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Late Effects of Treatment for Childhood Cancer (PDQ®)

Health Professional Version

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This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the late effects of treatment for childhood cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Pediatric Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

General Information About Late Effects of Treatment for Childhood Cancer

During the past five decades, dramatic progress has been made in the development of curative therapy for pediatric malignancies. Long-term survival into adulthood is the expectation for more than 80% of children with access to contemporary therapies for pediatric malignancies.[1,2] The therapy responsible for this survival can also produce adverse long-term health-related outcomes, referred to as *late effects*, which manifest months to years after completion of cancer treatment.

A variety of approaches have been used to advance knowledge about the very long-term morbidity associated with childhood cancer and its contribution to early mortality. These initiatives have utilized a spectrum of resources including investigation of data from the following:

- Population-based registries.[3-5]

- Self-reported outcomes (provided through large-scale cohort studies).[6,7]

- Medical assessments.[8,9]

Studies reporting outcomes in survivors who have been well characterized in regards to clinical status and treatment exposures, and comprehensively ascertained for specific effects through medical assessments, typically provide the highest quality of data to establish the occurrence and risk profiles for late cancer treatment–related toxicity. Regardless of study methodology, it is important to consider selection and participation bias of the cohort studies in the context of the findings reported.

Prevalence of Late Effects in Childhood Cancer Survivors

Late effects are commonly experienced by adults who have survived childhood cancer; the prevalence of late effects increases as time from cancer diagnosis elapses. Population-based studies support excess hospital-related morbidity among childhood and young adult cancer survivors compared with age- and gender-matched controls.[3-5,10-12]

Research has demonstrated that among adults treated for cancer during childhood, late effects contribute to a high burden of morbidity, including the following:[6,8,9,13]

- 60% to more than 90% develop one or more chronic health conditions.

- 20% to 80% experience severe or life-threatening complications during adulthood.

The variability in prevalence is related to differences in the following:

- Age and follow-up time of the cohorts studied.

- Methods and consistency of assessment (e.g., self-reported vs. risk-based medical evaluations).

Childhood Cancer Survivor Study (CCSS) investigators demonstrated that the elevated risk of morbidity and mortality among aging survivors in the cohort increases beyond the fourth decade of life. By age 50 years, the cumulative incidence of a self-reported severe, disabling, life-threatening, or fatal health condition was 53.6% among survivors, compared with 19.8% among a sibling control group. Among survivors who reached age 35 years without a previous severe, disabling, life-threatening, or fatal health condition, 25.9% experienced a new grade 3 to grade 5 health condition within 10 years, compared with 6.0% of healthy siblings.[6] The presence of serious, disabling, and life-threatening chronic health conditions adversely affects the health status of aging survivors, with the greatest impact on functional impairment and activity limitations. Female survivors demonstrate a steeper trajectory of age-dependent decline in health status compared with male survivors.[14] The even higher prevalence of late effects among clinically ascertained cohorts is related to the subclinical and undiagnosed conditions detected by screening and surveillance measures.[9]
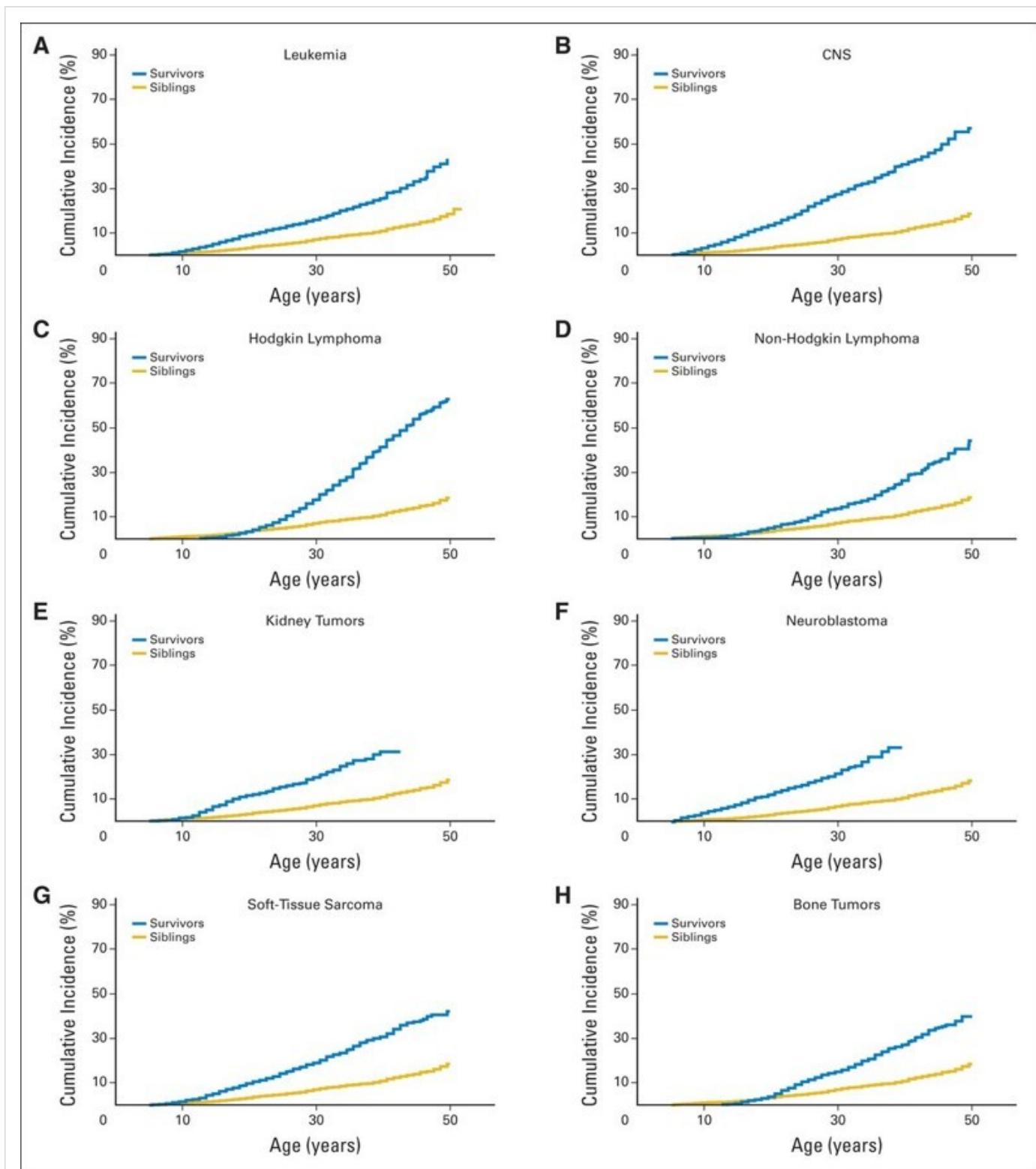
Figure 1. Cumulative incidence of chronic health conditions for severe, disabling, life-threatening, or fatal health conditions by primary childhood cancer diagnosis. (A) leukemia, (B) CNS tumors, (C) Hodgkin lymphoma, (D) non-Hodgkin lymphoma, (E) kidney tumors, (F) neuroblastoma, (G) soft tissue sarcoma, and (H) bone tumors. Gregory T. Armstrong, Toana Kawashima, Wendy Leisenring, Kayla Stratton, Marilyn Stovall, Melissa M. Hudson, Charles A. Sklar, Leslie L Robison, Kevin C. Oeffinger, Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study, Journal of Clinical Oncology, volume 32, issue 12, pages 1218-1227. Reprinted with permission. © (2014) American Society of Clinical Oncology. All rights reserved.

Recognition of late effects, concurrent with advances in cancer biology, radiological sciences, and supportive care, has resulted in a change in the prevalence and spectrum of treatment effects. In an effort to reduce and prevent late effects, contemporary therapy for most pediatric malignancies has evolved to a risk-adapted approach that is assigned based on a variety of clinical, biological, and sometimes genetic factors. With the exception of survivors requiring intensive multimodality therapy for aggressive or refractory/relapsed malignancies, life-threatening treatment effects are relatively uncommon after contemporary therapy in early follow-up (up to 10 years after diagnosis). However, survivors still frequently experience life-altering morbidity related to effects of cancer treatment on endocrine, reproductive, musculoskeletal, and neurologic function.

Mortality

Late effects also contribute to an excess risk of premature death among long-term survivors of childhood cancer. Several studies of very large cohorts of survivors have reported early mortality among individuals treated for childhood cancer compared with age- and gender-matched general population controls. Relapsed/refractory primary cancer remains the most frequent cause of death, followed by excess cause-specific mortality from subsequent primary cancers and cardiac and pulmonary toxicity.[15-20]; [21][Level of evidence: 3iA] An analysis of the CCSS and Surveillance, Epidemiology, and End Results (SEER) study evaluating conditional survival demonstrated a subsequent 5-year survival rate of 92% or higher among most diagnoses at 5 years, 10 years, 15 years, and 20 years. Among those who had survived at least 5 years from diagnosis, the probability of all-cause mortality in the next 10 years was 8.8% in the CCSS and 10.6% in the SEER study, with neoplasms accounting for cause of death in approximately 75% of survivors.[22]

Despite high premature morbidity rates, overall mortality has decreased over time.[15,23] This reduction is related to a decrease in deaths from the primary cancer without an associated increase in mortality from subsequent cancers or treatment-related toxicities. The former reflects improvements in therapeutic efficacy, and the latter reflects changes in therapy made subsequent to studying the causes of late effects. The expectation that mortality rates in survivors will continue to exceed those in the general population is based on the long-term sequelae that are likely to increase with attained age. If patients treated on therapeutic protocols are followed up for long periods into adulthood, it will be possible to evaluate the excess lifetime mortality in relation to specific therapeutic interventions.

Monitoring for Late Effects

Recognition of both acute and late modality–specific toxicity has motivated investigations evaluating the pathophysiology and prognostic factors for cancer treatment–related effects. The results of these studies have played an important role in the following areas:[15,23]

- Changing pediatric cancer therapeutic approaches to reduce treatment-related mortality among survivors treated in more recent eras.

- The development of risk counseling and health screening recommendations for long-term survivors by identifying the clinical and treatment characteristics of those at highest risk of treatment complications.

The common late effects of pediatric cancer encompass several broad domains including:

- Growth and development.

- Organ function.

- Reproductive capacity and health of offspring.

- Secondary carcinogenesis.

- Psychosocial sequelae related to the primary cancer, its treatment, or maladjustment associated with the cancer experience.

Late sequelae of therapy for childhood cancer can be anticipated based on therapeutic exposures, but the magnitude of risk and the manifestations in an individual patient are influenced by numerous factors. Factors that should be considered in the risk assessment for a given late effect include the following:

Tumor-related factors

- Tumor location.

- Direct tissue effects.

- Tumor-induced organ dysfunction.

- Mechanical effects.

Treatment-related factors

- Radiation therapy: Total dose, fraction size, organ or tissue volume, type of machine energy.

- Chemotherapy: Agent type, dose-intensity, cumulative dose, schedule.

- Surgery: Technique, site.

- Hematopoietic cell transplantation.

- Use of combined modality therapy.

- Blood product transfusion.

- Management of chronic graft-versus-host disease.

Host-related factors

- Gender.

- Genetic predisposition.

- Premorbid health state.

- Developmental status.

- Age at diagnosis.

- Time from diagnosis/therapy.

- Inherent tissue sensitivities and capacity for normal tissue repair.

- Hormonal milieu.

- Function of organs not affected by cancer treatment.

- Socioeconomic status.

- Health habits.

Resources to Support Survivor Care

Risk-based screening

The need for long-term follow-up for childhood cancer survivors is supported by the American Society of Pediatric Hematology/Oncology, the International Society of Pediatric Oncology, the American Academy of Pediatrics, the

Children's Oncology Group (COG), and the Institute of Medicine. A risk-based medical follow-up is recommended, which includes a systematic plan for lifelong screening, surveillance, and prevention that incorporates risk estimates based on the following:[24]

- Previous cancer.

- Cancer therapy.

- Genetic predisposition.

- Lifestyle behaviors.

- Comorbid conditions.

Part of long-term follow-up is also focused on appropriate screening of educational and vocational progress. Specific treatments for childhood cancer, especially those that directly impact nervous system structures, may result in sensory, motor, and neurocognitive deficits that may have adverse consequences on functional status, educational attainment, and future vocational opportunities.[25] In support of this, a CCSS investigation observed the following:[26]

- Treatment with cranial radiation doses of 25 Gy or higher was associated with higher odds of unemployment (health related: odds ratio [OR], 3.47; 95% confidence interval [CI], 2.54–4.74; seeking work: OR, 1.77; 95% CI, 1.15–2.71).

- Unemployed survivors reported higher levels of poor physical functioning than employed survivors, had lower education and income, and were more likely to be publicly insured than unemployed siblings.

These data emphasize the importance of facilitating survivor access to remedial services, which has been demonstrated to have a positive impact on education achievement,[27] which may in turn enhance vocational opportunities.

In addition to risk-based screening for medical late effects, the impact of health behaviors on cancer-related health risks is also emphasized. Health-promoting behaviors are stressed for survivors of childhood cancer. Targeted educational efforts appear to be worthwhile in the following areas:[28]

- Smoking, excess alcohol use, and illicit drug use to reduce the risk of organ toxicity and, potentially, subsequent neoplasms.

- Healthy dietary practices and active lifestyle to reduce treatment-related metabolic and cardiovascular complications.

Proactively addressing unhealthy and risky behaviors is pertinent, as several research investigations confirm that long-term survivors use tobacco and alcohol and have inactive lifestyles at higher rates than is ideal given their increased risk of cardiac, pulmonary, and metabolic late effects.[28-30]

Access to risk-based survivor care

Most childhood cancer survivors do not receive recommended risk-based care. The CCSS observed the following:

- 88.8% of survivors reported receiving some form of medical care.[31]

- 31.5% reported receiving care that focused on their previous cancer (survivor-focused care).[31]

- 17.8% reported receiving survivor-focused care that included advice about risk reduction and discussion or ordering of screening tests.[31]

- Surveillance for new cases of cancer was very low in survivors at the highest risk of colon, breast, or skin cancer,

suggesting that survivors and their physicians need education about the risk of subsequent neoplasms and recommended surveillance.[32]

Access to health insurance appears to play an important role in risk-based survivor care.[33,34] Lack of access to health insurance affects the following:

- **Cancer-related visits.** In a CCSS study, uninsured survivors were less likely than those privately insured to report a cancer-related visit (adjusted relative risk [RR], 0.83; 95% CI, 0.75–0.91) or a cancer center visit (adjusted RR, 0.83; 95% CI, 0.71–0.98). Uninsured survivors had lower levels of utilization in all measures of care than privately insured survivors. In contrast, publicly insured survivors were more likely to report a cancer-related visit (adjusted RR, 1.22; 95% CI, 1.11–1.35) or a cancer center visit (adjusted RR, 1.41; 95% CI, 1.18–1.70) than were privately insured survivors.[33]

- **Health outcomes.** In a study comparing health care outcomes for long-term survivors of adolescent and young adult (AYA) cancer with young adults who have a cancer history, the proportion of uninsured survivors did not differ between the two groups.[35]

- **Financial burden.** Subgroups of AYA survivors may be at additional risk of facing health care barriers. Younger survivors (aged 20–29 years), females, nonwhites, and survivors reporting poorer health faced more cost barriers, which may inhibit the early detection of late effects.[35]

Overall, lack of health insurance remains a significant concern for survivors of childhood cancer because of health issues, unemployment, and other societal factors.[36,37] Legislation, like the Health Insurance Portability and Accountability Act legislation,[38,39] has improved access and retention of health insurance among survivors, although the quality and limitations associated with these policies have not been well studied.

Transition of Survivor Care

Long-term follow-up programs

Transition of care from the pediatric to adult health care setting is necessary for most childhood cancer survivors in the United States.

When available, multidisciplinary long-term follow-up programs in the pediatric cancer center work collaboratively with community physicians to provide care for childhood cancer survivors. This type of shared-care has been proposed as the optimal model to facilitate coordination between the cancer center oncology team and community physician groups providing survivor care.[40]

An essential service of long-term follow-up programs is the organization of an individualized survivorship care plan that includes the following:

- Details about therapeutic interventions undertaken for childhood cancer and their potential health risks (e.g., chemotherapy type and cumulative dose, radiation treatment fields and dose, surgical procedures, blood product transfusions, and hematopoietic cell transplantation).

- Personalized health screening recommendations.

- Information about lifestyle factors that modify risks.

For survivors who have not been provided with this information, the COG offers a template that can be used by survivors to organize a personal treatment summary (refer to the COG Survivorship Guidelines, Appendix 1).

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

To facilitate survivor and provider access to succinct information to guide risk-based care, COG investigators have organized a compendium of exposure- and risk-based health surveillance recommendations, with the goal of standardizing the care of childhood cancer survivors.[41]

The compendium of resources includes the following:

- **Long-Term Follow-Up Guidelines.** COG *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* are appropriate for asymptomatic survivors presenting for routine exposure-based medical evaluation 2 or more years after completion of therapy.

- **Health Links.** Patient education materials called ''Health Links'' provide detailed information on guideline-specific topics to enhance health maintenance and promotion among this population of cancer survivors.[42]

- **Comprehensive reviews.** Multidisciplinary system-based (e.g., cardiovascular, neurocognitive, and reproductive) task forces who are responsible for monitoring the literature, evaluating guideline content, and providing recommendations for guideline revisions as new information becomes available have published several comprehensive reviews that address specific late effects of childhood cancer.[43-54]

Information concerning late effects is summarized in tables throughout this summary.

Several groups have undertaken research to evaluate the yield from risk-based screening as recommended by the COG and other pediatric oncology cooperative groups.[9,55,56] Pertinent considerations in interpreting the results of these studies include:

- Variability in the cohort's age at treatment.

- Age at screening.

- Time from cancer treatment.

- Participation bias.

Collectively, these studies demonstrate that screening identifies a substantial proportion of individuals with previously unrecognized, treatment-related health complications of varying degrees of severity. Study results have also identified low-yield evaluations that have encouraged revisions of screening recommendations. Ongoing research is evaluating cost effectiveness of screening in the context of consideration of benefits, risks, and harms.

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Subsequent Neoplasms

Subsequent neoplasms (SNs), which may be benign or malignant, are defined as histologically distinct neoplasms developing at least 2 months after completion of treatment for the primary malignancy. Childhood cancer survivors have an increased risk of developing SNs that varies according to the following:

- Host factors (e.g., genetics, immune function, hormone status).

- Primary cancer therapy.

- Environmental exposures.

- Lifestyle factors.

SNs are the leading cause of nonrelapse late mortality (standardized mortality ratio, 15.2; 95% confidence interval [CI], 13.9–16.6).[1] The Childhood Cancer Survivor Study (CCSS) reported the following 30-year cumulative incidence rates:[2]

- All SNs—20.5% (95% CI, 19.1%–21.8%).

