in the survivor's treatment summary.

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
79	**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 that may increase risk.

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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
80	**Abdomen** **TBI**	**Impaired glucose metabolism/Diabetes mellitus**	**SCREENING** **Fasting blood glucose OR HbA1c** Every 2 years	**HEALTH LINKS** Nutrition 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 dietitian for blood sugar management. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Impaired glucose metabolism may occur as a part of a constellation of conditions known as metabolic syndrome.

Definitions of metabolic syndrome generally include a combination of central (abdominal) obesity and ≥2 of the following: elevated blood pressure, atherogenic dyslipidemia (elevated triglycerides, reduced HDL cholesterol), abnormal glucose metabolism.

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 that may increase risk.

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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
81	**Abdomen** **TBI**	**Dyslipidemia**	**SCREENING** **Fasting lipid profile** Every 2 years	**HEALTH LINKS** Nutrition 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 dietitian. **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 that may increase risk.

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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
82	**Abdomen**	**Hepatic toxicity** Hepatic fibrosis Cirrhosis FNH	**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

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 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
- Health behaviors: Alcohol use (in relation to hepatic fibrosis and cirrhosis)

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
83	**Abdomen**	**Cholelithiasis**	**HISTORY** **Colicky abdominal pain related to fatty food intake** **Excessive flatulence** Yearly **PHYSICAL** **Epigastric or RUQ 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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
84	**Abdomen** **Pelvis** **Spine (lumbar, sacral, whole)**	**Bowel obstruction**	**HISTORY** **Abdominal pain** **Distension** **Vomiting** **Constipation** Yearly **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** Yearly	**HEALTH LINKS** Gastrointestinal Health **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Imaging 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 that may increase risk.

- Cancer/Treatment factors: Abdominal surgery, radiation dose ≥20 Gy (especially ≥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
85	**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 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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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
86	**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 selecting an option that is acceptable to the survivor and 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 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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
87	**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 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 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
88	**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 the iliac crest.

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

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

References

Chou R, Dana T: Screening adults for bladder cancer: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 153:461-8, 2010

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
90 (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 **SCREENING** **AM testosterone in high risk patients starting at 18 years**	**HEALTH LINKS** Testicular and Reproductive Health **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Testosterone insufficiency or deficiency requiring hormone replacement after alkylating agents only is rare. Endocrine referral for the following: • No signs of puberty by age 14 years • Failure of pubertal progression • Adults with low AM testosterone levels 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. Consider assessment of fertility status prior to initiation of testosterone replacement therapy. **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 that may increase risk.

- 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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
91 (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** **Testicular and Reproductive Health** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. Review previous fertility preservation counseling/interventions. Fertility recovery can be seen in the early years after completion of therapy and occasionally thereafter. **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 that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents)
- 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, cGVHD
- Health behaviors: Tobacco/Marijuana use

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
92 (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** Ovarian and Reproductive Health **COUNSELING** Review previous fertility preservation counseling/interventions. Higher cumulative doses of alkylating agents with or without radiation may increase risk. Dose can be estimated using CED dose calculation located in section 14. 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 by age 13 years • 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 the iliac crest.

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

- Patient factors: Older age at irradiation
- Cancer/Treatment factors: Radiation dose ≥5 Gy if pubertal (especially ≥10 Gy), dose ≥10 Gy if prepubertal (especially ≥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
93 (female)	**Pelvis** **Spine (sacral, whole)** **TBI**	**Diminished Ovarian Reserve (DOR)** Infertility	**HISTORY** **Menstrual and pregnancy history** **Hormonal Therapy** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly	**HEALTH LINKS** **Ovarian and Reproductive Health** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org Livestrong Foundation: www.livestrong.org/what-we-do/program/fertility Oncofertility Consortium: https://oncofertility.msu.edu **COUNSELING** Need for contraception. Review previous fertility preservation counseling/interventions. Fertility recovery can be seen in the early years after the completion of therapy and occasionally thereafter. Potential for shorter period of fertility in family planning. Those with DOR should consider discussing reproductive health options with a reproductive endocrinologist or fertility specialist. Higher cumulative doses of alkylating agents with or without radiation may increase risk. Dose can be estimated using CED dose calculation located in section 15. **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 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 the iliac crest.

AMH may be low in the presence of normal FSH. AMH should be interpreted relative to age-specific reference ranges. FSH is lowered and AMH may be lowered by concurrent hormonal contraceptive use.

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

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

References

Chemaitilly W, Li Z, Krasin MJ, et al: Premature ovarian insufficiency in childhood cancer survivors: a report from the St. Jude Lifetime Cohort. J Clin Endocrinol Metab 102(7):2242-50, 2017

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
94 (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 for women of reproductive age	**HEALTH LINKS** Ovarian and Reproductive Health **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 that may increase risk.
- Patient factors: Wilms tumor and associated Mullerian anomalies (i.e., agenesis, hypoplasia), 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
95 (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 (e.g., 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 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: cGVHD

References

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Spunt SL, Sweeney TA, Hudson MM, et al: Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. J Clin Oncol 23:7143-51, 2005

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
96	**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 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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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
97	**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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
98	**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 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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Im C, Li N, Moon W, et al: Genome-wide association studies reveal novel locus with sex-/therapy-specific fracture risk effects in childhood cancer survivors. J Bone Miner Res 36(4):685-695, 2021

Paulino AC: Late effects of radiotherapy for pediatric extremity sarcomas. Int J Radiat Oncol Biol Phys 60:265-74, 2004

Hematopoietic Cell Transplant Introductory Information

- Complications after HCT 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**
44	Both	Subsequent benign or malignant neoplasm occurring in or near radiation field
45	Both	Dermatologic toxicity
46	Both	Brain tumor (benign or malignant)
47	Both	Neurocognitive deficits
48	Both	Clinical leukoencephalopathy
53	Both	Growth hormone deficiency
58	Male	Gonadotropin deficiency
59	Female	Gonadotropin deficiency
61	Both	Cataracts
64	Both	Xerostomia; Salivary gland dysfunction
65	Both	Dental abnormalities; Temporomandibular joint dysfunction
67	Both	Thyroid nodules
68	Both	Thyroid cancer
69	Both	Hypothyroidism
73	Female	Breast cancer
74	Female	Breast tissue hypoplasia
75	Both	Pulmonary toxicity
76	Both	Lung cancer
80	Both	Impaired glucose metabolism/diabetes mellitus
81	Both	Dyslipidemia
86	Both	Colorectal cancer
87	Both	Renal toxicity
91	Male	Impaired spermatogenesis
92	Female	Ovarian hormone deficiencies
93	Female	Diminished ovarian reserve
94	Female	Uterine vascular insufficiency
96	Both	Musculoskeletal growth problems

HEMATOPOIETIC CELL TRANSPLANT

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
99	**Autologous Hematopoietic Cell Transplant (HCT)**	**Acute myeloid leukemia (AML)** **Myelodysplasia (MDS)**	**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 Subsequent 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 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

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
100 (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 Subsequent 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 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, ATG
- Pre-morbid/Co-morbid medical conditions: Hepatitis C infection, cGVHD, 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
101 (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 years (see "Screening" below for specific recommendations) **SCREENING** **Cervical PAP smear** Cervical cancer screening should begin at age 21 years Women: 21 to 29 years: PAP test every 3 years. Women: 30 to 65 years: HPV and PAP test every 5 years (optimal), or PAP test alone every 3 years (alternative). Women: >65 years: No testing for cervical cancer if normal screening results in past 10 years.	**HEALTH LINKS** Reducing the Risk of Subsequent 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 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, ATG
- Pre-morbid/Co-morbid medical conditions: Hepatitis C infection, HPV infection, cGVHD, 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
102	**Hematopoietic Cell Transplant (HCT)**	**Hepatic toxicity** Chronic hepatitis Cirrhosis Iron overload Cholelithiasis FNH	**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 to evaluate hypersplenism and prothrombin time fto evaluate 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 HCV in immunosuppressed patients 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

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 that may increase risk.