- SNs with malignant histologies (excluding nonmelanoma skin cancer [NMSC])—7.9% (95% CI, 7.2%–8.5%).

- NMSC—9.1% (95% CI, 8.1%–10.1%).

- Meningioma—3.1% (95% CI, 2.5%–3.8%).

This represents a sixfold increased risk of SNs among cancer survivors, compared with the general population.[2]

The excess risk of SNs persists even after the age of 40 years.[3] At the age of 55 years, the cumulative incidence of any new SN (including malignant neoplasms, NMSCs, benign meningiomas, and other benign neoplasms) occurring after the age of 40 years was 34.6% in the CCSS cohort. The incidence of malignant SNs was 16.3%. Female gender and therapeutic radiation exposure were associated with an increased risk of subsequent malignant neoplasms in multivariate analysis. Moreover, prolonged follow-up has established that multiple SNs are common among aging childhood cancer survivors.[4,5]

The development of an SN is likely multifactorial in etiology and results from a combination of influences including gene-environment and gene-gene interactions. Outcome after the diagnosis of an SN is variable, as treatment for some histological subtypes may be compromised if childhood cancer therapy included cumulative doses of agents and modalities at the threshold of tissue tolerance.[6]

The incidence and type of SNs depend on the following:

- Primary cancer diagnosis.

- Type of therapy received.

- Presence of genetic conditions.

Unique associations with specific therapeutic exposures have resulted in the classification of SNs into the following two distinct groups:

- Chemotherapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML).

- Radiation-related solid SNs.

Therapy-Related Myelodysplastic Syndrome and Leukemia

Therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML) has been reported after treatment of Hodgkin lymphoma (HL), acute lymphoblastic leukemia (ALL), and sarcomas, with the cumulative incidence approaching 2% at 15 years after therapy.[7-10]

Characteristics of t-MDS/AML include the following:[7,11,12]

- A short latency (<10 years from primary cancer diagnosis). The risk of t-MDS/AML plateaus after 10 to 15 years. Although the risk of subsequent leukemia remains significantly elevated beyond 15 years from primary diagnosis (standardized incidence ratio [SIR], 3.5; 95% CI, 1.9–6.0), these events are relatively rare, with an absolute excess risk of 0.02 cases per 1,000 person-years.[12]

- An association with alkylating agents and/or topoisomerase II inhibitors.

t-MDS/AML is a clonal disorder characterized by distinct chromosomal changes. The following two types of t-MDS/AML are recognized by the World Health Organization classification:[13]

- **Alkylating agent-related type:** Alkylating agents associated with t-MDS/AML include cyclophosphamide, ifosfamide, mechlorethamine, melphalan, busulfan, nitrosoureas, chlorambucil, and dacarbazine.[14]
  The risk of alkylating agent–related t-MDS/AML is dose dependent, with a latency of 3 to 5 years after exposure; it is associated with abnormalities involving chromosomes 5 (-5/del(5q)) and 7 (-7/del(7q)).[14]

- **Topoisomerase II inhibitor–related type:** Topoisomerase II inhibitor agents include etoposide, teniposide, and anthracycline-related drugs.
  Most of the translocations observed in patients exposed to topoisomerase II inhibitors disrupt a breakpoint cluster region between exons 5 and 11 of the band 11q23 and fuse *mixed lineage leukemia* with a partner gene.[14]
  Topoisomerase II inhibitor–related t-AML presents as overt leukemia after a latency of 6 months to 3 years and is associated with balanced translocations involving chromosome bands 11q23 or 21q22.[15]

Therapy-Related Solid Neoplasms

Therapy-related solid SNs represent 80% of all SNs and demonstrate a strong relationship with radiation exposure and are characterized by a latency that exceeds 10 years. The risk of solid SNs continues to increase with longer follow-up. The risk of solid SNs is highest when the following occur:[2]

- Radiation exposure at a younger age.

- High total dose of radiation.

- Longer period of follow-up after radiation exposure.

The histological subtypes of solid SNs encompass a neoplastic spectrum ranging from benign and low-grade malignant lesions (e.g., NMSC, meningiomas) to high-grade malignancies (e.g., breast cancers, glioblastomas).[2,9,16-20]

Solid SNs in childhood cancer survivors most commonly involve the following: [2,7,9,17,21,22]

- Breast.

- Thyroid.

- Central nervous system (CNS).

- Bone and soft tissue.

With more prolonged follow-up of adult survivors of childhood cancer cohorts, epithelial neoplasms have been observed in the following:[2,7,16]

- Lung.

- Gastrointestinal tract.

Benign and low-grade SNs, including NMSCs and meningiomas, have also been observed with increasing prevalence

in survivors who were treated with radiation therapy for childhood cancer.[2,17,18]

In addition to radiation exposure, exposure to certain anticancer agents may result in solid SNs. In recipients of a hematopoietic cell transplant conditioned with high-dose busulfan and cyclophosphamide (Bu-Cy), the cumulative incidence of new solid cancers appears to be similar regardless of exposure to radiation. In a registry-based, retrospective, cohort study, Bu-Cy conditioning without total-body irradiation (TBI) was associated with higher risks of solid SNs than in the general population. Chronic graft-versus-host disease increased the risk of SNs, especially those involving the oral cavity.[23]

Some well-established solid SNs include the following:[24]

- **Breast cancer:** Breast cancer is the most common therapy-related solid SN after HL, largely due to the high-dose of chest radiation used to treat HL (SIR of subsequent breast cancer, 25–55).[7,25] The following has been observed in female survivors of childhood HL:

  - Excess risk has been reported in female HL survivors treated with high-dose, extended-volume radiation at age 30 years or younger.[26] Emerging data indicate that females treated with low-dose, involved-field radiation also exhibit excess breast cancer risk.[27]

  - For female HL patients treated with radiation therapy to the chest before age 16 years, the cumulative incidence of breast cancer approaches 20% by age 45 years.[7]

  - The latency period after chest irradiation ranges from 8 to 10 years, and the risk of subsequent breast cancer increases in a linear fashion with radiation dose (P for trend < .001).[28]

  Radiation-induced breast cancer has been reported in one population-based study to have more adverse clinicopathological features, as evidenced by a twofold increased risk of estrogen receptor–negative, progesterone receptor–negative breast cancer observed among 15-year HL survivors, compared with women who had sporadic breast cancer.[29] In a Stanford investigation evaluating the histological subtypes of breast cancer among 65 patients treated with radiation therapy for HL (median age, 23 years at HL diagnosis), breast cancers arising in previously irradiated breast tissue were more likely to be triple negative than were age-matched sporadic invasive cancers, and less likely to be hormone receptor–positive breast cancer, particularly hormone receptor–positive/human epidermal growth factor receptor 2–positive breast cancer.[30] These findings are in contrast to other smaller hospital-based, case-control studies of breast cancer among HL survivors that have not identified a significant variation in hormone receptor status when compared with primary breast cancer controls. Previous studies have also not demonstrated significant difference in overall risk of high-grade versus low-grade tumors. [31-33]
  Treatment with higher cumulative doses of alkylating agents and ovarian radiation greater than or equal to 5 Gy (exposures predisposing to premature menopause) have been correlated with reductions in breast cancer risk, underscoring the potential contribution of hormonal stimulation on breast carcinogenesis.[34,35]
  Most data describing the risk of radiation-associated breast cancer are based on patients treated for HL, with doses ranging from 15 Gy to 50 Gy. Lower radiation doses used to treat cancer metastatic to the lungs (e.g., Wilms tumor, sarcoma) that expose the breast tissues also appear to increase the risk of breast cancer. In 116 children in the CCSS cohort treated with 2 Gy to 20 Gy to the lungs (median, 14 Gy), the SIR for breast cancer was 43.6 (95% CI, 27.1–70.1).[36] In a report of 2,492 female participants in the National Wilms Tumor Studies 1 through 4 (1969–1995), 16 of 369 women who received chest irradiation for metastatic Wilms tumor developed invasive breast cancer (cumulative risk at age 40 years, 14.8% [95% CI, 1.3–7.41]). The SIR of 27.6 (95% CI, 16.1–44.2) was based on 5,010 person-years of follow-up. Of the 369 patients, radiation doses to the chest were lower than 12 Gy in 4%, 12 Gy in 64%, 13 Gy to 15 Gy in 19%, and higher than 15 Gy in 13% of patients. For all patients who developed breast cancer (with or without chest irradiation), the median age at first breast cancer diagnosis

was 34.3 years (range, 15.5–48.4) and the median time from Wilms tumor diagnosis was 27.1 years (range, 7.9–35.7).[37]

Although currently available evidence is insufficient to demonstrate a survival benefit from the initiation of breast cancer surveillance in women treated with radiation therapy to the chest for childhood cancer, interventions to promote detection of small and early-stage tumors may improve prognosis, particularly for those who may have more limited treatment options because of previous exposure to radiation or anthracyclines.

- **Thyroid cancer:** Thyroid cancer is observed after the following:[2,7,38]

  - Neck radiation therapy for HL, ALL, and brain tumors.

  - Iodine I 131 metaiodobenzylguanidine (^{131}I-mIBG) treatment for neuroblastoma.

  - TBI for hematopoietic stem cell transplantation.

  The risk of thyroid cancer has been reported to be 18-fold that of the general population.[39] Significant modifiers of the radiation-related risk of thyroid cancer include the following:[40,41]

  - Female gender.

  - Younger age at exposure.

  - Longer time since exposure.

  - Radiation dose. A linear dose-response relationship between radiation exposure and thyroid cancer is observed up to 29 Gy, with a decline in the odds ratio (OR) at higher doses, especially in children younger than 10 years at treatment, demonstrating evidence for a cell kill effect.[40,42]

- **CNS tumors:** Brain tumors develop after cranial irradiation for histologically distinct brain tumors [17] or for management of disease among ALL or non-Hodgkin lymphoma patients.[8,43] SIRs reported for subsequent CNS neoplasms after treatment for childhood cancer range from 8.1 to 52.3 across studies.[44]
  The risk of subsequent brain tumors demonstrates a linear relationship with radiation dose.[2,17]

  - The risk of meningioma after radiation not only increases with radiation dose but also with increased dose of intrathecal methotrexate.[45]

  - Cavernomas have also been reported with considerable frequency after CNS irradiation but have been speculated to result from angiogenic processes as opposed to true tumorigenesis.[46-48]

  Despite the well-established increased risk of subsequent CNS neoplasms among childhood cancer survivors treated with cranial irradiation, the current literature is insufficient to evaluate the potential harms and benefits of routine screening for these lesions.[44]

- **Bone and soft tissue tumors:** The risk of subsequent bone tumors has been reported to be 133-fold that of the general population, with an estimated 20-year cumulative risk of 2.8%.[49] Survivors of hereditary retinoblastoma, Ewing sarcoma, and other malignant bone tumors are at a particularly increased risk.[50,51] Radiation therapy is associated with a linear dose-response relationship.[50,52] After adjustment for radiation therapy, treatment with alkylating agents has also been linked to bone cancer, with the risk increasing with cumulative drug exposure.[50] These data from earlier studies concur with the following data observed by the CCSS and other investigators:

  - In a CCSS cohort, an increased risk of subsequent bone or soft tissue sarcoma was associated with radiation therapy, a primary diagnosis of sarcoma, a history of other SNs, and treatment with higher doses of anthracyclines or alkylating agents.[53] The 30-year cumulative incidence of subsequent sarcoma in CCSS

participants was 1.08% for survivors who received radiation therapy and 0.5% for survivors who did not receive radiation therapy.[53]

- In a retrospective cohort of 4,171 survivors of a solid childhood cancer treated between 1942 and 1986 (median follow-up, 26 years), dose-risk modeling demonstrated that the risk of bone sarcoma increased slightly up to a cumulative organ-absorbed radiation dose of 15 Gy (hazard ratio [HR], 8.2; 95 % CI, 1.6–42.9) and then rapidly increased for higher radiation doses (HR for 30 Gy or more, 117.9; 95 % CI, 36.5–380.6), compared with patients not treated with radiation therapy. The excess relative risk per Gy in this model was 1.77 (95 % CI, 0.62–5.94).[52]

- In survivors of bilateral retinoblastoma, the most common SNs seen are sarcomas, specifically osteosarcoma. [54-56] The contribution of chemotherapy to solid malignancy carcinogenesis was highlighted in a long-term follow-up study of 906 5-year hereditary retinoblastoma survivors who were diagnosed between 1914 and 1996 and observed through 2009.[51] Treatment with alkylating agents significantly increased risk of subsequent bone tumors (HR, 1.60; 95% CI, 1.03–2.49) and leiomyosarcoma (HR, 2.67; 95% CI, 1.22–5.85) among members of the cohort. Leiomyosarcoma occurrence was more common after treatment with alkylating agent chemotherapy and radiation therapy compared with radiation therapy alone (5.8% vs. 1.6% at age 40 years; P = .01).

Soft tissue sarcomas can be of various histologic subtypes, including nonrhabdomyosarcoma soft tissue sarcomas, rhabdomyosarcoma, malignant peripheral nerve sheath tumors, Ewing/primitive neuroectodermal tumors, and other rare types. The CCSS reported the following on 105 cases and 422 matched controls in a nested case-control study of 14,372 childhood cancer survivors:[57]

- Soft tissue sarcomas occurred at a median of 11.8 years (range, 5.3–31.3 years) from original diagnoses.

- Any exposure to radiation was associated with increased risk of soft tissue sarcoma (OR, 4.1; 95% CI, 1.8–9.5), which demonstrated a linear dose-response relationship.

- Anthracycline exposure was associated with soft tissue sarcoma risk (OR, 3.5; 95% CI, 1.6–7.7), independent of radiation dose.

- **Skin cancer:**
  Nonmelanoma skin cancers (NMSCs) represent one of the most common SNs among childhood cancer survivors and exhibit a strong association with radiation therapy.[58] The CCSS has observed the following:

  - Compared with participants who did not receive radiation therapy, CCSS participants treated with radiation therapy had a 6.3-fold increase in risk of NMSC (95% CI, 3.5–11.3).[59]

  - Ninety percent of tumors occurred within the radiation field.

  - A CCSS case-control study of the same cohort reported on subsequent basal cell carcinoma. Children who received 35 Gy or more to the skin site had an almost 40-fold excess risk of developing basal cell cancer (OR, 39.8; 95% CI, 8.6–185), compared with those who did not receive radiation therapy; results were consistent with a linear dose-response relationship, with an excess OR per Gy of 1.09 (95% CI, 0.49–2.64).[59]

  These data underscore the importance of counseling survivors about sun protection behaviors to reduce ultraviolet radiation exposure that may exacerbate this risk.[18]

The occurrence of an NMSC as the first SN has been reported to identify a population at high risk of a future invasive malignant SN.[4] CCSS investigators observed a cumulative incidence of a malignant neoplasm of 20.3% (95% CI, 13.0%–27.6%) at 15 years among radiation-exposed survivors who developed NMSC as a first

SN compared with 10.7% (95% CI, 7.2%–14.2%) whose first SN was an invasive malignancy.

Malignant melanoma has also been reported as an SN in childhood cancer survivor cohorts, although at a much lower incidence than NMSCs. A systematic review including data from 19 original studies (total N = 151,575 survivors; median follow-up of 13 years) observed an incidence of 10.8 cases of malignant melanoma per 100,000 childhood cancer survivors per year.[60]

Risk factors for malignant melanoma identified among these studies include the following:[60]

- Radiation therapy.

- Combination of alkylating agents and antimitotic drugs.

Melanomas most frequently developed in survivors of HL, hereditary retinoblastoma, soft tissue sarcoma, and gonadal tumors, but the relatively small number of survivors represented in the relevant studies preclude assessment of melanoma risk among other types of childhood cancer.[60]

CCSS investigators observed an approximate 2.5-fold increased risk (SIR, 2.42; 95% CI, 1.77–3.23) of melanoma among members of their cohort (median time to development, 21.0 years). The cumulative incidence of first subsequent melanoma at 35 years from initial cancer diagnosis was 0.55% (95% CI, 0.37–0.73), and absolute excess risk was 0.10 per 1,000 person-years (95% CI, 0.05–0.15). Family history of cancer, demographic, or treatment-related factors did not predict risk of melanoma.[61]

- **Lung cancer:** Among pediatric childhood cancer survivor cohorts, lung cancer represents a relatively uncommon SN; the 30-year cumulative incidence of lung cancer among CCSS participants was 0.1% (95% CI, 0.0%–0.2%). [2] The following has been observed in adult survivors of childhood HL:[62]

  - Lung cancer has been reported after chest irradiation for HL. The risk increases in association with longer elapsed time from diagnosis.

  - Smoking has been linked with the occurrence of lung cancer that develops after radiation therapy for HL. The increase in risk of lung cancer with increasing radiation dose is greater among patients who smoke after exposure to radiation than among those who refrain from smoking ($P = .04$).

- **Gastrointestinal (GI) cancer:** There is emerging evidence that childhood cancer survivors develop GI malignancies more frequently and at a younger age than the general population.[7,63-65]

  The Late Effects Study Group reported a 63.9-fold increased risk of gastric cancers and 36.4-fold increased risk of colorectal cancers in adult survivors of childhood HL. In addition to previous radiation therapy, younger age (0–5 years) at the time of the primary cancer therapy significantly increased risk.[7]

  In a French and British cohort-nested, case-control study of childhood solid cancer survivors diagnosed before age 17 years, the risk of developing an SN in the digestive organs varied with therapy. The following was also observed:[63]

  - The risk of GI cancer was 9.7-fold higher than in population controls.

  - The SNs most often involved the colon/rectum (42%), liver (24%), and stomach (19%).

  - A strong radiation dose-response relationship, with an OR of 5.2 (95% CI, 1.7–16.0) for local radiation doses between 10 Gy and 29 Gy and 9.6 (95% CI, 2.6–35.2) for doses of 30 Gy and above, compared with the dose response in survivors who had not received radiation therapy.

  - Chemotherapy alone and combined-modality therapy were associated with a significantly increased risk of developing a GI SN (SIR, 9.1; 95% CI, 2.3–23.6; SIR 29.0; 95% CI, 20.5–39.8).

CCSS investigators reported a 4.6-fold higher risk of GI SNs among their study participants than in the general

population (95% CI, 3.4–6.1). They also reported the following:[64]

- The SNs most often involved the colon (39%), rectum/anus (16%), liver (18%), and stomach (13%).

- The SIR for colorectal cancer was 4.2 (CI, 2.8–6.3).

- The most prevalent GI SN histology was adenocarcinoma (56%).

- The highest risk of GI SNs was associated with abdominal irradiation (SIR, 11.2; CI, 7.6–16.4), but survivors not exposed to radiation also had a significantly increased risk (SIR, 2.4; CI, 1.4–3.9).

- High-dose procarbazine (relative risk [RR], 3.2; CI 1.1–9.4) and platinum drugs (RR, 7.6; CI, 2.3–25.5) independently increased the risk of GI SNs.

St. Jude Children's Research Hospital investigators observed that the SIR for subsequent colorectal carcinoma was 10.9 (95% CI, 6.6–17.0) compared with U.S. population controls. Investigators also observed the following:
[65]

- Incidence of a subsequent colorectal carcinoma increased steeply with advancing age, with a 40-year cumulative incidence of 1.4% ± 0.53% among the entire cohort (N = 13,048) and 2.3% ± 0.83% for 5-year survivors.

- Colorectal carcinoma risk increased by 70% with each 10 Gy increase in radiation dose, and increasing radiation volume also increased risk.

- Treatment with alkylating agent chemotherapy was also associated with an 8.8-fold excess risk of subsequent colorectal carcinoma.

Collectively, these studies support the need for initiation of colorectal carcinoma surveillance at a young age among survivors receiving high-risk exposures.[7,63-65]

- **Renal carcinoma:** Consistent with reports among survivors of adult-onset cancer, CCSS investigators reported a significant excess of subsequent renal carcinoma among 14,358 5-year survivors in the cohort (SIR, 8.0; 95% CI, 5.2–11.7) compared with the general population. The reported overall absolute excess risk of 8.4 per 10^5 person-years indicates that these cases are relatively rare. Highest risk was observed among the following:

  - Neuroblastoma survivors (SIR, 85.8; 95% CI, 38.4–175.2).[66] Radiation has been hypothesized to predispose children with high-risk neuroblastoma to renal carcinoma.[67]

  - Those treated with renal-directed radiation therapy of 5 Gy or greater (RR, 3.8; 95% CI, 1.6–9.3).[66]

  - Those treated with platinum-based chemotherapy (RR, 3.5; 95% CI, 1.0–11.2).[66] Cases of secondary renal carcinoma associated with Xp11.2 translocations and *TFE3* gene fusions have also been reported and suggest that cytotoxic chemotherapy may contribute to renal carcinogenesis.[68,69]

Underlying genetic predisposition may also play a role because rare cases of renal carcinoma have been observed in children with tuberous sclerosis.[66]

Subsequent Neoplasms and Genetic Susceptibility

Literature clearly supports the role of chemotherapy and radiation therapy in the development of SNs. However, interindividual variability exists, suggesting that genetic variation has a role in susceptibility to genotoxic exposures, or that genetic susceptibility syndrome confers an increased risk of cancer, such as Li-Fraumeni syndrome.[70] Previous studies have demonstrated that childhood cancer survivors with a family history of Li-Fraumeni syndrome in particular,

or a family history of cancer, carry an increased risk of developing an SN.[71,72]

The risk of SNs could potentially be modified by mutations in high-penetrance genes that lead to these serious genetic diseases (e.g., Li-Fraumeni syndrome).[72] However, the attributable risk is expected to be very small because of the extremely low prevalence of mutations in high-penetrance genes.

Table 1 below summarizes the spectrum of neoplasms, affected genes, and Mendelian mode of inheritance of selected syndromes of inherited cancer predisposition.

Table 1. Selected Syndromes of Inherited Cancer Predisposition[a]

Syndrome	Major Tumor Types	Affected Gene	Mode of Inheritance
Adenomatous polyposis of the colon	Colon, hepatoblastoma, intestinal cancers, stomach, thyroid cancer	*APC*	Dominant
Ataxia-telangiectasia	Leukemia, lymphoma	*ATM*	Recessive
Beckwith-Wiedemann syndrome	Adrenal carcinoma, hepatoblastoma, rhabdomyosarcoma, Wilms tumor	*CDKN1C/NSD1*	Dominant
Bloom syndrome	Leukemia, lymphoma, skin cancer	*BLM*	Recessive
Diamond-Blackfan anemia	Colon cancer, osteogenic sarcoma, AML/MDS	*RPS19* and other *RP* genes	Dominant, spontaneous[b]
Fanconi anemia	Gynecological tumors, leukemia, squamous cell carcinoma	*FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG*	Recessive
Juvenile polyposis syndrome	Gastrointestinal tumors	*SMAD4/DPC4*	Dominant
Li-Fraumeni syndrome	Adrenocortical carcinoma, brain tumor, breast carcinoma, leukemia, osteosarcoma, soft tissue sarcoma	*TP53*	Dominant
Multiple endocrine neoplasia 1	Pancreatic islet cell tumor, parathyroid adenoma, pituitary adenoma	*MEN1*	Dominant
Multiple endocrine neoplasia 2	Medullary thyroid carcinoma, pheochromocytoma	*RET*	Dominant
Neurofibromatosis type 1	Neurofibroma, optic pathway glioma, peripheral nerve sheath tumor	*NF1*	Dominant
Neurofibromatosis type 2	Vestibular schwannoma	*NF2*	Dominant
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma, medulloblastoma	*PTCH*	Dominant

Peutz-Jeghers syndrome	Intestinal cancers, ovarian carcinoma, pancreatic carcinoma	STK11	Dominant
Retinoblastoma	Osteosarcoma, retinoblastoma	RB1	Dominant
Tuberous sclerosis	Hamartoma, renal angiomyolipoma, renal cell carcinoma	TSC1/TSC2	Dominant
von Hippel-Lindau syndrome	Hemangioblastoma, pheochromocytoma, renal cell carcinoma, retinal and central nervous system tumors	VHL	Dominant
WAGR syndrome	Gonadoblastoma, Wilms tumor	WT1	Dominant
Wilms tumor syndrome	Wilms tumor	WT1	Dominant
Xeroderma pigmentosum	Leukemia, melanoma	XPA, XPB, XPC, XPD, XPE, XPF, XPG, POLH	Recessive

AML = acute myeloid leukemia; MDS = myelodysplastic syndromes; WAGR = Wilms tumor, aniridia, genitourinary anomalies, mental retardation.

[a]Adapted from Strahm et al.[73]

[b]Dominant in a fraction of patients, spontaneous mutations can occur.

Drug-metabolizing enzymes and DNA repair polymorphisms

The interindividual variability in risk of SNs is more likely related to common polymorphisms in low-penetrance genes that regulate the availability of active drug metabolites or are responsible for DNA repair. Gene-environment interactions may magnify subtle functional differences resulting from genetic variations.

Drug-metabolizing enzymes

Metabolism of genotoxic agents occurs in two phases.

1. Phase I involves activation of substrates into highly reactive electrophilic intermediates that can damage DNA, a reaction principally performed by the cytochrome p450 (CYP) family of enzymes.

2. Phase II enzymes (conjugation) function to inactivate genotoxic substrates. The phase II proteins comprise the glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase-1 (NQO1), and others.

The balance between the two sets of enzymes is critical to the cellular response to xenobiotics; for example, high activity of a phase I enzyme and low activity of a phase II enzyme can result in DNA damage.

DNA repair polymorphisms

DNA repair mechanisms protect somatic cells from mutations in tumor suppressor genes and oncogenes that can lead to cancer initiation and progression. An individual's DNA repair capacity appears to be genetically determined.[74] A number of DNA repair genes contain polymorphic variants, resulting in large interindividual variations in DNA repair capacity.[74] Evaluation of the contribution of polymorphisms influencing DNA repair to the risk of SN represents an active area of research.

Screening and Follow-up for Subsequent Neoplasms

Vigilant screening is important for childhood cancer survivors at risk.[75] Because of the relatively small size of the pediatric cancer survivor population and the prevalence and time to onset of therapy-related complications, undertaking

clinical studies to assess the impact of screening recommendations on the morbidity and mortality associated with the late effect is not feasible.

Well-conducted studies on large populations of childhood cancer survivors have provided compelling evidence linking specific therapeutic exposures and late effects. This evidence has been used by several national and international cooperative groups (Scottish Collegiate Guidelines Network, Children's Cancer and Leukaemia Group, Children's Oncology Group [COG], Dutch Children's Oncology Group) to develop consensus-based clinical practice guidelines to increase awareness and standardize the immediate care needs of medically vulnerable childhood cancer survivors.[76]

All pediatric cancer survivor health screening guidelines employ a hybrid approach that is 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). The screening recommendations in these guidelines represent a statement of consensus from a panel of experts in the late effects of pediatric cancer treatment.[75,76]

The COG Guidelines for malignant SNs indicate that certain high-risk populations of childhood cancer survivors merit heightened surveillance because of predisposing host, behavioral, or therapeutic factors.[75]

- **Screening for leukemia:** t-MDS/AML usually manifests within 10 years after exposure. Recommendations include monitoring with history and physical examination for signs and symptoms of pancytopenia for 10 years after exposure to alkylating agents or topoisomerase II inhibitors.

- **Screening after radiation exposure:** Most other SNs are associated with radiation exposure and usually manifest more than 10 years after exposure. Screening recommendations include careful annual physical examination of the skin and underlying tissues in the radiation field.
  Specific comments about screening for more common radiation-associated SNs are as follows:

  - **Screening for early-onset skin cancer:** Annual dermatological exam focusing on skin lesions and pigmented nevi in the radiation field is recommended. Survivors are counseled about the following:

    - Increased risk of skin cancer.

    - Potential exacerbation of risk through tanning.

    - Benefits of adhering to behaviors to protect the skin from excessive ultraviolet radiation exposure.

  - **Screening for early-onset breast cancer:** Because outcome after breast cancer is directly linked to stage at diagnosis, close surveillance resulting in early diagnosis may confer survival advantage.[77] Several pediatric cancer groups have endorsed the recommendation for early (before population breast cancer screening) initiation of breast cancer surveillance using mammography, breast magnetic resonance imaging (MRI), or both imaging modalities in young women who were treated with chest irradiation.[78]

    Mammography, the most widely accepted screening tool for breast cancer in the general population, may not be the ideal screening tool by itself for radiation-related breast cancers occurring in relatively young women with dense breasts. On the basis of research among young women with inherited susceptibility to breast cancer, dual-imaging modalities may enhance early detection related to the higher sensitivity of MRI in detecting lesions in premenopausal dense breasts and the superiority of mammography in identifying ductal carcinoma *in situ*;[79-81] therefore, the American Cancer Society recommends including adjunct screening with MRI.[82] The high sensitivity and specificity in detecting early-stage lesions with dual-imaging surveillance is offset by a substantial rate of additional investigations attributable to false-positive results.[81]

    Many clinicians are concerned about potential harms related to radiation exposure associated with annual mammography in these young women. In this regard, it is important to consider that the estimated mean breast

dose with contemporary standard two-view screening mammograms is about 3.85 mGy to 4.5 mGy.[83-85] Thus, 15 additional surveillance mammograms from age 25 to 39 years would increase the total radiation exposure in a woman treated with 20 Gy of chest radiation to 20.05775 Gy. The benefits of detection of early breast cancer lesions in high-risk women must be balanced by the risk predisposed by a 0.3% additional radiation exposure.

To keep young women engaged in breast health surveillance, the COG Guideline recommends the following for females who received a radiation dose of **20 Gy or higher** to the mantle, mediastinal, whole lung, and axillary fields:

- Monthly breast self-examination beginning at puberty.

- Annual clinical breast examinations beginning at puberty until age 25 years.

- A clinical breast examination every 6 months, with annual mammograms and MRIs beginning 8 years after radiation therapy or at age 25 years (whichever occurs later).

The risk of breast cancer in patients who received **less than 20 Gy** of radiation with potential impact to the breast is of a lower magnitude compared with those who received more than 20 Gy. Monitoring of patients treated with less than 20 Gy of radiation with potential impact to the breast is determined on an individual basis after a discussion with the provider regarding the benefits and risk/harms of screening. If a decision is made to screen, the recommendations for women exposed to more than 20 Gy are used.

- **Screening for early-onset colorectal cancer:** Screening of those at risk of early-onset colorectal cancer (i.e., radiation doses of 30 Gy or higher to the abdomen, pelvis, or spine) includes colonoscopy every 5 years beginning at age 35 years or 10 years after radiation therapy (whichever occurs later).

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Late Effects of the Cardiovascular System

Cardiovascular disease, after recurrence of the original cancer and development of second primary cancers, has been reported to be the leading cause of premature mortality among long-term childhood cancer survivors.[1-5]

Evidence supports the excess risk of premature cardiovascular mortality as follows:

- Among more than 20,000 North American 5-year survivors of childhood cancer (in the Childhood Cancer Survivor Study [CCSS]) treated from 1970 to 1986, participants had a standardized mortality ratio of 7.0 (95% confidence interval [CI], 5.9–8.2) for cardiac mortality, which translated to 0.36 excess deaths per 1,000 person-years.[1]

- All-cause circulatory disease was associated with an absolute excess risk of 3.4% (95% CI, 2.8–4.2) among nearly 18,000 5-year survivors in the British Childhood Cancer Survivor Study who were diagnosed with cancer between 1950 and 1991. Individual standardized mortality ratios for cardiac, cerebrovascular, and other circulatory diseases ranged from 3.5 to 5.2.[2]

- All-cause cardiovascular and cardiac-specific mortality was analyzed in 4,122 5-year survivors from select centers in France and the United Kingdom, with an average follow-up of 27 years. Importantly, even radiation doses of 5 Gy to 14 Gy to the heart were associated with an increased risk of cardiac death (relative risk [RR], 12.5; $P <$ .05).[3]

By age 45 years, the overall cumulative incidence of severe, life-threatening, or fatal cardiac events has been reported to be approximately 5% for coronary artery disease and heart failure separately and 1% to 2% for valve disorders and arrhythmias.[6] Compared with siblings, 5-year survivors had RRs approaching, if not exceeding, tenfold for heart failure, coronary artery disease, and cerebrovascular disease.[7] The burden of subclinical disease is likely much greater. [8]

The specific late effects covered in this section include the following:

- Cardiomyopathy/heart failure.

- Ischemic heart disease.

- Pericardial heart disease.

- Valve disease.

- Conduction disorders.

- Cerebrovascular disease.

The section will also briefly discuss the influence of related conditions such as hypertension, dyslipidemia, and diabetes in relation to these late effects, but not directly review in detail those conditions as a consequence of childhood cancer treatment. A comprehensive review on long-term cardiovascular toxicity in childhood and young adult survivors of cancer, issued by the American Heart Association, has been published.[5]

Overall, there has been a wealth of studies focused on the topic of cardiac events among childhood cancer survivors. In addition to many smaller studies not covered in detail here, the literature includes very large cohort studies that are either hospital-based,[3,6,8-11] clinical trial based,[12] or population-based,[2,4] many with up to several decades of follow-up. However, even with decades of follow-up, the average age of these populations may still be relatively young (middle or young adulthood). And while the risk of serious cardiovascular outcomes may be very high relative to the age-matched general population, the absolute risk often remains low, limiting the power of many studies. Among the

very large studies featuring thousands of survivors, the main limitation has been inadequate ability to clinically ascertain late cardiovascular complications, with a greater reliance on either administrative records (e.g., death registries) and/or self-report or proxy-report.

While each study design has some inherent biases, the cumulative literature, based on a combination of self-reported outcomes, clinical ascertainment, and administrative data sources, is robust in concluding that certain cancer-related exposures predispose survivors towards a significantly greater risk of cardiovascular morbidity and mortality. Although late effects research often lags behind changes in contemporary therapy, many therapies linked to cardiovascular late effects remain in common use today.[13,14] Ongoing research will be important to ensure that newer *targeted* agents being introduced today do not result in unexpected cardiovascular effects.[15]

Results of selected cohort studies describing the prevalence of cardiovascular outcomes include the following:

- Austrian-German investigators evaluated the development of cardiac disease (via patient self-report supplemented by physician report) in a cohort of 1,132 pediatric Hodgkin lymphoma (HL) survivors monitored for a median of 20 years. The 25-year cumulative incidence of heart disease increased with higher mediastinal radiation doses: 3% (unirradiated), 5% (20 Gy), 6% (25 Gy), 10% (30 Gy), and 21% (36 Gy). Valve defects were most common, followed by coronary artery disease, cardiomyopathy, rhythm disorders, and pericardial abnormalities.[16]

- In a Dutch hospital-based cohort of 1,362 5-year childhood cancer survivors (median attained age, 29.1 years; median follow-up time from diagnosis, 22.2 years), the 30-year cause-specific cumulative incidence of symptomatic cardiac events (congestive heart failure, cardiac ischemia, valve disease, arrhythmia, and/or pericarditis) was significantly increased after treatment with both anthracyclines and cardiac radiation (12.6%; 95% CI, 4.3–10.3), anthracyclines alone (7.3%; 95% CI, 3.8–10.7), and cardiac radiation alone (4.0%; 95% CI, 0.5–7.4) compared with other treatments. There appeared to be an exponential relationship between cumulative anthracycline dose, cardiac radiation dose, and the risk of developing a symptomatic cardiac event.[11]

- A report from the CCSS that featured over 14,000 5-year survivors examined detailed dose-response to both radiation therapy and chemotherapy (anthracycline) in relation to self-reported (or death due to) myocardial infarction, congestive heart failure, pericardial disease, and valvular abnormalities. Cardiac radiation doses of 15 Gy or higher were associated with substantially greater risk compared with the risk seen in nonirradiated survivors, while anthracycline doses of 250 mg/m^2 or more were associated with a substantially increased risk of congestive heart failure, pericardial disease, and valvular abnormalities, independent of radiation exposure. Overall, the cumulative incidence of adverse cardiac outcomes continued to rise more than 30 years after original cancer diagnosis.[10]

- A follow-up study from the CCSS demonstrated that the cumulative incidence of these serious cardiac events continued to increase beyond age 45 years. Furthermore, the risk of these events was potentiated (i.e., beyond what would be expected by an additive model) by the presence of concurrent, but potentially modifiable, conditions such as obesity, dyslipidemia, diabetes, and, in particular, hypertension. Hypertension was independently associated with all serious cardiac outcomes (RRs, 6-fold to 19-fold), even after adjustment for anthracycline use and chest irradiation.[6]

- Using data from four large, well-annotated childhood cancer survivor cohorts (CCSS and data from the National Wilms Tumor Study Group, the Netherlands, and St. Jude Children's Research Hospital), a heart failure risk calculator based on readily available demographic and treatment characteristics has been created and validated, which may provide more individualized clinical heart failure risk estimation for 5-year survivors of childhood cancer who have recently completed therapy and up through age 40 years. One limitation of this estimator is that because of the young age of participants at the time of baseline prediction (5-year survival), information on conventional cardiovascular conditions such as hypertension, dyslipidemia, or diabetes could not be incorporated. [17]