- Cancer/Treatment factors: History of multiple transfusions, radiation to the liver, antimetabolite therapy
- Pre-morbid/Co-morbid medical conditions: cGVHD, viral hepatitis, history of SOS, 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
103	**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 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 cGVHD), TBI, high dose radiation to any bone, allogeneic HCT > autologous HCT
- Pre-morbid/Co-morbid medical conditions: Sickle cell disease, cGVHD, pre-transplant osteonecrosis

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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)**	**Reduced bone mineral density (BMD)** Defined as Z-score >2 SD below the mean in male survivors <50 years old and premenopausal women or T-score >1 SD below the mean in male survivors >50 years old and postmenopausal women	**SCREENING** **Bone density evaluation (DXA)** **Adjust for height-age Z-score in survivors <age 20 years*** Baseline BMD at entry into long-term follow-up (2 to 5 years after completion of therapy) with the following recommended actions: • If Z-score >1 SD above the mean (normal), repeat at 25 years of age when peak bone mass should be achieved • Between these two measurements and thereafter, screen as clinically indicated based on BMD and ongoing risk assessment • If Z-score >2 SD below the mean, referral to (or consultation of) a bone health specialist • If Z-score >1 and <2 SD below the mean, evaluation for endocrine defects (e.g., hypogonadism or GH deficiency) and consultation with a bone health specialist for further evaluation and interpretation of findings as clinically indicated. Repeat DXA after 2 years and thereafter as clinically indicated based on BMD change (i.e., BMD decline is greater than the DXA least significant change) and ongoing risk assessment *Pediatric Z-score calculator adjusted for height age: https://zscore.research.chop.edu/calcpedbonedens.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 infants <12 months, 600 IU/day for those aged 12 months through aged 70 years, 800 IU/day for those >70 years 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, GH 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 BMD of young adults at peak bone age and defined as a T-score.
A T-score is the number of standard deviations the BMD measurement is above or below the mean.
Current definitions of osteopenia (T-scores between 1.0 and 2.5 SD below the mean) and osteoporosis (T-scores >2.5 SD below the mean) were developed primarily in the context of postmenopausal women. In this population, T-scores have a well-validated correlation with fracture risk that increases with age.
The fracture risk associated with T-scores in younger populations, including cancer survivors with treatment-related hypogonadism, has not been established.
T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass.
Pediatric BMD reference data sets calculate Z-scores based on age and gender.
A Z-score is the number of standard deviations the measurement is above or below the age-matched mean BMD.
The fracture risk in pediatric patients with low bone density for chronologic age based on Z-scores has not been established.
There are no defined standards for referral or treatment of low BMD in children.

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

- Patient factors: Caucasian race, lower weight/BMI.
- Cancer/Treatment factors: Corticosteroids (especially prolonged therapy, e.g., for cGVHD), CRT, craniospinal radiation, HCT/TBI
- Pre-morbid/Co-morbid medical conditions: GH deficiency, hypogonadism/delayed puberty, hyperthyroidism, central and primary hypogonadism
- Health behaviors: Intake of calcium and vitamin D, intake of alcohol and carbonated beverages, lack of weight bearing exercise, smoking

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HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
105	**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 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 cGVHD

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
106	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**Dermatologic toxicity** Permanent alopecia Nail dystrophy Vitiligo Sclerodermatous changes Squamous cell carcinoma of the skin Melanoma Altered skin pigmentation	**PHYSICAL** **Skin self exam** Every 3 months **Hair (alopecia)** **Nails (dystrophy)** **Skin (vitiligo, atypical and changing skin lesions, 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 cGVHD; effects may persist after cGVHD resolves.

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
107	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 cGVHD; effects may persist after cGVHD resolves.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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)

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
108	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 intraoral malignancy screening. 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 cGVHD; effects may persist after cGVHD resolves.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors that may increase risk.

- Cancer/Treatment factors: Use of azathioprine for cGVHD 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 cGVHD, Fanconi anemia, dyskeratosis congenita, HPV infection

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
109	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 and Environmental tobacco smoke avoidance/Smoking cessation. Influenza and Pneumococcal vaccinations. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. 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 cGVHD; effects may persist after cGVHD resolves.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors that may increase risk.
- Cancer/Treatment factors: Prolonged immunosuppression related to cGVHD, 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
110	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 pneumonia prophylaxis, consider antibiotic prophylaxis for encapsulated organisms, and anti-viral and anti-fungal prophylaxis in patients with active cGVHD 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. Some patients with hypogammaglobulinemia require lifelong IgG replacement. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Immunologic complications related to cGVHD 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 that may increase risk.
- Pre-morbid/Co-morbid medical conditions: Active cGVHD, prolonged immunosuppression related to cGVHD and its treatment

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
111	**Hematopoietic Cell Transplant (HCT) with CURRENTLY ACTIVE cGVHD**	**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 cGVHD **SCREENING** **Blood culture** When febrile T ≥101°F (38.3°C) as indicated for patients with active cGVHD	**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. Discuss importance of immunization 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. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Antibiotic prophylaxis for encapsulated organisms and bacteremia/endocarditis prophylaxis for duration of immunosuppressive therapy for cGVHD (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. **SYSTEM = Immune** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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
112	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 cGVHD is generally not reversible over time.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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
113 (female)	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 cGVHD 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 cGVHD is made.
Vaginal fibrosis/stenosis related to cGVHD is generally not reversible over time.
Physical examination should be done with each assessment for cGVHD to detect vulvar lesions before vaginal stenosis develops.
Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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
114	**Hematopoietic Cell Transplant (HCT) with any history of cGVHD**	**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 cGVHD are generally not reversible over time.

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
115	**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, activity, and fitness 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, sexual health, or high-risk behaviors (e.g., alcohol or tobacco use). 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 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
116	**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**

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
117	**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
118	**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 that may increase risk.

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

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
119 (female)	**Hysterectomy**	**Pelvic floor dysfunction** **Urinary incontinence** **Sexual dysfunction**	**HISTORY** **Psychosocial assessment** **Urinary leakage** **Abdominal pain** **Dyspareunia** Yearly	**HEALTH LINKS** Ovarian and Reproductive Health **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 136-137 (unilateral oophorectomy) or section 138 (bilateral oophorectomy).

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

- Cancer/Treatment factors: Pelvic radiation

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
120	**Laparotomy**	**Adhesions** **Bowel obstruction**	**HISTORY** **Abdominal pain** **Distension** **Vomiting** **Constipation** Yearly **PHYSICAL** **Tenderness** **Abdominal guarding** **Distension** Yearly	**HEALTH LINKS** Gastrointestinal Health **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Imaging 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 that may increase risk.

- Cancer/Treatment factors: Combined with radiation

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
121	**Limb sparing procedure**	**Conditions 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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
122 (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	**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.

*eGFR Calculator available at: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/recommended

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

- Cancer/Treatment factors: Bilateral Wilms tumor, 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
123 (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	**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.

*eGFR Calculator available at: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/recommended

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

- Cancer/Treatment factors: Bilateral Wilms tumor, 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

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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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
124	**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** School After Treatment **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 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, CRT
- Pre-morbid/Co-morbid medical conditions: Pre-morbid learning or attention problems, hydrocephalus/history of shunt placement, seizures, posterior fossa syndrome, CNS infection, neurologic and pulmonary conditions

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
125	**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. 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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
126	**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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
127	**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, but not 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 that may increase risk.

- Cancer/Treatment factors: Primary CNS tumor

References

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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
128	**Neurosurgery-Brain** (applies only to neurosurgery with potential to affect the hypothalamic-pituitary axis)	**Overweight** **Obesity**	**PHYSICAL** **Height** **Weight** **BMI** Yearly	**HEALTH LINKS** Nutrition and Physical Activity Cardiovascular Risk Factors **COUNSELING** Obesity-related health risks. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Evaluate for central endocrinopathies, including GH 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 dietitian 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 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

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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
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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
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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
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
129	**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 GH deficiency, central hypothyroidism, central adrenal insufficiency, precocious puberty, and gonadotropin deficiency. Refer to endocrine to manage hormonal dysfunction. Diabetes insipidus is unlikely to occur as a late effect past two years from therapeutic exposure, other causes should be considered in the presence of symptoms. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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