Treatment Risk Factors

Chemotherapy (in particular, anthracyclines and anthraquinones) along with radiation therapy both independently and in combination, increase the risk of cardiovascular disease in survivors of childhood cancer and are felt to be the most important risk factors contributing to premature cardiovascular disease in this population (refer to Figure 2).[11]
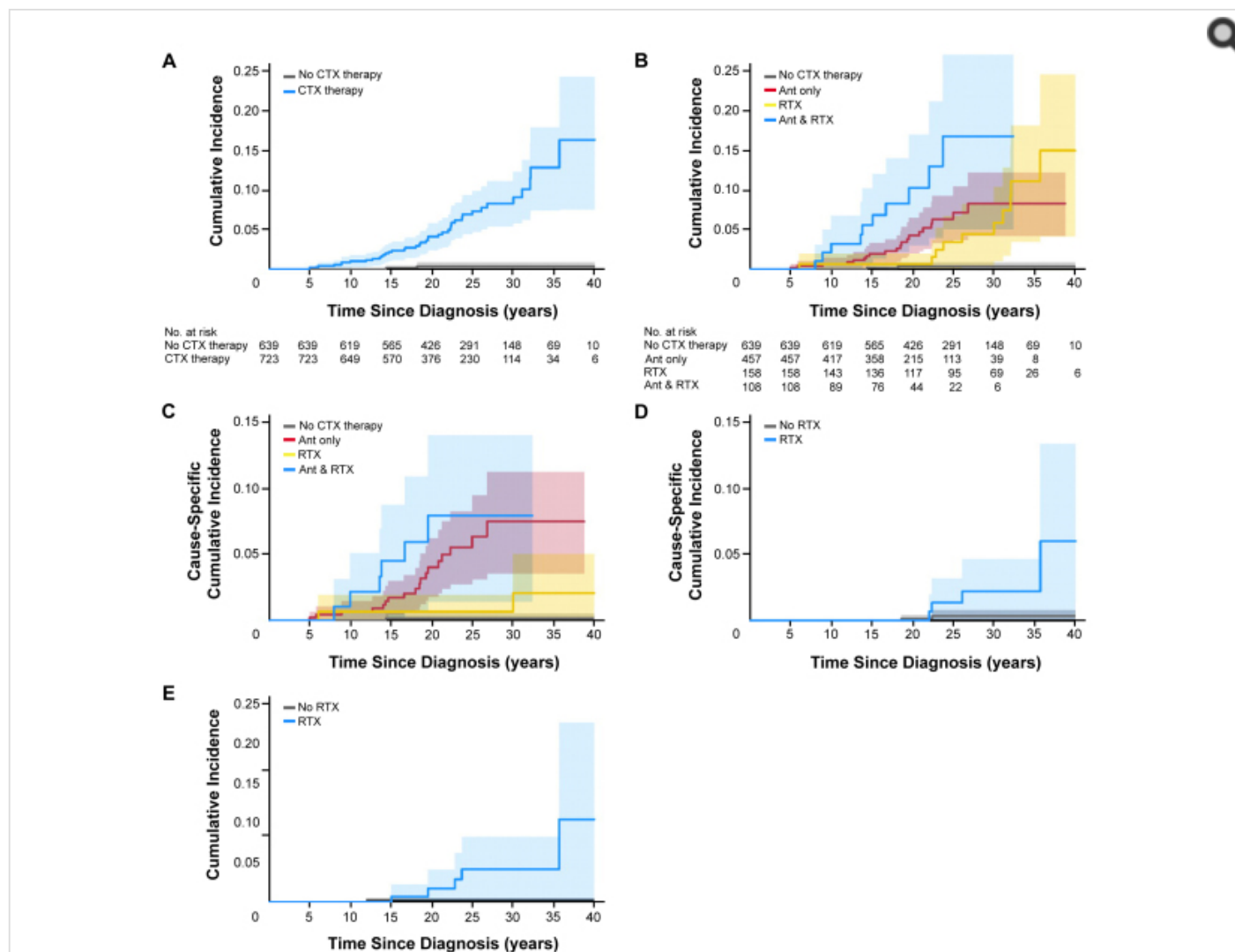
Figure 2. (A, B) Marginal (Kaplan-Meier) and (C–E) cause-specific (competing risk) cumulative incidence of cardiac events (CEs) in childhood cancer survivors stratified according to different treatment groups. (A) Marginal cumulative incidence for all CEs, stratified according to potential cardiotoxic (CTX) therapy or no CTX therapy, log-rank $P < .001$. (B) Marginal cumulative incidence for all CEs, stratified according to different CTX therapies, log-rank $P < .001$. (C) Cause-specific cumulative incidence for congestive heart failure, stratified according to different treatment groups, log-rank $P < .001$. (D) Cause-specific cumulative incidence for cardiac ischemia, stratified according to cardiac irradiation (RTX) or no RTX, log-rank $P = .01$. (E) Cause-specific cumulative incidence for valvular disease, stratified according to RTX or no RTX, log-rank $P < .001$. The shaded colorized background areas refer to the 95% CIs. Ant, anthracycline. Helena J. van der Pal, Elvira C. van Dalen, Evelien van Delden, Irma W. van Dijk, Wouter E. Kok, Ronald B. Geskus, Elske Sieswerda, Foppe Oldenburger, Caro C. Koning, Flora E. van Leeuwen, Huib N. Caron, Leontien C. Kremer, High Risk of Symptomatic Cardiac Events in Childhood Cancer Survivors, Journal of Clinical Oncology, volume 30, issue 13, pages 1429-1437. Reprinted with permission. © (2012) American Society of Clinical Oncology. All rights reserved.

Anthracyclines and related agents

Anthracyclines (e.g., doxorubicin, daunorubicin, idarubicin, and epirubicin) and anthraquinones (e.g., mitoxantrone) are known to directly injure cardiomyocytes through the formation of reactive oxygen species and inducing mitochondrial apoptosis.[5,18] The downstream results of cell death are changes in heart structure, including wall thinning, which leads to ventricular overload and pathologic remodeling that over time leads to dysfunction and eventual clinical heart failure.[19-22]

Risk factors for anthracycline-related cardiomyopathy include the following:[23]

- Cumulative dose, particularly greater than 250 mg/m^2 to 300 mg/m^2.

- Younger age at time of exposure, particularly children younger than 5 years.

- Increased time from exposure.

Among these factors, cumulative dose appears to be the most significant (refer to Figure 3).[9] While it is not completely certain whether there is a truly safe lower dose threshold, doses in excess of 250 mg/m^2 to 300 mg/m^2 have been associated with a substantially increased risk of cardiomyopathy, with cumulative incidences exceeding 5% after 20 years of follow-up, and in some subgroups, reaching or exceeding 10% cumulative incidence by age 40 years. [9,10,17,20,22] Concurrent chest or heart radiation therapy also further increases risk of cardiomyopathy,[11,17] as does the presence of other cardiometabolic traits such as hypertension.[6,24] While development of clinical heart failure can occur within a few years after anthracycline exposure, in most survivors, even those who received very high doses, clinical manifestations may not occur for decades.
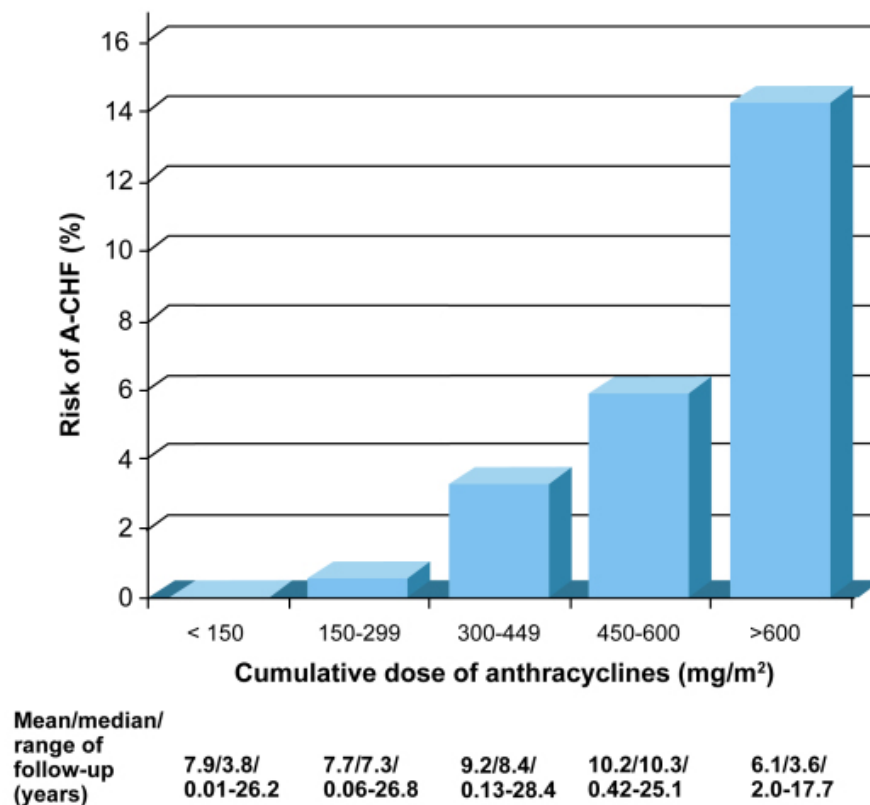
Figure 3. Risk of anthracycline-induced clinical heart failure (A-CHF) according to cumulative anthracycline dose. Reprinted from European Journal of Cancer, Volume 42, Elvira C. van Dalen, Helena J.H. van der Pal, Wouter E.M. Kok, Huib N. Caron, Leontien C.M. Kremer, Clinical heart failure in a cohort of children treated with anthracyclines: A long-term follow-up study, Pages 3191-3198, Copyright (2006), with permission from Elsevier.

Anthracycline Dose Equivalency

It remains unclear how best to add together doses of different anthracycline agents. A variety of anthracycline equivalence formulas (in relation to doxorubicin) have been used; however, they are largely based on hematologic toxicity equivalence, and may not necessarily be the same for cardiac toxicity.[17,25,26] Most pediatric professional societies and groups have generally considered daunorubicin equivalent, or near equivalent, to doxorubicin, although historically lower ratios have been proposed as well.[27] A collaborative study of North American and European pediatric cancer cohorts evaluated the hazard ratio (HR) for clinical heart failure through age 40 years for doses of daunorubicin and doxorubicin (per 100 mg/m^2 increments).[28] Among 15,815 5-year survivors of childhood cancer (median follow-up time after cohort entry of 17.3 years), the cumulative incidence of heart failure at age 40 years was 3.2% (95% CI, 2.8–3.7). The average ratio of HRs for daunorubicin to doxorubicin was 0.45 (95% CI, 0.23–0.73) by regression analysis after adjustment for sex, age at diagnosis, treatment with other anthracycline agents and chest radiation, and cohort membership; the ratio was 0.49 (95% CI, 0.28–0.70) based on a linear dose-response model. These data provide support that the relative cardiotoxicity of daunorubicin, per mg dose, is less than that of doxorubicin.

Other agents such as idarubicin, epirubicin, and mitoxantrone (an anthraquinone) were designed to reduce cardiac

toxicity while maintaining similar antitumor effect, although data supporting this are primarily limited to adult cancer patients.[29] Similarly, data on whether liposomal formulations of anthracyclines reduce cardiac toxicity in children also are limited.[29]

Anthracycline Cardioprotection

In addition to new, less cardiotoxic agents and liposomal formulations, other cardioprotective strategies that have been explored include the following:[23]

- Prolonged infusion time. Prolonged infusion time has been associated with reduced heart failure in adult patients but not in children.[30,31]

- Concurrent administration of cardioprotectants. A variety of agents have been tested as cardioprotectants (amifostine, acetylcysteine, calcium channel blockers, carvedilol, coenzyme Q10, and L-carnitine), but none have been definitively shown to be beneficial and are not considered standard of care.[32,33] There are more data for dexrazoxane as a cardioprotectant, but again, mainly in adult cancer patients, for whom it is approved by the U.S. Food and Drug Administration for women with metastatic breast cancer who have received 300 mg/m^2 of anthracyclines and who may benefit from further anthracycline-based therapy.[32] Pediatric data show that dexrazoxane may ameliorate some surrogate markers of early cardiac toxicity.[34,35] While these data suggest that dexrazoxane does protect the heart, there are not yet long-term data showing the impact of dexrazoxane on cardiac health.
  However, concerns about dexrazoxane's possible association with an increased risk of second cancers have limited its use in pediatric cancer patients.[34,35] Among Children's Oncology Group (COG) trials for T-cell acute lymphoblastic leukemia/lymphoma and HL that randomly assigned patients to doxorubicin with or without dexrazoxane (median follow-up, 12.6 years), no significant association was observed between dexrazoxane use and increased mortality, second cancer–related mortality (including acute myeloid leukemia/myelodysplastic syndrome), or relapse of the original cancer.[36]
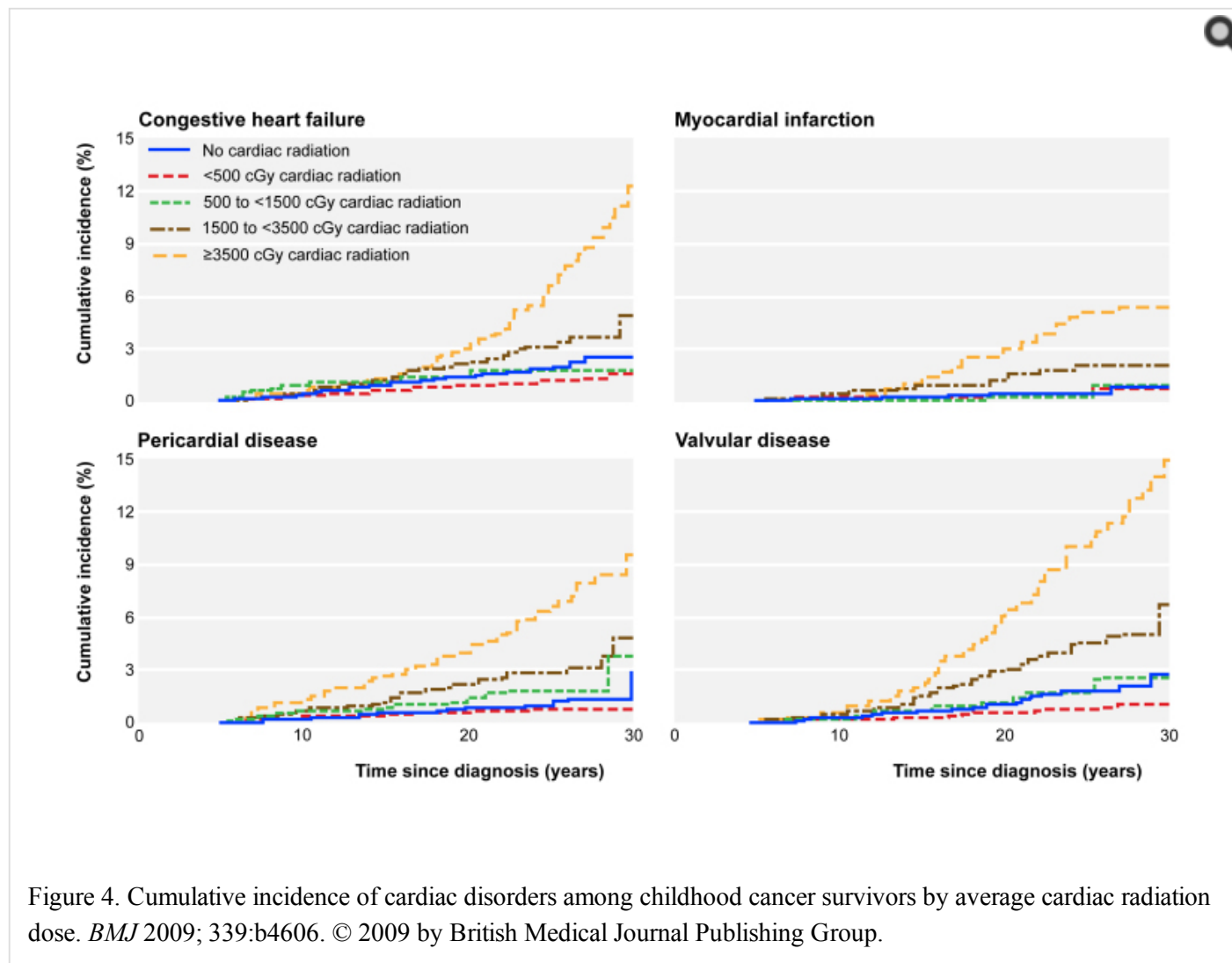
Radiation therapy

While anthracyclines directly damage cardiomyocytes, radiation therapy primarily affects the fine vasculature of affected organs.[5] Late effects of radiation therapy to the heart specifically include the following:

- Delayed pericarditis, which can present abruptly or as a chronic pericardial effusion.

- Pancarditis, which includes pericardial and myocardial fibrosis, with or without endocardial fibroelastosis.

- Cardiomyopathy (in the absence of significant pericardial disease), which can occur even without anthracycline exposure.

- Ischemic heart disease.

- Functional valve injury, often aortic.

- Conduction defects.

These cardiac late effects are related to total radiation dose, individual radiation fraction size, and the volume of the heart that is exposed. Various studies have demonstrated a substantially increased risk of these outcomes with higher radiation doses, particularly doses to the heart exceeding 35 Gy.[3,10,11,16,37,38] At higher radiation doses, rates of heart failure, pericardial disease, and valvular disease have been reported to exceed 10% after 20 to 30 years. However, even doses as low as 5 Gy have been associated with an increased risk of cardiac mortality and other serious cardiac morbidity, with possibly an exponential dose relationship.[3,11] Similar to anthracyclines, manifestation of these late effects may take years, if not decades, to present. Finally, patients who were exposed to both radiation therapy affecting

the cardiovascular system and cardiac toxic chemotherapies are at even greater risk of late cardiovascular outcomes.
[6,11]

Figure 4. Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose. *BMJ* 2009; 339:b4606. © 2009 by British Medical Journal Publishing Group.

Cerebrovascular disease after radiation therapy exposure is another potential late effect for survivors. While brain tumor survivors have had traditionally the greatest risk, other survivors exposed to cranial radiation (≥18 Gy) and neck radiation (≥40 Gy), such as leukemia and lymphoma survivors, have also been reported to be at increased risk.[39-41] In lymphoma survivors who only received chest and/or neck radiation therapy, cerebrovascular disease is thought to be caused by large-vessel atherosclerosis and cardiac embolism.[40]

As with cardiac outcomes, risk increases with cumulative dose received. One study (N = 325) reported that the stroke hazard increased by 5% (hazard ratio [HR], 1.05; 95% CI, 1.01–1.09; P = .02), with each 1 Gy increase in the radiation dose, leading to a cumulative incidence of 2% for the first stroke after 5 years and 4% after 10 years.[42] Survivors who experienced stroke were then at significantly greater risk of experiencing recurrent strokes.