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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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
130	**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 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
131	**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 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
132 (male)	**Neurosurgery-Spinal cord**	**Psychosexual dysfunction** Erectile dysfunction Ejaculatory dysfunction	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly	**HEALTH LINKS** Testicular and Reproductive Health **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 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

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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
133 (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 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, cGVHD, injury above the level of the sacrum

References

Bjornard KL, Howell CR, Klosky JL, et al: Psychosexual functioning of female childhood cancer survivors: a report from the St. Jude Lifetime Cohort Study. J Sex Med 17(10):1981-1994, 2020

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

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
134	**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 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

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Paulino AC, Fowler BZ: Risk factors for scoliosis in children with neuroblastoma. Int J Radiat Oncol Biol Phys 61:865-869, 2005

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
135 (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 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
136 (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** Ovarian and Reproductive Health **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 by age 13 years • 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 that may increase risk.

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

References

Bercow A, Nitecki R, Brady PC, et al: Outcomes after fertility-sparing surgery for women with ovarian cancer: a systematic review of the literature. J Minim Invasive Gynecol 28(3):527-536.e1, 2021

Chen J, Wang FF, Zhang Y, et al: Oncological and reproductive outcomes of fertility-sparing surgery in women with early-stage epithelial ovarian carcinoma: a multicenter retrospective study. Curr Med Sci 40(4):745-752, 2020

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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** unilateral	**Diminished Ovarian Reserve (DOR)** Infertility	**HISTORY** **Menstrual and pregnancy history** **Hormonal therapy** Yearly **PHYSICAL** **Tanner staging until sexually mature** Yearly	**HEALTH LINKS** **Ovarian and Reproductive Health** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org Livestrong Foundation: www.livestrong.org/what-we-do/program/fertility Oncofertility Consortium: https://oncofertility.msu.edu **COUNSELING** Potential for shorter period of fertility in family planning. Those with DOR should consider discussing reproductive health options with a reproductive endocrinologist or fertility specialist. Review previous fertility preservation counseling/interventions. 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 to assess for DOR. 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. AMH should be interpreted relative to age-specific reference ranges. FSH is lowered and AMH may be lowered by concurrent hormonal contraceptive use.

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

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

References

Chemaitilly W, Li Z, Krasin MJ, et al. Premature ovarian insufficiency in childhood cancer survivors: a report from the St. Jude Lifetime Cohort. J Clin Endocrinol Metab 102(7):2242-50, 2017

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
138 (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 years or immediately for post-pubertal patients	**HEALTH LINKS** Ovarian and Reproductive Health **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org Livestrong Foundation www.livestrong.org/what-we-do/program/fertility Oncofertility Consortium https://oncofertility.msu.edu **COUNSELING** Benefits of hormone replacement therapy in promoting pubertal progression, bone and cardiovascular health. Counsel women regarding pregnancy potential with donor eggs (if intact uterus). Review previous fertility preservation counseling/interventions. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Reproductive endocrinology referral regarding assisted reproductive technologies. BMD 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
139 (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** Testicular and Reproductive Health **COUNSELING** Wear athletic supporter with protective cup during athletic activities. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Testosterone insufficiency or deficiency requiring hormone replacement after alkylating agents only is rare. Endocrine referral for the following: • No signs of puberty by age 14 years • Failure of pubertal progression • Adults with low AM testosterone levels 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 that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents)
- 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

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
140 (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** **Testicular and Reproductive Health** **RESOURCES** American Society for Reproductive Medicine: www.asrm.org Alliance for Fertility Preservation: www.allianceforfertilitypreservation.org **COUNSELING** Need for contraception. Review previous fertility preservation counseling/interventions. Wear athletic supporter with protective cup during athletic activities. **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 that may increase risk.

- Patient factors: Medications (anabolic steroids, testosterone), occupational exposures (pesticides, heavy metals, solvents)
- 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

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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 (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 years or immediately for post-pubertal patients	**HEALTH LINKS** Testicular and Reproductive Health **COUNSELING** Review previous fertility preservation counseling/interventions. **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
142	**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 117.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors 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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
143	**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 that may increase risk.

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

References

Hale GA, Marina NM, Jones-Wallace D, et al: Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol 21:115-22, 1999

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
144 (male)	**Pelvic surgery** **Cystectomy**	**Psychosexual dysfunction** Erectile dysfunction	**HISTORY** **Sexual function (erections, nocturnal emissions, libido)** **Medication use** Yearly	**HEALTH LINKS** Testicular and Reproductive Health **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 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

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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
145 (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** Testicular and Reproductive Health **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 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
146 (female)	**Pelvic surgery** **Cystectomy**	**Sexual dysfunction**	**HISTORY** **Altered or diminished sensation, loss of sensation** **Dyspareunia** **Medication use** Yearly	**HEALTH LINKS** Ovarian and Reproductive Health **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 that may increase risk.

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

Bjornard KL, Howell CR, Klosky JL, et al: Psychosexual functioning of female childhood cancer survivors: a report from the St. Jude Lifetime Cohort Study. J Sex Med 17(10):1981-1994, 2020

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
147	**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 of malaria and tick-borne diseases if living in or visiting endemic areas. Obtain medical alert bracelet/card noting asplenia. Discuss importance of immunization 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. **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. Discuss with dental provider potential need for antibiotic prophylaxis based on planned procedure. **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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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
148	**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 and Environmental tobacco smoke avoidance/Smoking cessation. Influenza and Pneumococcal vaccinations. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. 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 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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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
149	**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 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

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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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
150	**Thyroidectomy**	**Hypothyroidism**	**SCREENING** **Endocrine 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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Lallier M, St-Vil D, Giroux M, et al: Prophylactic thyroidectomy for medullary thyroid carcinoma in gene carriers of MEN2 syndrome. J Pediatr Surg 33:846-8, 1998

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
151	**Thyroidectomy** partial	**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 that may increase risk.

- Cancer/Treatment factors: Thyroid gland in radiation field

References

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Lallier M, St-Vil D, Giroux M, et al: Prophylactic thyroidectomy for medullary thyroid carcinoma in gene carriers of MEN2 syndrome. J Pediatr Surg 33:846-8, 1998

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
152	**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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
153	**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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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
154	**Radioiodine therapy (I-131 thyroid ablation)**	**Xerostomia** **Salivary gland dysfunction** **Chronic sialadenitis**	**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 = Oral/Dental SCORE**

References

Albano D, Bertagna F, Panarotto MB, et al: Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatr Blood Cancer 64(11), 2017
Clement SC, Peeters RP, Ronckers CM, et al: Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma--a systematic review. Cancer Treat Rev 41(10):925-34, 2015
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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
155	**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

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
156	**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
157	**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, Kremer LCM, Verburg FA, et al: Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. Cancer Treat Rev 63:28-39, 2018

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

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
159	**BCR-ABL tyrosine kinase inhibitors (e.g., imatinib, dasatinib, nilotinib)**	**Growth attenuation**	**HISTORY** **Parental heights at baseline** **Growth rate** **Signs of puberty** Yearly **PHYSICAL** **Tanner staging every 6 months until sexually mature** **Height and weight measured at every visit, at least every 6 months** **Plot growth velocity** **SCREENING** **None recommended aside from History and Physical items listed above**	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** 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. Need for systematic study of the use of GH in children on chronic TKI therapy. **SYSTEM = Endocrine/Metabolic** **SCORE = 2A**

Additional Information

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

- Cancer/Treatment factors: Cranial/CRT, HCT, chronic steroid treatment

References

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Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
160	**BCR-ABL tyrosine kinase inhibitors (e.g., imatinib, dasatinib, nilotinib)**	**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** Other forms of thyroid dysfunction (hyperthyroidism) may occur. Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 2B**

Additional Information

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

- Cancer/Treatment factors: Thyroid gland in radiation field

References

Lodish MB. Kinase Inhibitors: Adverse Effects Related to the Endocrine System. J Clin Endocrinol Metab 98(4):1333-1342, 2013

Patel S, Nayernama A, Jones SC, et al: BCR-ABL1 tyrosine kinase inhibitor-associated thyroid dysfunction: a review of cases reported to the FDA Adverse Event Reporting System and published in the literature. Am J Hematol 95(12):E332-35, 2020