Results of selected studies describing prevalence of and risk factors for cerebrovascular accident/vascular disease in childhood cancer survivors include the following:

- In a multicenter retrospective Dutch study, among 2,201 5-year survivors of HL diagnosed before age 51 years (25% pediatric-aged), with median follow-up of 18 years, 96 patients developed cerebrovascular disease (cerebrovascular accidents [CVA] and transient ischemic attacks [TIA]). Most ischemic events were from large-artery atherosclerosis (36%) or cardiac embolism (24%). The cumulative incidence of ischemic CVA or TIA 30

years after lymphoma treatment was 7%. The overall standardized incidence ratio (SIR) was 2.2 for CVA and 3.1 for TIA. However, SIR estimates appeared to be greater among childhood cancer survivors, with SIRs of 3.8 for CVA and 7.6 for TIA. Irradiation to the neck and mediastinum was an independent risk factor for ischemic cerebrovascular disease (HR, 2.5; 95% CI, 1.1–5.6) versus no radiation therapy. Treatment with chemotherapy was not associated with increased risk. Finally, hypertension, diabetes mellitus, and hypercholesterolemia were associated with the occurrence of ischemic cerebrovascular disease.[40]

- French investigators observed a significant association between radiation dose to the brain and long-term cerebrovascular mortality among 4,227 5-year childhood cancer survivors (median follow-up, 29 years). Survivors who received more than 50 Gy to the prepontine cistern had an HR of 17.8 (95% CI, 4.4–73) for death from cerebrovascular disease, compared with those who had not received radiation therapy or who had received less than 0.1 Gy in the prepontine cistern region.[41]

- A retrospective single-center cohort study of 325 survivors of pediatric cancer treated with cranial irradiation or cervical irradiation determined that cranial irradiation put survivors at a high risk of first and recurrent strokes. The cumulative incidence of first stroke was 4% (95% CI, 2.0–8.4) at 10 years after radiation therapy. The stroke hazard increased by 5% (HR, 1.05; 95% CI, 1.01–1.09; P = .02) with each 1 Gy increase in the radiation dose. The cumulative incidence of recurrent stroke was 38% (95% CI, 17–69) at 5 years and 59% (95% CI, 27–92) at 10 years after the first stroke.[42]

Conventional cardiovascular conditions

Various cancer treatment exposures may also directly or indirectly influence the development of hypertension, diabetes mellitus, and dyslipidemia.[5] These conditions remain important among cancer survivors, as they do in the general population, in that they are independent risk factors in the development of cardiomyopathy, ischemic heart disease, and cerebrovascular disease.[6,40,43,44] Childhood cancer survivors should be closely screened for the development of these conditions because they represent potentially modifiable targets for intervention. This includes being aware of related conditions such as obesity and various endocrinopathies (e.g., hypothyroidism, hypogonadism, growth hormone deficiency) that may be more common among subsets of childhood cancer survivors, and if these conditions are untreated/uncontrolled, they may be associated with a metabolic profile that increases cardiovascular risk.[8,45]

Other Risk Factors

Some, but not all, studies suggest that female gender may be associated with a greater risk of anthracycline-related cardiomyopathy.[5] In addition, there is emerging evidence that genetic factors, such as single nucleotide polymorphisms in genes regulating drug metabolism and distribution, could explain the heterogeneity in susceptibility to anthracycline-mediated cardiac injury.[46-48] However, these genetic findings still require additional validation before being incorporated into any clinical screening algorithm.[49]

Knowledge Deficits

While much knowledge has been gained over the past 20 years in better understanding the long-term burden and risk factors for cardiovascular disease among childhood cancer survivors, many areas of inquiry remain, and include the following:

- Radiation may have both direct and indirect effects on vascular endothelium, contributing to vascular damage beyond the primary radiation field.[50]

- The long-term effects of lower radiation doses, particularly in light of newer technology that allows radiation oncologists to reduce the dose to critical organs outside of the tumor field, remain to be determined.[51]

- The long-term effects of many newer anticancer agents that are based on molecular targets remains unclear, although some of them are known to have shorter-term cardiac toxicity.[15]

- The efficacy of cardioprotective strategies, including the use of alternative anthracycline formulations that appear promising in adults, requires further study in children.[23]

Screening, Surveillance, and Counseling

Various national groups, including the National Institutes of Health–sponsored COG (refer to Table 2), have published recommendations regarding screening and surveillance for cardiovascular and other late effects among childhood cancer survivors.[52-56] An effort to harmonize some of these guidelines is currently underway.[57] Adult oncology professional and national groups have also issued recommendations related to cardiac toxicity monitoring.[58] At this point, there is no clear evidence (at least through age 50 years or 30 to 40 years posttreatment) that there is a plateau in risk that occurs after a certain time among survivors exposed to cancer treatments associated with cardiovascular late effects.[3,4,10,11,39,59] Thus, some form of life-long surveillance is recommended, even if the cost-effectiveness of certain screening strategies remains unclear.[60,61]

However, a growing amount of literature is beginning to establish the yield from these screening studies, which will help inform future guidelines.[8,62] In these studies, for example, among adult-aged survivors of childhood cancer, evidence for cardiomyopathy on the basis of echocardiographic changes was found in approximately 6% of at-risk survivors. Overall, in a cohort of more than 1,000 survivors (median age, 32 years), nearly 60% of screened at-risk survivors had some clinically ascertained cardiac abnormality identified.[8]

Survivors should also be counseled regarding the cardiovascular benefits of the following factors:

- Maintaining a healthy weight.

- Adhering to a heart-healthy diet.

- Participating in regular physical activity.

- Abstaining from smoking.

Survivors should obtain medical clearance before engaging in extreme exercise programs. Given the growing evidence that conventional cardiovascular conditions such as hypertension, dyslipidemia, and diabetes substantially increase the risk of more serious cardiovascular disease among survivors, clinicians should carefully consider baseline and follow-up screening and treatment of these comorbid conditions that impact cardiovascular health.[6,40,43,44]

In addition to releasing a comprehensive, publically available (online) set of guidelines, the COG has also put together a series of handouts on cardiovascular and related topics, including lifestyle choices written for a lay audience, available on the same website.

Table 2. Cardiovascular Late Effects[a,b]

Predisposing Therapy	Potential Cardiovascular Effects	Health Screening
Any anthracycline and/or any radiation to the heart	Cardiac toxicity (arrhythmia, cardiomyopathy/heart failure, pericardial disease, valve disease, ischemic heart disease)	Yearly medical history and physical exam
		Electrocardiogram at entry into long-term follow-up
		Echocardiogram at entry into long-term follow-up, periodically repeat based on previous exposures and other risk factors
Radiation to the area (≥40 Gy)	Carotid and/or subclavian artery disease	Yearly medical history and physical exam; consider Doppler ultrasound

		10 years after exposure
Radiation to the brain/cranium (≥18 Gy)	Cerebrovascular disease (cavernomas, Moyamoya, occlusive cerebral vasculopathy, stroke)	Yearly medical history and physical exam
Total-body irradiation	Dyslipidemia	Fasting lipid profile every 2 years
Heavy metals (carboplatin, cisplatin), ifosfamide, and methotrexate exposure; radiation to the kidneys; hematopoietic cell transplantation; nephrectomy	Hypertension (as a consequence of renal toxicity)	Yearly blood pressure and urinalysis; renal function laboratory studies at entry into long-term follow-up

[a]The Children's Oncology Group (COG) guidelines also cover other conditions that may influence cardiovascular risk also exist, such as obesity and diabetes mellitus/impaired glucose metabolism.

[b]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

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Late Effects of the Central Nervous System

Neurocognitive

Neurocognitive late effects are most commonly observed after treatment of malignancies that require central nervous system (CNS)–directed therapies. While there is considerable evidence published about this outcome, its quality is often limited by small sample size, cohort selection and participation bias, cross-sectional versus prospective evaluations, and variable time of assessment from treatment exposures. CNS-directed therapies include the following:

- Cranial radiation therapy.

- Systemic therapy with high-dose methotrexate or cytarabine.

- Intrathecal chemotherapy.

Children with brain tumors or acute lymphoblastic leukemia (ALL) are most likely to be affected. Risk factors for the development of neurocognitive late effects include the following:[1-7]

- Female gender.

- Younger age at the time of treatment.

- Tumor location.

- Higher cranial radiation dose.

- Treatment with both cranial radiation therapy and chemotherapy (systemic or intrathecal).

- Lower socioeconomic status.

It should be noted that the cognitive phenotypes observed in childhood survivors of ALL and CNS tumors may differ from traditional developmental disorders. For example, the phenotype of attention problems in ALL and brain tumor survivors appears to differ from developmental attention-deficit/hyperactivity disorder in that few survivors demonstrate significant hyperactivity/impulsivity, but instead have associated difficulties with processing speed and executive function.[8,9]

Neuroimaging studies of irradiated and nonirradiated ALL survivors demonstrate a variety of CNS abnormalities, including leukoencephalopathy, cerebral lacunes, cerebral atrophy, and dystrophic calcifications (mineralizing microangiopathy). Among these, abnormalities of cerebral white matter integrity and volume have been correlated with neurocognitive outcomes.[10-13]

Cavernomas have also been observed in ALL survivors treated with cranial irradiation. They have been speculated to result from angiogenic processes as opposed to tumorigenesis.[14]

Neurocognitive outcomes in brain tumor survivors

Survival rates have increased over recent decades for children with brain tumors; however, long-term cognitive effects caused by illness and associated treatments are a well-established morbidity in this group of survivors. In childhood and adolescent brain tumor survivors, risk factors for adverse neurocognitive effects include the following:

- Cranial radiation therapy. Cranial radiation therapy has been associated with the highest risk of long-term cognitive morbidity, particularly in younger children.[15] There is an established dose-response relationship, with patients who receive higher-dose cranial radiation therapy consistently performing more poorly on intellectual measures.[16] Radiation dose to specific subvolumes of the brain, including the temporal lobes and hippocampi, have been shown to significantly impact longitudinal intelligence quotient (IQ) scores and academic achievement scores among children treated with craniospinal irradiation for medulloblastoma.[17]

- Tumor site.[15]

- Shunted hydrocephalus.[15,18,19]

- Postsurgical cerebellar mutism.[20]

- Auditory difficulties.[18]

- History of stroke.[21]

The negative impact of radiation treatment has been characterized by changes in IQ scores, which have been noted to drop about 2 to 5 years after diagnosis; the decline continues 5 to 10 years afterward, although less is known about potential stabilization or further decline of IQ scores several decades after diagnosis.[22-24] The decline in IQ scores over time typically reflects the child's failure to acquire new abilities or information at a rate similar to that of his or her peers, rather than a progressive loss of skills and knowledge.[16] Affected children also may experience deficits in other cognitive areas, including academic difficulties (reading and math) and problems with attention, processing speed, memory, and visual or perceptual motor skills.[23,25,26]

These changes in cognitive functioning may be partially explained by radiation-induced reduction of normal-appearing white matter volume or integrity of white matter pathways, as evaluated through magnetic resonance imaging (MRI). [27-29] In fact, reduced white matter integrity has been directly linked to slowed cognitive processing speed in survivors of brain tumors,[30] while greater white matter volume has been associated with better working memory, particularly in females.[29] It should be noted that data emerging from contemporary protocols show that using lower doses of cranial radiation and more targeted treatment volumes appears to reduce the severity of neurocognitive effects of therapy. [19,31]

Longitudinal cohort studies have provided insight into the trajectory and predictors of cognitive decline among survivors of CNS tumors. Results of representative cohort studies include the following:

- A report from St. Jude Children's Research Hospital showed cognitive decline after 54 Gy of conformal cranial radiation therapy in 78 children younger than 20 years (mean, 9.7 years) diagnosed with low-grade glioma (refer to Figure 5). Age at time of cranial irradiation was more important than was cranial radiation dose in predicting cognitive decline, with children younger than 5 years estimated to experience the greatest cognitive decline.[32]
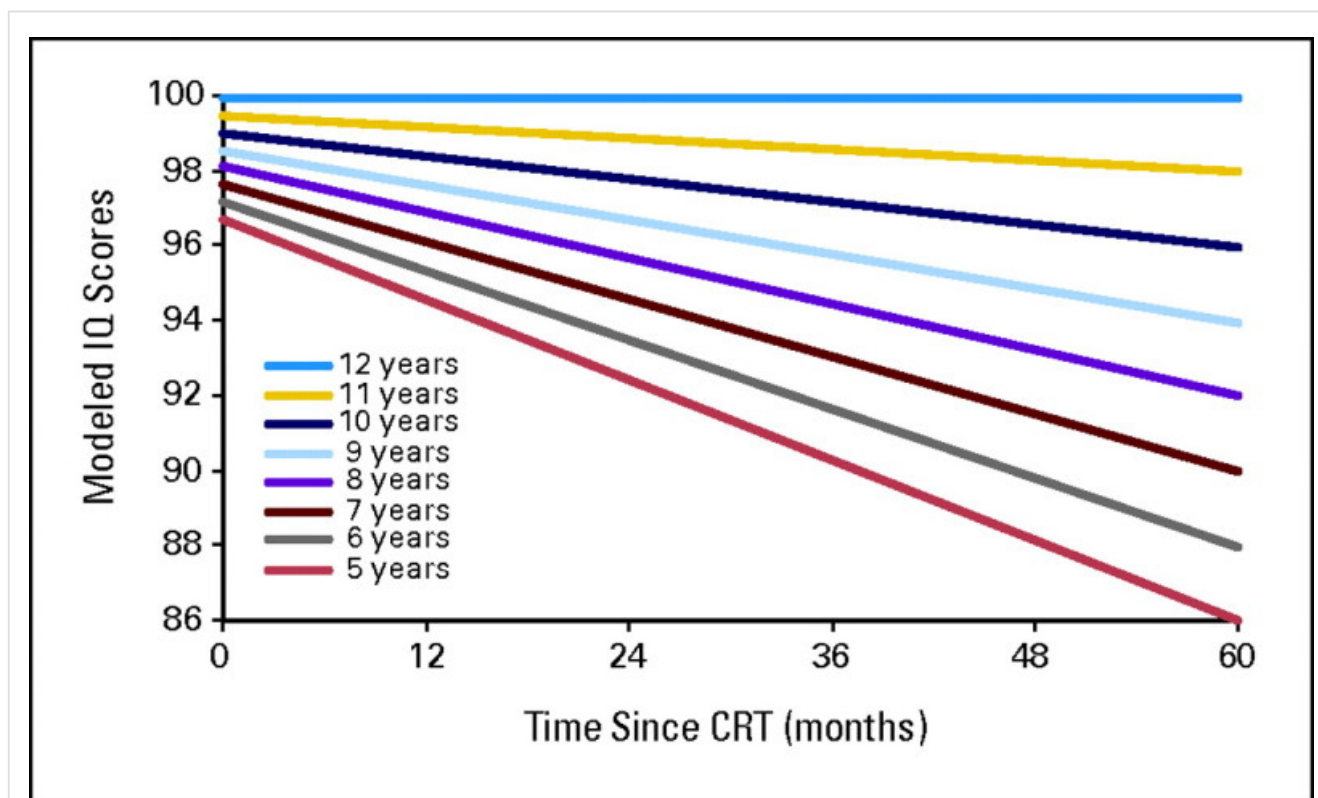

Figure 5. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age for pediatric low-grade glioma. Age is measured in years, and time is measured in months after the start of CRT. Thomas E. Merchant, Heather M. Conklin, Shengjie Wu, Robert H. Lustig, and Xiaoping Xiong, Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits, Journal of Clinical Oncology, volume 27, issue 22,

- In a study of 126 medulloblastoma survivors treated with 23.4 Gy or 36 Gy to 39.6 Gy of cranial spinal radiation (with a conformal boost dose of 55.8 Gy to the primary tumor bed), processing speed scores declined significantly over time, while less decline was observed in attention and memory performance. Higher doses of radiation and younger age at diagnosis predicted slower processing speed over time.[33] Studies of working memory and academic achievement in patients enrolled on the same medulloblastoma trial (St. Jude SJMB03 [NCT00085202]) indicated that performance was largely within the age-expected range up to 5 years postdiagnosis,[34,35] although in both studies, posterior fossa syndrome, higher cranial radiation dose, and younger age at diagnosis predicted worse performance over time. In addition, serious hearing loss was associated with intellectual and academic decline over time.[35]

- Canadian investigators evaluated the impact of radiation (dose and boost volume) and neurologic complications on patterns of intellectual functioning in a cohort of 113 medulloblastoma survivors (mean age at diagnosis, 7.5 years; mean time from diagnosis to last assessment, 6 years). Survivors treated with reduced-dose craniospinal radiation therapy plus tumor bed boost showed stable intellectual functioning. Neurological complications, such as hydrocephalus requiring cerebrospinal fluid diversion and mutism, and treatment with higher doses and larger boost volumes of radiation resulted in intellectual declines with distinctive trajectories.[36]

Although adverse neurocognitive outcomes observed 5 to 10 years after treatment are presumed to be pervasive, and potentially worsen over time, few empirical data are available regarding the neurocognitive functioning in very long-term survivors of CNS tumors.

- Among adult survivors participating in the Childhood Cancer Survivor Study (CCSS), CNS tumor survivors (n = 802) reported significantly more problems with attention/processing speed, memory, emotional control, and organization than did survivors of non-CNS malignancies (n = 5,937) and sibling controls (n = 382).[4] Moreover, a large proportion of CNS tumor survivors treated with cranial irradiation reported impairment on measures of attention/processing speed (42.9%–73.3%) and memory (14.3%–37.4%), with differences observed by diagnosis and cranial radiation dose.[37]

The neurocognitive consequences of CNS disease and treatment may have a considerable impact on functional outcomes for brain tumor survivors.

- In childhood and adolescence, neurocognitive deficits have been associated with poor social adjustment, including problems with peer relations, social withdrawal, and reduced social skills.[38,39]

- CNS tumor survivors are more likely to need special education services than are survivors of other malignancies. [40]

- Adult CNS tumor survivors are less likely to live independently, marry, and graduate from college than are survivors of other malignancies and siblings.[40-42]

Neurocognitive outcomes in acute lymphoblastic leukemia (ALL) survivors

The increase in cure rates for children with ALL over the past decades has resulted in greater attention to the neurocognitive morbidity and quality of life of survivors. The goal of current ALL treatment is to minimize adverse late effects while maintaining high survival rates. To minimize the risk of late sequelae, patients are stratified for treatment according to their risk of relapse. Cranial irradiation is reserved for the fewer than 20% of children who are considered at high risk for CNS relapse.[43]

Although low-risk, standard-risk, and most high-risk patients are treated with chemotherapy-only protocols, early reports of neurocognitive late effects for ALL patients were based on heterogeneously treated groups of survivors who were treated with combinations (simultaneously or sequentially) of intrathecal chemotherapy, radiation therapy, and high-dose chemotherapy, making it difficult to differentiate the impact of the individual treatment components. However, outcome data are increasingly available regarding the risk of neurocognitive late effects in survivors of childhood ALL treated with chemotherapy only.

ALL and cranial radiation

In survivors of ALL, cranial radiation therapy may result in clinical and radiographic neurologic late sequelae. Clinical leukoencephalopathy characterized by spasticity, ataxia, dysarthria, dysphagia, hemiparesis, and seizures is uncommon after contemporary ALL therapy. In contrast, neuroimaging frequently demonstrates white matter abnormalities among survivors treated with cranial irradiation and/or high-dose methotrexate. Radiographic leukoencephalopathy has been reported in up to 80% of children on some treatment regimens. Higher doses and more courses of intravenous methotrexate have been reported to increase risk of leukoencephalopathy.[10] In many patients, white matter anomalies are transient and decrease in prevalence, extent, and intensity with longer elapsed time from completion of therapy.[10] Leukoencephalopathy results in smaller white matter volumes that have been correlated with cognitive deficits. Although these abnormalities are mild among the irradiated patients (overall IQ fall of approximately 10 points), those who have received higher doses at a young age may have significant learning difficulties.[44,45] Deficits in neuropsychological functions such as visual-motor integration, processing speed, attention, and short-term memory are reported in children treated with 18 Gy to 24 Gy.[44,46,47] Girls and children treated at a younger age are more vulnerable to cranial radiation.[48] The decline in intellectual functioning appears to be progressive, showing more impairment of cognitive function with increasing time since radiation therapy.[48,49]

ALL and chemotherapy-only CNS therapy

Because of its penetrance into the CNS, systemic methotrexate has been used in a variety of low-dose and high-dose regimens for leukemia CNS prophylaxis. Systemic methotrexate in high doses with or without radiation therapy can lead to an infrequent but well-described leukoencephalopathy, which has been linked to neurocognitive impairment.[10] When neurocognitive outcomes after radiation therapy and chemotherapy-only regimens are directly compared, the evidence suggests a better outcome for those treated with chemotherapy alone, although some studies show no significant difference.[50,51]

Compared with cranial irradiation, chemotherapy-only CNS-directed treatment produces neurocognitive deficits involving processes of attention, speed of information processing, memory, verbal comprehension, visual-spatial skills, visual-motor functioning, and executive functioning; global intellectual function is typically preserved.[46,50,52-54] Few longitudinal studies evaluating long-term neurocognitive outcome report adequate data for a decline in global IQ after treatment with chemotherapy alone.[53] The academic achievement of ALL survivors in the long term seems to be generally average for reading and spelling, with deficits mainly affecting arithmetic performance.[50,55,56] Risk factors for poor neurocognitive outcome after chemotherapy-only CNS-directed treatment are younger age and female gender. [57,58]

Studies of neurocognitive functioning in large pediatric cancer survivor cohorts observed the following:

- In the St. Jude Total XV (NCT00137111) trial, which omitted prophylactic cranial irradiation, comprehensive cognitive testing of 243 participants at week 120 revealed higher risk for below-average performance on a measure of sustained attention but not on measures of intellectual functioning, academic skills, or memory. The risk of cognitive deficits correlated with treatment intensity but not with age at diagnosis or gender. These results underscore the need for longitudinal follow-up to better characterize the prevalence and magnitude of cognitive deficits after CNS-directed therapy with chemotherapy alone.[59]

- In a large prospective study (N = 555) of neurocognitive outcomes in children with newly diagnosed ALL who were randomly assigned to receive CNS-directed therapy according to risk group (low risk: intrathecal methotrexate vs. high-dose methotrexate; high risk: high-dose methotrexate vs. 24 Gy cranial radiation therapy), a significant reduction in IQ scores (4–7 points) was observed in all patient groups when compared with controls, regardless of the CNS treatment delivered. Children younger than 5 years at diagnosis were more likely to have IQs below 80 at 3 years posttherapy than were children older than 5 years at diagnosis, irrespective of treatment allocation, suggesting that younger children are more vulnerable to treatment-related neurologic toxic effects.[60]

- Persistent cognitive deficits and progressive intellectual decline have been observed in cohorts of adults treated for ALL during childhood and associated with reduced educational attainment and unemployment.[12,45,48] According to the results of neurocognitive testing and patient reported outcomes in more than 500 adult survivors of childhood ALL at 26 years postdiagnosis, survivors demonstrated increased rates of impairment in most neurocognitive and behavioral domains. Impairment was common in survivors treated with lower doses of cranial radiation and in those treated with chemotherapy only. Impairment in executive function skills increased with time since diagnosis; impairment in intellect, academics, and memory progressively increased with younger age at treatment in a cranial radiation dose-dependent manner; and neurocognitive function was related to functional outcomes as adults, including college graduation and full-time employment. Continued monitoring by health professionals is recommended to identify neurocognitive problems that may emerge over time.[45]

ALL and steroid therapy

The type of steroid used for ALL systemic treatment may affect cognitive functioning. In a study that involved long-term neurocognitive testing (mean follow-up, 9.8 years) in 92 children with a history of standard-risk ALL who had received either dexamethasone or prednisone during treatment, no meaningful differences in mean neurocognitive and academic performance scores were observed.[61] In contrast, in a study of 567 adult survivors of childhood leukemia (mean age, 33 years; mean time since diagnosis, 26 years) dexamethasone exposure was associated with increased risk of impairment in attention (relative risk [RR], 2.12; 95% confidence interval [CI], 1.11–4.03) and executive function (RR, 2.42; 95% CI, 1.20–4.91), independent of methotrexate exposure. Intrathecal hydrocortisone also increased risk of attention problems (RR, 1.24; 95% CI, 1.05–1.46).[45]

Other cancers

Neurocognitive abnormalities have been reported in other groups of cancer survivors. In a study of adult survivors of childhood non-CNS cancers (including ALL, n = 5,937), 13% to 21% of survivors reported impairment in task efficiency, organization, memory, or emotional regulation. This rate of impairment was approximately 50% higher than that reported in the sibling comparison group. Factors such as diagnosis before age 6 years, female gender, cranial radiation therapy, and hearing impediment were associated with impairment.[47]

Stem cell transplantation

Cognitive and academic consequences of stem cell transplantation in children have also been evaluated and include the following:

- In a report from St. Jude Children's Research Hospital in which 268 patients were treated with stem cell transplantation, minimal risk of late cognitive and academic sequelae was observed. Subgroups of patients were at relatively higher risk, including patients who underwent unrelated donor transplantation, received total-body irradiation, and developed graft-versus-host disease (GVHD). However, these differences were small relative to differences in premorbid functioning, particularly those associated with socioeconomic status.[62]

- In a series of 38 patients who underwent hematopoietic stem cell transplantation (HSCT) and received intrathecal chemotherapy, significant declines in visual motor skills and memory scores were noted within the first year posttransplant. By 3 years posttransplant, there was an improvement in visual motor development scores and

memory scores, but new deficits were evident in long-term memory scores. By 5 years posttransplant, there were progressive declines in verbal skills and performance skills, and new deficits were seen in long-term verbal memory scores. The greatest decline in neurocognitive function occurred in patients who received cranial irradiation, either as part of their initial therapy or as part of their HSCT conditioning.[63]

Most neurocognitive late effects after stem cell transplantation are thought to be related to white matter damage in the brain. This was investigated in children with leukemia who were treated with HSCT. In a series of 36 patients, performance on neurocognitive measures typically associated with white matter was compared with performance on measures thought to correlate with gray matter function. Composite white matter scores were significantly lower than composite gray matter scores, thereby supporting the belief that white matter damage contributes to neurocognitive late effects in this population.[64]

Neurologic Sequelae

Risk of neurologic complications may be predisposed by the following:

- Tumor location.

- Neurosurgery.

- Cranial radiation therapy.

- Specific neurotoxic chemotherapeutic agents.

In children with CNS tumors, mass effect, tumor infiltration, and increased intracranial pressure may result in motor or sensory deficits, cerebellar dysfunction, and secondary effects such as seizures and cerebrovascular complications. Numerous reports describe abnormalities of CNS integrity and function, but such studies are typically limited by small sample size, cohort selection and participation bias, cross-sectional ascertainment of outcomes, and variable time of assessment from treatment exposures. In contrast, relatively few studies comprehensively or systematically ascertain outcomes related to peripheral nervous system function.

Neurologic complications that may occur in adult survivors of childhood cancer include the following:

- **Leukoencephalopathy.** Clinical or radiographic leukoencephalopathy has been reported after cranial irradiation and high-dose systemic methotrexate administration. Younger patients and those treated with cranial radiation doses higher than 24 Gy are more vulnerable to reduced white matter volumes associated with leukoencephalopathy.[11-13,46] White matter changes may be accompanied by other neuroimaging abnormalities, including dystrophic calcifications, cerebral lacunae, and cerebral atrophy.

- **Peripheral neuropathy.** Vinca alkaloid agents (vincristine and vinblastine) and cisplatin may cause peripheral neuropathy. This condition presents during treatment and appears to clinically resolve after completion of therapy. However, higher cumulative doses of vincristine and/or intrathecal methotrexate have been linked to neuromuscular impairments in long-term survivors of childhood ALL, which suggests that persistent effects of these agents may affect functional status in aging survivors.[65]
  Among adult survivors of extracranial solid tumors of childhood (median time from diagnosis, 25 years), standardized assessment of neuromuscular function disclosed motor impairment in association with vincristine exposure and sensory impairment in association with cisplatin exposure.[66] Survivors with sensory impairment demonstrated a higher prevalence of functional performance limitations related to poor endurance and mobility restrictions. These studies underscore the importance of assessment and referral to rehabilitative services to optimize functional outcomes among long-term survivors.

- **Stroke.** Refer to the cerebrovascular disease section of this summary for information on stroke.

- **Other neurologic sequelae.** In a report from the CCSS that compared self-reported neurologic late effects among 4,151 adult survivors of childhood ALL with siblings, survivors were at elevated risk for late-onset coordination problems, motor problems, seizures, and headaches. The overall cumulative incidence was 44% at 20 years. Serious headaches were most common, with a cumulative incidence of 25.8% at 20 years, followed by focal neurologic dysfunction (21.2%) and seizures (7%). Children who were treated with regimens that included cranial irradiation for ALL and those who suffered relapse were at increased risk for late-onset neurologic sequelae.[67]

In a cross-sectional study that evaluated neurologic morbidity and quality of life in 162 survivors of childhood ALL (median age at evaluation, 15.7 years; median time from completion of therapy, 7.4 years) in concert with a clinical neurologic exam, neurologic symptoms were present in 83% of survivors, but symptom-related morbidity was low and quality of life was high in most survivors. The most commonly reported symptoms included neuropathy (63%), headache (46.9%), dizziness (33.3%), and back pain (22.8%). Female gender, ten doses or more of intrathecal chemotherapy, and history of relapse were significant predictors for impaired quality of life.[7]

Table 3. Central Nervous System Late Effects[a]

Predisposing Therapy	Neurologic Effects	Health Screening
Platinum agents (carboplatin, cisplatin)	Peripheral sensory neuropathy	Neurologic exam
Plant alkaloid agents (vinblastine, vincristine)	Peripheral sensory or motor neuropathy (areflexia, weakness, foot drop, paresthesias)	Neurologic exam
Methotrexate (high dose IV or IT); cytarabine (high dose IV or IT); radiation impacting the brain	Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures); headaches; seizures; sensory deficits	History: cognitive, motor, and/or sensory deficits, seizures
		Neurologic exam
Radiation impacting cerebrovascular structures	Cerebrovascular complications (stroke, moyamoya, occlusive cerebral vasculopathy)	History: transient/permanent neurological events
		Blood pressure
		Neurologic exam
Neurosurgery–brain	Motor and/or sensory deficits (paralysis, movement disorders, ataxia, eye problems [ocular nerve palsy, gaze paresis, nystagmus, papilledema, optic atrophy]); seizures	Neurologic exam
		Neurology evaluation
Neurosurgery–brain	Hydrocephalus; shunt malfunction	Abdominal x-ray
		Neurosurgery evaluation
Neurosurgery–spine	Neurogenic bladder; urinary incontinence	History: hematuria, urinary urgency/frequency, urinary incontinence/retention, dysuria, nocturia, abnormal urinary stream
Neurosurgery–spine	Neurogenic bowel; fecal incontinence	History: chronic constipation, fecal soiling
		Rectal exam
Predisposing Therapy	**Neuropsychological Effects**	**Health Screening**
Methotrexate (high-dose IV or IT); cytarabine (high-dose IV or	Neurocognitive deficits (executive function, memory, attention, processing speed, etc.);	Assessment of educational and vocational progress

IT); radiation impacting the brain; neurosurgery–brain	learning deficits; diminished IQ; behavioral change	Formal neuropsychological evaluation

IQ = intelligence quotient; IT = intrathecal; IV = intravenous.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Psychosocial

Many childhood cancer survivors report reduced quality of life or other adverse psychosocial outcomes. Evidence for adverse psychosocial adjustment after childhood cancer has been derived from a spectrum of sources, ranging from patient-reported or proxy-reported outcomes to data from population-based registries. The former may be limited by small sample size, cohort selection and participation bias, and variable methods and venues (clinical vs. distance-based survey) of assessments. The latter is often not well correlated with clinical and treatment characteristics that permit the identification of survivors at high risk of psychosocial deficits.

Survivors with neurocognitive deficits are particularly vulnerable to adverse psychosocial outcomes that affect achievement of expected social competence during adulthood.

- In a series of CNS malignancy survivors (n = 802) reported from the CCSS, adverse outcome in indicators of successful adult adaptation (educational attainment, income, employment, and marital status) were most likely in survivors who report neurocognitive dysfunction.[4]

- Collectively, studies evaluating psychosocial outcomes among CNS tumor survivors indicate deficits in social competence that worsen over time.[68]

- In a CCSS study that evaluated predictors of independent living status across diagnostic groups, adult survivors of childhood cancer with neurocognitive, psychological, or physical late effects were less likely to live independently as adults than were siblings in the control group.[41]

Childhood cancer survivors are also at risk of developing symptoms of psychological distress. In a longitudinal study of more than 4,500 survivors, subgroups of survivors were found to be at risk of developing persistent and increasing symptoms of anxiety and depression during a 16-year period. Survivors who reported pain and worsening health status were at the greatest risk of developing symptoms of anxiety, depression, and somatization over time.[69]

Adult survivors of childhood cancer are also at risk of suicide ideation compared with siblings, with survivors of CNS tumors being most likely to report thoughts of suicide. In a CCSS study that evaluated the prevalence of recurrent suicidal ideation among 9,128 adult long-term survivors of childhood cancer, survivors were more likely to report late suicidal ideation (odds ratio [OR], 51.9; 95% CI, 51.5–2.5) and recurrent suicidal ideation (OR, 52.6; 95% CI, 51.8–3.8) compared with siblings.[70] History of seizure was associated with a twofold increased likelihood of suicide ideation in survivors.

The presence of chronic health conditions can also impact aspects of psychological health. In a study that evaluated psychological outcomes among long-term survivors treated with HSCT, 22% of survivors and 8% of sibling controls reported adverse outcomes. Somatic distress was the most prevalent condition and affected 15% of HSCT survivors, representing a threefold higher risk compared with siblings. HSCT survivors with severe or life-threatening health conditions and active chronic GVHD had a twofold increased risk of somatic distress.[71]

Incorporation of psychological screening into clinical visits for childhood cancer survivors may be valuable; however, limiting such evaluations to those returning to long-term follow-up clinics may result in a biased subsample of survivors with more difficulties, and precise prevalence rates may be difficult to establish. A review of behavioral, emotional, and

social adjustment among survivors of childhood brain tumors illustrates this point, with the prevalence of psychological maladjustment ranging from 25% to 93%.[72] In a study of 101 adult cancer survivors of childhood cancer, psychological screening was performed during a routine annual evaluation at the survivorship clinic at the Dana Farber Cancer Institute. On the Symptom Checklist 90 Revised, 32 subjects had a positive screen (indicating psychological distress), and 14 subjects reported at least one suicidal symptom. Risk factors for psychological distress included subjects' dissatisfaction with physical appearance, poor physical health, and treatment with cranial irradiation. In this study, the instrument was shown to be feasible for use in the clinic visit setting because the psychological screening was completed in less than 30 minutes. In addition, completion of the instrument itself did not appear to cause distress in the survivors in 80% of cases.[73] These data support the feasibility and importance of consistent assessment of psychosocial distress in a medical clinic setting.

(Refer to the PDQ summary on Adjustment to Cancer: Anxiety and Distress for more information about psychological distress and cancer patients.)

Post-traumatic stress after childhood cancer

Despite the many stresses associated with the diagnosis of cancer and its treatment, studies have generally shown low levels of post-traumatic stress symptoms and post-traumatic stress disorder (PTSD) in children with cancer, typically no higher than those in healthy comparison children.[74] Patient and parent adaptive style are significant determinants of PTSD in the pediatric oncology setting.[75,76]

The prevalence of PTSD and post-traumatic stress symptoms has been reported in 15% to 20% of young adult survivors of childhood cancer, with estimates varying based on criteria used to define these conditions.[77]

- Survivors with PTSD reported more psychological problems and negative beliefs about their illness and health status than did those without PTSD.[78,79]

- A subset of adult survivors (9%) from the CCSS reported functional impairment and/or clinical distress in addition to the set of symptoms consistent with a full diagnosis of PTSD. This was significantly more prevalent in survivors than in sibling comparisons.[80] In this study, PTSD was significantly associated with being unmarried, having an annual income of less than $20,000, being unemployed, having a high school education or less, and being older than 30 years. Survivors who were treated with cranial irradiation before age 4 years were at particularly high risk for PTSD. Intensive treatment was also associated with increased risk of full PTSD.