Samis J, Lee P, Zimmerman D, et al: Recognizing endocrinopathies associated with tyrosine kinase inhibitor therapy in children with chronic myelogenous leukemia. Pediatr Blood Cancer 63(8):1332-1338, 2016

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
161	**Other targeted biologic therapies**	**Insufficient information currently available regarding late effects**		**SYSTEM = No Known Late Effects** **SCORE = N/A**

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
162	**B-cell directed antibody-based therapies (rituximab)**	**Immunologic complications** Hypogammaglobulinemia	**HISTORY** **Recurrent unusual infections** **SCREENING** **Serum quantitative immunoglobulins** Baseline at entry into long-term follow-up, repeat as clinically indicated in patients with abnormal results	**POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Immunology or infectious diseases consultation for assistance with management of infections. Some patients with hypogammaglobulinemia require lifelong IgG replacement. **SYSTEM = Immune** **SCORE = 2A**

Additional Information

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

- Cancer/Treatment factors: Prior HCT
- Pre-morbid/Co-morbid medical conditions: Underlying primary immunodeficiency

References

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Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for high-risk, mature B-Cell Non-Hodgkin's Lymphoma in children. N Engl J Med 382(23):2207-19, 2020

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
163	Other antibody-based immune therapies, including antibody drug conjugates (e.g., blinatumomab, brentuximab vedotin, inotuzumab, gemtuzumab ozogamicin, dinutuximab, naxitamab, pembrolizumab, ipilimumab, nivolumab, atezolizumab)	Insufficient information currently available regarding late effects		SYSTEM = No Known Late Effects SCORE = N/A

GENERAL HEALTH SCREENING

Sec #	Screening	Health Counseling/ Further Considerations
164	**SCREENING** **Refer to the Centers for Disease Control and Prevention recommendations for screening, vaccines, and healthy choices:** www.cdc.gov/cancer/dcpc/prevention	**COUNSELING** Importance of general health maintenance based on age and gender, including all recommended immunizations and cancer screening. **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. Follow preventive screening recommendations for common adult-onset cancers for average risk individuals.

References

Agency for Healthcare Research and Quality: Clinical Guidelines and Recommendations: U.S. Preventive Services Task Force. www.ahrq.gov/clinic/uspstfi.htm

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Sec #	Screening	Health Counseling/ Further Considerations
165	**SCREENING** **Review age-appropriate vaccination history yearly**	**HEALTH LINKS** **Vaccines after Treatment for Cancer Survivors Treated with HCT** **Vaccines after Treatment for Cancer Survivors Treated with Chemotherapy and/or Radiation (Non-HCT)** **COUNSELING** **For survivors who have NOT received HCT:** • At entry into long-term follow-up, confirm survivors have been offered catch-up vaccinations for any that were missed during therapy according to national or regional guidelines **For survivors who have received HCT:** • Revaccinate allogeneic and autologous HCT survivors per international guidelines and after discussing with primary HCT team **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** All cancer survivors: screen for HPV vaccination - all cancer survivors should receive the 3-dose series regardless of age at first HPV vaccine dose. Regarding all other immunizations, reimmunize as indicated below: HCT patients consider current recommendations (Tomblyn et al, 2009: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3103296) Non-HCT patients, some survivors treated with conventional therapy may lose vaccine-related immunity. Shared decision-making regarding revaccinations/boosters for previously received vaccines may include any of the following approaches: • Give boosters for all routine vaccinations • Measure antibody titres (serology check) to assess for seroprotection and boosting as needed • Observe and manage as needed. See https://www.cdc.gov/vaccines/schedules/index.html for current immunization schedules

Additional Information

Testing of immune function and referral to immunology in survivors (other than allogeneic HCT survivors) should be considered only if there is clinical suspicion of immune dysfunction.

Allogeneic HCT recipients undergo testing of immune reconstitution at some centers, but there are no universal standards.

New therapies (eg immunotherapy such as chimeric antigen receptor T-cell therapy) may impact immunologic function in both the short and long term; challenges exist in recommending standard testing or re-vaccination in survivors due to paucity of long-term data.

References

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