Because avoidance of places and persons associated with the cancer is part of PTSD, the syndrome may interfere with obtaining appropriate health care. Those with PTSD perceive greater current threats to their lives or the lives of their children. Other risk factors include poor family functioning, decreased social support, and noncancer stressors.[81]

Psychosocial outcomes among childhood, adolescent, and young adult cancer survivors

Most research on late effects after cancer has focused on individuals with a cancer manifestation during childhood. Little is known about the specific impact of a cancer diagnosis with an onset in adolescence or the impact of childhood cancer on adolescent and young adult psychosocial outcomes. The following studies describe psychosocial outcomes among these groups:

- In 820 adult survivors of cancer diagnosed during adolescence (between ages 15 and 18 years), when compared with an age-matched sample from the general population and a control group of adults without cancer, female survivors of adolescent cancers achieved fewer developmental milestones in their psychosexual development, such as having their first boyfriend, or reached these milestones later. Male survivors were more likely to live with their parents than were same-sex controls. Adolescent cancer survivors were less likely to have ever married or have had children. Survivors were significantly older at their first marriage and at the birth of their first child than were their age-matched samples.[82]

Survivors in this cohort were also significantly less satisfied with their general and health-related life than were people in a community-based control group. Impaired general and health-related life satisfaction were associated with somatic late effects, symptoms of depression and anxiety, and lower rates of posttraumatic growth.[83]

- In a survey of 4,054 adolescent and young adult (AYA) cancer survivors and 345,592 respondents who had no history of cancer, AYA cancer survivors were more likely to smoke (26% vs. 18%), be obese (31% vs. 27%), and have chronic conditions such as cardiovascular disease (14% vs. 7%), hypertension (35% vs. 9%), asthma (15% vs. 8%), disability (36% vs. 18%), and poor mental health (20% vs. 10%). They were also less likely to receive medical care because of cost (24% vs. 15%).[84]

- The CCSS evaluated outcomes of 2,979 adolescent survivors and 649 siblings of cancer survivors to determine the incidence of difficulty in six behavioral and social domains (depression/anxiety, being headstrong, attention deficit, peer conflict/social withdrawal, antisocial behaviors, and social competence).[85] Survivors were 1.5 times (99% CI, 1.1–2.1) more likely than were siblings to have symptoms of depression/anxiety and 1.7 times (99% CI, 1.3–2.2) more likely than were siblings to have antisocial behaviors. Scores in the depression/anxiety, attention deficit, and antisocial domains were significantly elevated in adolescents treated for leukemia or CNS tumors, compared with the scores in siblings. In addition, survivors of neuroblastoma had difficulty in the depression/anxiety and antisocial domains. CNS-directed treatments (cranial radiation therapy and/or intrathecal methotrexate) were specific risk factors for adverse behavioral outcomes.

- Another CCSS study evaluated psychological and neurocognitive function in 2,589 long-term cancer survivors who were diagnosed during adolescence and young adulthood.[86] Compared with a sibling cohort, these survivors reported higher rates of depression (OR, 1.55; 95% CI, 1.04–2.30) and anxiety (OR, 1.55; 95% CI, 1.04–2.30) and reported more cognitive problems affecting task efficiency (OR, 1.72; 95% CI, 1.21–2.43), emotional regulation (OR, 1.74; 95% CI, 1.26–2.40), and memory (OR, 1.44; 95% CI, 1.09–1.89). Survivors of lymphoma and sarcoma diagnosed during later adolescence were at reduced risk of psychosocial and neurocognitive problems than were those diagnosed before age 11 years, whereas no differences were observed in these outcomes among CNS tumor and leukemia survivors. Survivors diagnosed during adolescence and young adulthood were also significantly less likely than sibling controls to have attained a post–high school education, be working full time, be married, or be living independently; inferior social outcomes were related to neurocognitive symptoms.

It should be noted that social withdrawal in adolescence was associated with adult obesity and physical inactivity.[87] As a result, these psychological problems may increase future risk for chronic health conditions and support the need to routinely screen and treat psychological problems after cancer therapy.

Because of the challenges experienced by adolescents and young adults at cancer diagnosis and during long-term follow-up, this group needs to have access to programs to address the unique psychosocial, educational, and vocational issues that impact their transition to survivorship.[88,89]

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for CNS and psychosocial late effects information, including risk factors, evaluation, and health counseling.

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Late Effects of the Digestive System

Dental

Overview

Chemotherapy, radiation therapy, and local surgery can cause multiple cosmetic and functional abnormalities of the oral cavity and dentition. The quality of current evidence regarding this outcome is limited by retrospective data collection, small sample size, cohort selection and participation bias, and heterogeneity in treatment approach, time since treatment, and method of ascertainment.

Oral and dental complications reported in childhood cancer survivors include the following:

- Abnormalities of tooth development.

- Salivary gland dysfunction.

- Abnormalities of craniofacial development.

Abnormalities of tooth development

Abnormalities of dental development reported in childhood cancer survivors include absence of tooth development, hypodontia, microdontia, enamel hypoplasia, and root malformation.[1-9] The prevalence of hypodontia has varied widely in series depending on age at diagnosis, treatment modality, and method of ascertainment. Cancer treatments that have been associated with dental maldevelopment include head and neck radiation therapy, any chemotherapy, and hematopoietic stem cell transplantation (HSCT). Children younger than 5 years are at greatest risk for dental anomalies, such as root agenesis, delayed eruption, enamel defects, and/or excessive caries related to disruption of ameloblast (enamel producing) and odontoblast (dentin producing) activity early in life.[3]

Key findings related to cancer treatment effect on tooth development include the following:

- Radiation directed at oral cavity or surrounding structures increases the risk of dental anomalies because ameloblasts can be permanently damaged by doses as low as 10 Gy.[3,5,6,10] However, the most significant degree of tooth aplasia or delayed eruption occurs in younger children (aged <4 years) who are exposed to radiation doses of 20 Gy or higher.[11] Developing teeth may be irradiated in the course of treating head and neck sarcomas, Hodgkin lymphoma, neuroblastoma, central nervous system leukemia, nasopharyngeal cancer, and as a component of total-body irradiation (TBI). Doses of 10 Gy to 40 Gy can cause root shortening or abnormal curvature, dwarfism, and hypocalcification.[12] Significant dental abnormalities, including mandibular or maxillary hypoplasia, increased caries, hypodontia, microdontia, root stunting, and xerostomia have been reported in more than 85% of survivors of head and neck rhabdomyosarcoma treated with radiation doses higher than 40 Gy.[4,5]

- Chemotherapy, especially exposure to alkylating agents, can affect tooth development.[3,6,7] Chemotherapy for the treatment of leukemia can cause shortening and thinning of the premolar roots and enamel abnormalities.[13-15] Childhood Cancer Survivor Study (CCSS) investigators identified age younger than 5 years and increased exposure to cyclophosphamide as significant risk factors for developmental dental abnormalities in long-term survivors of childhood cancer.[3]

- HSCT conditioning, especially regimens containing TBI, may result in tooth agenesis and root malformation. Younger children who have not developed secondary teeth are most vulnerable.[1,2,6] Children who undergo HSCT with TBI may develop short V-shaped roots, microdontia, enamel hypoplasia, and/or premature apical closure.[1,2,8] The younger a patient is when treated with HSCT, the more severely disturbed dental development will be and the more deficient vertical growth of the lower face will be. These high-risk patients require close surveillance and appropriate interventions.[9]

Salivary gland dysfunction

Xerostomia, the sensation of dry mouth, is a potential side effect following head and neck irradiation or HSCT that can severely impact quality of life. Complications of reduced salivary secretion include increased caries, susceptibility to oral infections, sleep disturbances, and difficulties with chewing, swallowing, and speaking.[16,17] The prevalence of salivary gland dysfunction after cancer treatment varies based on measurement techniques (patient report vs. stimulated or unstimulated salivary secretion rates).[18] In general, the prevalence of self-reported persistent posttherapy xerostomia is infrequent among childhood cancer survivors. In the CCSS, the prevalence of self-reported xerostomia in survivors was 2.8 % compared with 0.3% in siblings, with an increased risk in survivors older than 30 years.[3]

- Salivary gland irradiation incidental to treatment of head and neck malignancies or Hodgkin lymphoma causes a qualitative and quantitative change in salivary flow, which can be reversible after doses of less than 40 Gy but may be irreversible after higher doses, depending on whether sensitizing chemotherapy is also administered.[16]

- The association of chemotherapy alone with xerostomia remains controversial.[16] Only one study of pediatric patients demonstrated an excess risk (odds ratio, 12.32 [2.1–74.4]) of decreased stimulated saliva flow rates among patients treated with cyclophosphamide; however, no increased dental caries were noted and patient-reported xerostomia was not evaluated.[7]

- HSCT recipients are at increased risk of salivary gland dysfunction related to transplant conditioning or graft-versus-host disease (GVHD). GVHD can cause hyposalivation and xerostomia with resultant dental disease. In a study of pediatric HSCT survivors, 60% of those exposed to a conditioning regimen with cyclophosphamide and 10 Gy single-dose TBI had decreased salivary secretion rates, compared with 26% in those who received cyclophosphamide and busulfan.[19] In contrast, in another study, the prevalence of reduced salivary secretion did not differ among long-term survivors based on conditioning regimen (single-dose TBI, 47%; fractionated TBI, 47%; busulfan, 42%).[20]

- The impact of infectious complications and alterations in the microflora during and after therapy is not known.[6]

Abnormalities of craniofacial development

Craniofacial maldevelopment is a common adverse outcome among children treated with high-dose radiation therapy to the head and neck that frequently occurs in association with other oral cavity sequelae such as dental anomalies, xerostomia, and trismus.[5,21,22] The extent and severity of musculoskeletal disfigurement is related to age at treatment and radiation therapy volume and dose, with higher risk observed among younger patients and those who received 30 Gy or more. Remediation of cosmetic and functional abnormalities often requires multiple surgical interventions.

Posttherapy management

Some studies suggest there may be a benefit of fluoride products or chlorhexidine rinses in patients who have undergone radiation therapy.[23] Dental caries are a problematic consequence of reduced salivary quality and flow. The use of topical fluoride can dramatically reduce the frequency of caries, and saliva substitutes and sialagogues can ameliorate sequelae such as xerostomia.[17]

It has been reported that the incidence of dental visits for childhood cancer survivors falls below the American Dental Association's recommendation that all adults visit the dentist annually.[24] The Children's Oncology Group Long-term Follow-Up Guidelines recommend biannual dental cleaning and exams for all survivors of childhood cancer. These findings give health care providers further impetus to encourage routine dental care and dental hygiene evaluations for survivors of childhood treatment. (Refer to the PDQ summary on Oral Complications of Chemotherapy and Head/Neck Radiation for more information about oral complications in cancer patients.)

Table 4. Oral/Dental Late Effects[a]

Predisposing Therapy	Oral/Dental Effects	Health Screening/Interventions
Any chemotherapy; radiation impacting oral cavity	Dental developmental abnormalities; tooth/root agenesis; microdontia; root thinning/shortening; enamel dysplasia	Dental evaluation and cleaning every 6 months
		Regular dental care including fluoride applications
		Consultation with orthodontist experienced in management of irradiated childhood cancer survivors

		Baseline panorex before dental procedures to evaluate root development
Radiation impacting oral cavity	Malocclusion; temporomandibular joint dysfunction	Dental evaluation and cleaning every 6 months
		Regular dental care including fluoride applications
		Consultation with orthodontist experienced in management of irradiated childhood cancer survivors
		Baseline panorex before dental procedures to evaluate root development
Radiation impacting oral cavity; hematopoietic cell transplantation with history of chronic GVHD	Xerostomia/salivary gland dysfunction; periodontal disease; dental caries; oral cancer (squamous cell carcinoma)	Dental evaluation and cleaning every 6 months
		Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine)
		Regular dental care including fluoride applications
Radiation impacting oral cavity (≥40 Gy)	Osteoradionecrosis	History: impaired or delayed healing after dental work
		Exam: persistent jaw pain, swelling or trismus
		Imaging studies (x-ray, CT scan and/or MRI) may assist in making diagnosis
		Surgical biopsy may be needed to confirm diagnosis
		Consider hyperbaric oxygen treatments

CT = computed tomography; GVHD = graft-versus-host disease; MRI = magnetic resonance imaging.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Digestive Tract

Overview

The gastrointestinal (GI) tract is sensitive to the acute toxicities of chemotherapy, radiation therapy, and surgery. However, these important treatment modalities can also result in some long-term issues in a treatment- and dose-dependent manner. Reports published about long-term GI tract outcomes are limited by retrospective data collection, small sample size, cohort selection and participation bias, heterogeneity in treatment approach, time since treatment, and

method of ascertainment.

Key concepts about GI complications observed in childhood cancer survivors include the following:

- Treatment-related late effects include the following:

  - Cancer and its therapy can increase the risk of upper and lower digestive tract late effects.

  - Dose intensity of chemotherapy and use of abdominal irradiation influences the risk of digestive tract late effects.

  - Abdominal surgery increases risk of adhesions and predisposes patients to postoperative bowel obstruction.

- Digestive tract–related late effects include the following:

  - Esophageal dysmotility.

  - Gastroesophageal reflux.

  - Gastritis, enteritis, or colitis.

  - GI motility dysfunction (diarrhea, constipation, bowel obstruction).

  - Subsequent malignant neoplasms

GI outcomes from selected cohort studies

GI outcomes from selected cohort studies include the following:

- Among 5-year childhood cancer survivors participating in the CCSS, the cumulative incidence of self-reported GI conditions was 37.6% at 20 years (25.8% for upper GI complications and 15.5% for lower GI complications) from cancer diagnosis, representing an almost twofold excess risk of upper GI complications (relative risk [RR], 1.8; 95% confidence interval [CI], 1.6–2.0) and lower GI complications (RR, 1.9; 95% CI, 1.7–2.2), compared with sibling controls. Factors predicting higher risk of specific GI complications include the following:[25]

  - Older age at diagnosis.

  - Intensified therapy (anthracyclines for upper GI complications and alkylating agents for lower GI complications).

  - Abdominal radiation therapy.

  - Abdominal surgery.

- Another cohort study of children treated for acute myeloid leukemia with chemotherapy alone found that reported GI disorders were relatively rare and not significantly different from those reported by sibling controls.[26]

- Late radiation injury to the digestive tract is attributable to vascular injury. Necrosis, ulceration, stenosis, or perforation can occur and are characterized by malabsorption, pain, and recurrent episodes of bowel obstruction, as well as perforation and infection.[27-29] In general, fractionated doses of 20 Gy to 30 Gy can be delivered to the small bowel without significant long-term morbidity. Doses greater than 40 Gy cause bowel obstruction or chronic enterocolitis.[30] Sensitizing chemotherapeutic agents such as dactinomycin or anthracyclines can increase this risk.

Impact of cancer histology on GI outcomes

Intra-abdominal tumors represent a relatively common location for several pediatric malignancies, including rhabdomyosarcoma, Wilms tumor, lymphoma, germ cell tumors, and neuroblastoma. Intra-abdominal tumors often require multimodal therapy, occasionally necessitating resection of bowel and bowel-injuring chemotherapy and/or radiation therapy. Thus, these tumors would be expected to be particularly prone to long-term digestive tract issues.

A limited number of reports describe GI complications in pediatric patients with genitourinary solid tumors treated with radiation therapy:[31-35]

- One study comprehensively evaluated intestinal symptoms in 44 children with cancer who underwent whole-abdominal (10–40 Gy) and involved-field (25–40 Gy) radiation therapy and received additional interventions predisposing them to GI tract complications including abdominal laparotomy in 43 patients (98%) and chemotherapy in 25 patients (57%).[31] Late small-bowel obstruction was observed in 36% of patients surviving for 19 months to 7 years, which was uniformly preceded by small bowel toxicity during therapy.

- The CCSS evaluated the incidence and risk of late-occurring intestinal obstruction requiring surgery in 12,316 5-year survivors (2,002 with and 10,314 without abdominopelvic tumors) and 4,023 siblings. The most common diagnoses among survivors with abdominopelvic tumors were Wilms tumors and neuroblastomas but also included soft tissue sarcomas, lymphomas, and bone tumors. The cumulative incidence of late intestinal obstruction requiring surgery at 35 years was 5.8% among survivors with abdominopelvic tumors, 1.0% among those without abdominopelvic tumors, and 0.3% among siblings. Elevated risk of intestinal obstruction requiring surgery was associated with presence of an abdominopelvic tumor (adjusted rate ratio [ARR], 3.6; $P < .001$) and exposure to abdominal or pelvic radiation therapy within 5 years of cancer diagnosis (ARR, 2.4; $P < .001$). Among survivors of abdominopelvic tumors, the median time from diagnosis to the first late intestinal obstruction requiring surgery was 12 years (range, 8–19 years). Lymphoma resulted in the highest cumulative incidence of late-occurring intestinal obstruction requiring surgery (7.2% at 35 years after diagnosis). An elevated risk of obstruction was associated with the presence of an abdominopelvic tumor and previous exposure to abdominal or pelvic radiation therapy.[36][Level of evidence: 3iiiC]

- Reports from the Intergroup Rhabdomyosarcoma Study evaluating GI toxicity in long-term survivors of genitourinary rhabdomyosarcoma infrequently observed abnormalities of the irradiated bowel.[32,33,35] Radiation-related complications occurred in approximately 10% of long-term survivors of paratesticular and bladder/prostate rhabdomyosarcoma and included intraperitoneal adhesions with bowel obstruction, chronic diarrhea, and stricture or enteric fistula formation.[32,35]

Table 5. Digestive Tract Late Effects[a]

Predisposing Therapy	Gastrointestinal Effects	Health Screening/Interventions
Radiation impacting esophagus; hematopoietic cell transplantation with any history of chronic GVHD	Esophageal stricture	History: dysphagia, heart burn
		Esophageal dilation, antireflux surgery
Radiation impacting bowel	Chronic enterocolitis; fistula; strictures	History: nausea, vomiting, abdominal pain, diarrhea
		Serum protein and albumin levels yearly in patients with chronic diarrhea or fistula
		Surgical and/or gastroenterology consultation for symptomatic patients
Radiation impacting bowel; laparotomy	Bowel obstruction	History: abdominal pain, distention, vomiting, constipation

		Exam: tenderness, abdominal guarding, distension (acute episode)
		Obtain KUB in patients with clinical symptoms of obstruction
		Surgical consultation in patients unresponsive to medical management
Pelvic surgery; cystectomy	Fecal incontinence	History: chronic constipation, fecal soiling
		Rectal exam

GVHD = graft-versus-host disease; KUB = kidneys, ureter, bladder (plain abdominal radiograph).

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Hepatobiliary Complications

Overview

Hepatic complications resulting from childhood cancer therapy are observed primarily as acute treatment toxicities.[37] Because many chemotherapy agents and radiation are hepatotoxic, transient liver function anomalies are common during therapy. Severe acute hepatic complications occur rarely. Survivors of childhood cancer can occasionally exhibit long-standing hepatic injury. Some general concepts regarding hepatotoxicity related to childhood cancer include the following:

- The risk of long-term hepatotoxicity is not well defined.

- Children with primary liver tumors requiring significant liver resection, or even transplant, are at higher risk for liver injury.

- Children receiving radiation therapy to the liver are at higher risk for liver injury.

- Children undergoing bone marrow transplant are at higher risk for liver injury.

Certain factors, including the type of chemotherapy, the dose and extent of radiation exposure, the influence of surgical interventions, and the evolving impact of viral hepatitis and/or other infectious complication, need additional attention in future studies.

Types of hepatobiliary complications

- **Asymptomatic elevations of blood biomarkers.** Blood biomarkers include the following: serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT). Liver injury related to treatment for childhood cancer is often asymptomatic and indolent in course. Dutch investigators observed hepatobiliary dysfunction in 8.7% of 1,362 long-term survivors (12.4 years of median follow-up since diagnosis) evaluated by ALT for hepatocellular injury and GGT for biliary tract injury. Cases with a history of viral hepatitis and a history of veno-occlusive disease were excluded. Predictors for elevated ALT and GGT by multivariable analysis included treatment with radiation therapy involving the liver, higher body mass index (BMI), higher alcohol intake, and longer follow-up time; older age at diagnosis was only significantly associated with elevated GGT levels.[38] In a CCSS report, survivors of childhood cancer were more than two times more likely to report a hepatic-related health issue and were nearly nine times more likely to report cirrhosis, compared with sibling controls.[25]

Less commonly reported hepatobiliary complications include the following:

- **Cholelithiasis.** In limited studies, an increased risk of cholelithiasis has been linked to ileal conduit, parenteral nutrition, abdominal surgery, abdominal radiation therapy, and HSCT.[39,40] Gallbladder disease was the most frequent late-onset liver condition reported among participants in the CCSS, and they had a twofold excess risk compared with sibling controls (RR, 2.0; 95% CI, 2.0–40.0).[25]

- **Focal nodular hyperplasia.** Lesions made up of regenerating liver called focal nodular hyperplasia have been incidentally noted after chemotherapy or HSCT.[41,42] These lesions are thought to be iatrogenic manifestations of vascular damage and have been associated with veno-occlusive disease, high-dose alkylating agents (e.g., busulfan and melphalan), and liver irradiation. The prevalence of this finding is unknown; while noted at less than 1% in some papers,[42] this is likely an underestimate. In one study of patients who were followed by magnetic resonance imaging (MRI) after transplant to assess liver iron stores, the cumulative incidence was 35% at 150 months posttransplant.[41] The lesions can mimic metastatic or subsequent tumors, but MRI imaging is generally diagnostic, and unless the lesions grow or patients have worrisome symptoms, biopsy or resection is generally not necessary.

- **Nodular regenerative hyperplasia.** Nodular regenerative hyperplasia is a rare condition characterized by the development of multiple monoacinar regenerative hepatic nodules and mild fibrosis. The pathogenesis is not well established but may represent a nonspecific tissue adaptation to heterogeneous hepatic blood flow.[43] Nodular regenerative hyperplasia has rarely been observed in survivors of childhood cancer treated with chemotherapy, with or without liver irradiation.[44,45] Biopsy may be necessary to distinguish nodular regenerative hyperplasia from a subsequent malignancy.

- **Microvesicular fatty change.** In a cohort who recently completed intensified therapy for acute lymphoblastic leukemia, histologic evidence of fatty infiltration was noted in 93% and siderosis in up to 70% of patients.[46] Fibrosis developed in 11% and was associated with higher serum low-density lipoprotein (LDL) cholesterol. Fatty liver with insulin resistance has also been reported to develop more frequently in long-term childhood cancer survivors treated with cranial radiation therapy before allogeneic stem cell transplantation who were not overweight or obese.[47] Prospective studies are needed to define whether acute posttherapy fatty liver change contributes to the development of steatohepatitis or the metabolic syndrome in this population.

- **Transfusion-related iron overload.** Red blood cell transfusions can result in an accumulation of excess iron due to disruption of the homeostasis of iron storage and distribution when exogenous iron is loaded into organs. Transfusional iron overload has been reported in pediatric oncology patients, but its prevalence, organ distribution, and severity remain incompletely characterized. MRI has emerged as an accurate, noninvasive means for measuring iron in multiple organ systems.[48,49] In a cross-sectional study of 75 patients (4.4 years of median follow-up time; 4.9 years since last transfusion), MRI iron concentrations were elevated in the liver (49.3%) and pancreas (26.4%), but not in the heart. In a multivariable analysis, cumulative packed red blood cell volume and older age at diagnosis predicted elevated liver iron concentration.[48] Further research is needed to better characterize survivors at risk of clinically significant transfusion-related iron overload who may benefit from interventions to reduce iron loading and organ dysfunction.

Treatment-related risk factors for hepatobiliary complications

The type and intensity of previous therapy influences risk for late-occurring hepatobiliary complications. In addition to the risk of treatment-related toxicity, recipients of HSCT frequently experience chronic liver dysfunction related to microvascular, immunologic, infectious, metabolic, and other toxic etiologies.

- **Chemotherapy.** Chemotherapeutic agents with established hepatotoxic potential include antimetabolite agents like 6-mercaptopurine, 6-thioguanine, methotrexate, and rarely, dactinomycin. Veno-occlusive disease/sinusoidal

obstruction syndrome (VOD/SOS) and cholestatic disease have been observed after thiopurine administration, especially 6-thioguanine. Progressive fibrosis and portal hypertension has been reported in a subset of children who developed VOD/SOS after treatment with 6-thioguanine.[50-52] Acute, dose-related, reversible VOD/SOS has been observed in children treated with dactinomycin for pediatric solid tumors.[53,54]

In the transplant setting, VOD/SOS has also been observed after conditioning regimens that have included cyclophosphamide/TBI, busulfan/cyclophosphamide and carmustine/cyclophosphamide/etoposide.[55] Because high-dose cyclophosphamide is common to all of these regimens, toxic cyclophosphamide metabolites resulting from the agent's variable metabolism have been speculated as a causative factor.

- **Radiation therapy.** Acute radiation-induced liver disease also causes endothelial cell injury that is characteristic of VOD/SOS.[56] In adults, the whole liver has tolerance up to 30 Gy to 35 Gy with conventional fractionation, the prevalence of radiation-induced liver disease varies from 6% to 66% based on the volume of liver involved and on hepatic reserve.[56,57]

  Based on limited data from pediatric cohorts treated in the 1970s and 1980s, persistent radiation hepatopathy after contemporary treatment appears to be uncommon in long-term survivors without predisposing conditions such as viral hepatitis or iron overload.[58] The risk of injury in children increases with radiation dose, hepatic volume, younger age at treatment, previous partial hepatectomy, and concomitant use of radiomimetic chemotherapy like dactinomycin and doxorubicin.[59-62] Survivors who received radiation doses of 40 Gy to at least one-third of liver volume, doses of 30 Gy or more to whole abdomen, or an upper abdominal field involving the entire liver are at highest risk for hepatic dysfunction.[63]

- **Hematopoietic stem cell transplantation.** Chronic liver dysfunction in patients undergoing HSCT is multifactorial in etiology. The most common etiologies for chronic liver dysfunction include iron overload, chronic GVHD, and viral hepatitis.[64] Patients with chronic GVHD of the GI tract who exhibit an elevated bilirubin have a worse prognosis and quality of life.[65] While chronic liver dysfunction may be seen in more than half of long-term stem cell transplantation survivors, the course of the disease is mild and indolent in most patients. [66]

Infectious risk factors for hepatobiliary complications

Viral hepatitis B and C may complicate the treatment course of childhood cancer and result in chronic hepatic dysfunction. Hepatitis B tends to have a more aggressive acute clinical course and a lower rate of chronic infection. Hepatitis C is characterized by a mild acute infection and a high rate of chronic infection. The incidence of transfusion-related hepatitis C in childhood cancer survivors has ranged from 5% to 50% depending on the geographic location of the reporting center.[67-73]

Chronic hepatitis predisposes the childhood cancer survivor to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Concurrent infection with both viruses accelerates the progression of liver disease. Because most patients received some type of blood product during childhood cancer treatment and many are unaware of their transfusion history, 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.[74] Therefore, all children who received blood transfusions before 1972 should be screened for hepatitis B, and all children who received blood transfusions before 1993 should be screened for hepatitis C and referred for discussion of treatment options.

Posttherapy management

Survivors with liver dysfunction should be counseled regarding risk-reduction methods to prevent hepatic injury. Standard recommendations include maintenance of a healthy body weight, abstinence from alcohol use, and immunization against hepatitis A and B viruses. In patients with chronic hepatitis, precautions to reduce viral transmission to household and sexual contacts should also be reviewed.

Table 6. Hepatobiliary Late Effects[a]

Predisposing Therapy	Hepatic Effects	Health Screening/Interventions
Methotrexate; mercaptopurine/thioguanine; HSCT	Hepatic dysfunction	Lab: ALT, AST, bilirubin levels
		Ferritin in those treated with HSCT
Mercaptopurine/thioguanine; HSCT	Veno-occlusive disease/sinusoidal obstructive syndrome	Exam: scleral icterus, jaundice, ascites, hepatomegaly, splenomegaly
		Lab: ALT, AST, bilirubin, platelet levels
		Ferritin in those treated with HSCT
Radiation impacting liver/biliary tract; HSCT	Hepatic fibrosis/cirrhosis	Exam: jaundice, spider angiomas, palmar erythema, xanthomata hepatomegaly, splenomegaly
		Lab: ALT, AST, bilirubin levels
		Ferritin in those treated with HSCT
		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 before 1993
		Gastroenterology/hepatology consultation in patients with persistent liver dysfunction
		Hepatitis A and B immunizations in patients lacking immunity
		Consider phlebotomy and chelation therapy for iron overload
Radiation impacting liver/biliary tract	Cholelithiasis	History: colicky abdominal pain related to fatty food intake, excessive flatulence
		Exam: right upper quadrant or epigastric tenderness (acute episode)
		Consider gallbladder ultrasound in patients with chronic abdominal pain

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HSCT = hematopoietic stem cell transplantation.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Pancreas

The pancreas has been thought to be relatively radioresistant because of a paucity of information about late pancreatic-related effects. However, children and young adults treated with TBI or abdominal irradiation are known to have an increased risk of insulin resistance and diabetes mellitus.[75-77]

A summary of the results of selected cancer cohort studies supporting this association include the following:

- A retrospective cohort study, based on self-reports of 2,520 5-year survivors of childhood cancer treated in France

and the United Kingdom, investigated the relationship between radiation dose to the pancreas and risk of a subsequent diabetes mellitus diagnosis. Sixty-five cases of diabetes mellitus were validated; the risk increased with radiation therapy to the tail of the pancreas, where the islets of Langerhans are concentrated. Risk increased up to 20 to 29 Gy and then plateaued. The estimated RR at 1 Gy was 1.61. Radiation dose to other parts of the pancreas did not have a significant effect. Compared with patients who did not receive radiation therapy, the RR of diabetes mellitus was 11.5 in patients who received more than 10 Gy to the pancreas. Children younger than 2 years at the time of radiation therapy were more sensitive than were older patients (RR at 1 Gy was 2.1 for the young age group vs. 1.4 for older patients). For the 511 patients who received more than 10 Gy, the cumulative incidence of diabetes mellitus was 16%.[78]

- Another study evaluated the risk of diabetes mellitus in 2,264 5-year survivors of Hodgkin lymphoma (42% younger than 25 years at diagnosis) After a median follow-up of 21.5 years, the cumulative incidence of diabetes mellitus was 8.3% (95% CI, 6.9%–9.8%) for the overall cohort and 14.2% (95% CI, 10.7%–18.3%) for those treated with more than 36 Gy para-aortic radiation. Survivors treated with more than 36 Gy of radiation to the para-aortic lymph nodes and spleen had a 2.3-fold increased risk of diabetes mellitus compared with those who did not receive radiation therapy. The risk of diabetes mellitus increased with higher doses to the pancreatic tail. [79]

- In a report from the CCSS that compared 8,599 childhood cancer survivors to 2,936 randomly selected sibling controls, and after adjustment for age, BMI, and several demographic factors, the risk of diabetes mellitus was 1.8 times higher in survivors (95% CI, 1.3–2.5; $P < .001$). Significant associations were found between diabetes mellitus and young age at diagnosis (0–4 years), the use of alkylating agents, and TBI or abdominal irradiation. Also, survivors were significantly more likely to be receiving medication for hypertension, dyslipidemia, and/or diabetes mellitus than were sibling controls.[80]

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for digestive system late effects information including risk factors, evaluation, and health counseling.

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Late Effects of the Endocrine System

Endocrine dysfunction is very common among childhood cancer survivors treated with radiation therapy that involves hormone-producing organs.
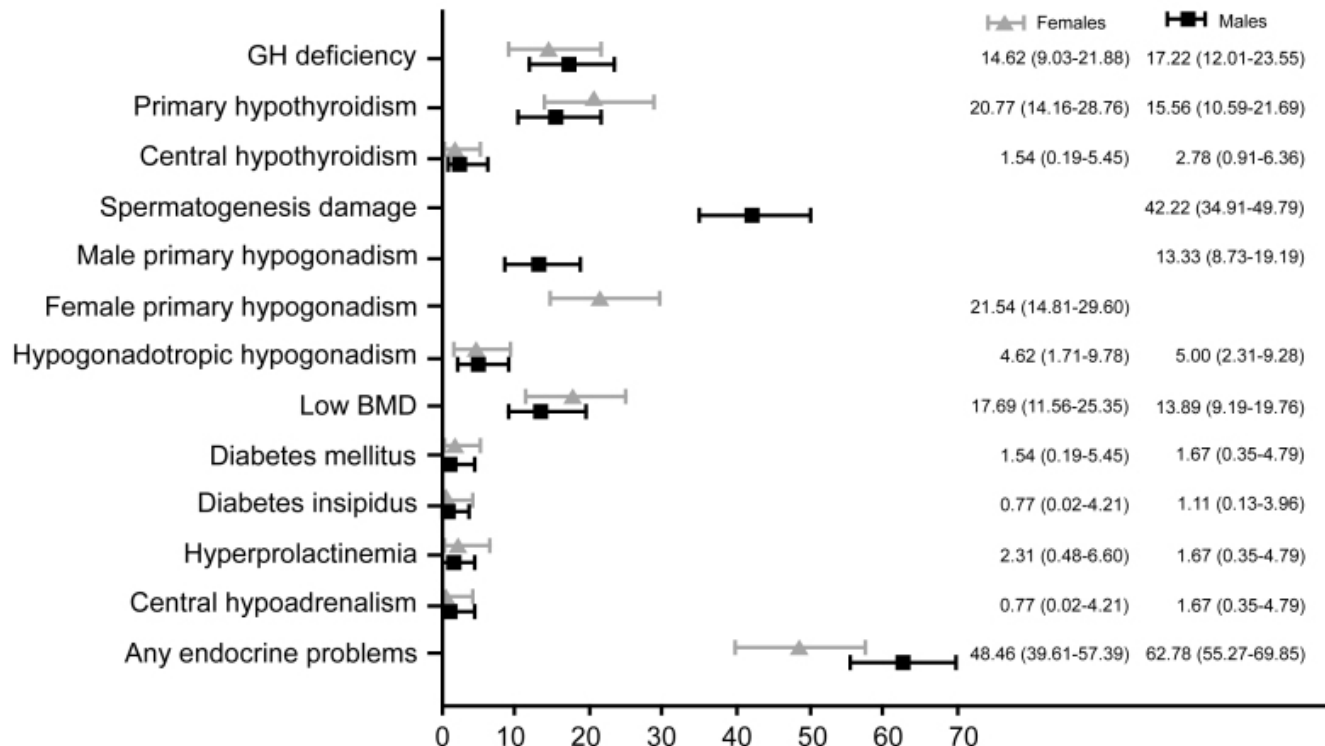
Figure 6. Prevalence of endocrine disorders at the last follow-up visit, by gender. Copyright © 2013, European Society of Endocrinology.

The prevalence of specific endocrine disorders varies by patient (e.g., age at treatment, sex) and treatment factors (e.g., radiation dose and treatment volume), and typically increases with longer time from radiation exposure.[1] The following sections summarize research that characterizes the clinical features of survivors at risk of endocrine dysfunction that impacts pituitary, thyroid, adrenal, and gonadal function.

Thyroid Gland

Thyroid dysfunction is a common delayed effect of radiation therapy fields that include the thyroid gland incidental to treating Hodgkin lymphoma (HL), brain tumors, head and neck sarcomas, and acute lymphoblastic leukemia. There is considerable evidence linking radiation exposure to thyroid abnormalities, but the prevalence of specific conditions varies widely because studies are limited by cohort selection and participation bias, heterogeneity in radiation treatment approach, time since radiation exposure, and method of ascertainment (e.g., self-report vs. clinical or diagnostic imaging assessment).

Thyroid abnormalities observed in excess in childhood cancer survivors include the following:

- Primary hypothyroidism.

- Hyperthyroidism.

- Goiter.

- Nodules.

Hypothyroidism

Of children treated with radiation therapy, most develop hypothyroidism within the first 2 to 5 years posttreatment, but new cases can occur later. Reports of thyroid dysfunction differ depending on the dose of radiation, the length of follow-up, and the biochemical criteria utilized to make the diagnosis.[2] The most frequently reported abnormalities include:

- Elevated thyroid-stimulating hormone (TSH).

- Depressed thyroxine (T_4).

- Elevated TSH and depressed T_4.

Compensated hypothyroidism includes an elevated TSH with a normal T_4 and is asymptomatic. The natural history is unclear, but most endocrinologists support treatment. Uncompensated hypothyroidism includes both an elevated TSH and a depressed T_4. Thyroid hormone replacement is beneficial for correction of the metabolic abnormality, and has clinical benefits for cardiovascular, gastrointestinal, and neurocognitive function.

An increased risk of hypothyroidism has been reported among childhood cancer survivors treated with head and neck radiation exposing the thyroid gland, especially among survivors of HL. Results from selected studies include the following:

- The German Group of Paediatric Radiation Oncology reported on 1,086 patients treated at 62 centers, including 404 patients (median age, 10.9 years) who received radiation therapy to the thyroid gland and/or hypophysis.[3] Follow-up information was available for 264 patients (60.9%; median follow-up, 40 months), with 60 patients (22.7%) showing pathologic values. The following was observed:

  - In comparison to patients treated with prophylactic cranial irradiation (median dose, 12 Gy), patients treated with radiation doses of 15 Gy to 25 Gy to the thyroid gland had a hazard ratio (HR) of 3.072 (P = .002) for the development of pathologic thyroid blood values.

  - Patients treated with more than 25 Gy of radiation to the thyroid gland had an HR of 3.769 (P = .009), and patients treated with craniospinal irradiation had an HR of 5.674 (P < .001).

  - The cumulative incidence of thyroid hormone substitution therapy did not differ between defined subgroups.

- In a cohort of childhood HL survivors treated between 1970 and 1986, survivors were evaluated for thyroid disease by use of a self-report questionnaire in the Childhood Cancer Survivor Study (CCSS).[4] Among 1,791 survivors, 34% reported that they had been diagnosed with at least one thyroid abnormality. For hypothyroidism, there was a clear dose response, with a 20-year risk of:

  - 20% for those who received less than 35 Gy of radiation to the thyroid gland.

  - 30% for those who received 35 Gy to 44.9 Gy of radiation to the thyroid gland.

  - 50% for those who received more than 45 Gy of radiation to the thyroid gland.

  The relative risk (RR) was 17.1 for hypothyroidism; 8.0 for hyperthyroidism; and 27.0 for thyroid nodules. Elapsed time since diagnosis was a risk factor for both hypothyroidism and hyperthyroidism, with the risk increasing in the first 3 to 5 years postdiagnosis. For nodules, the risk increased beginning at 10 years postdiagnosis. Females were at increased risk for hypothyroidism and thyroid nodules.
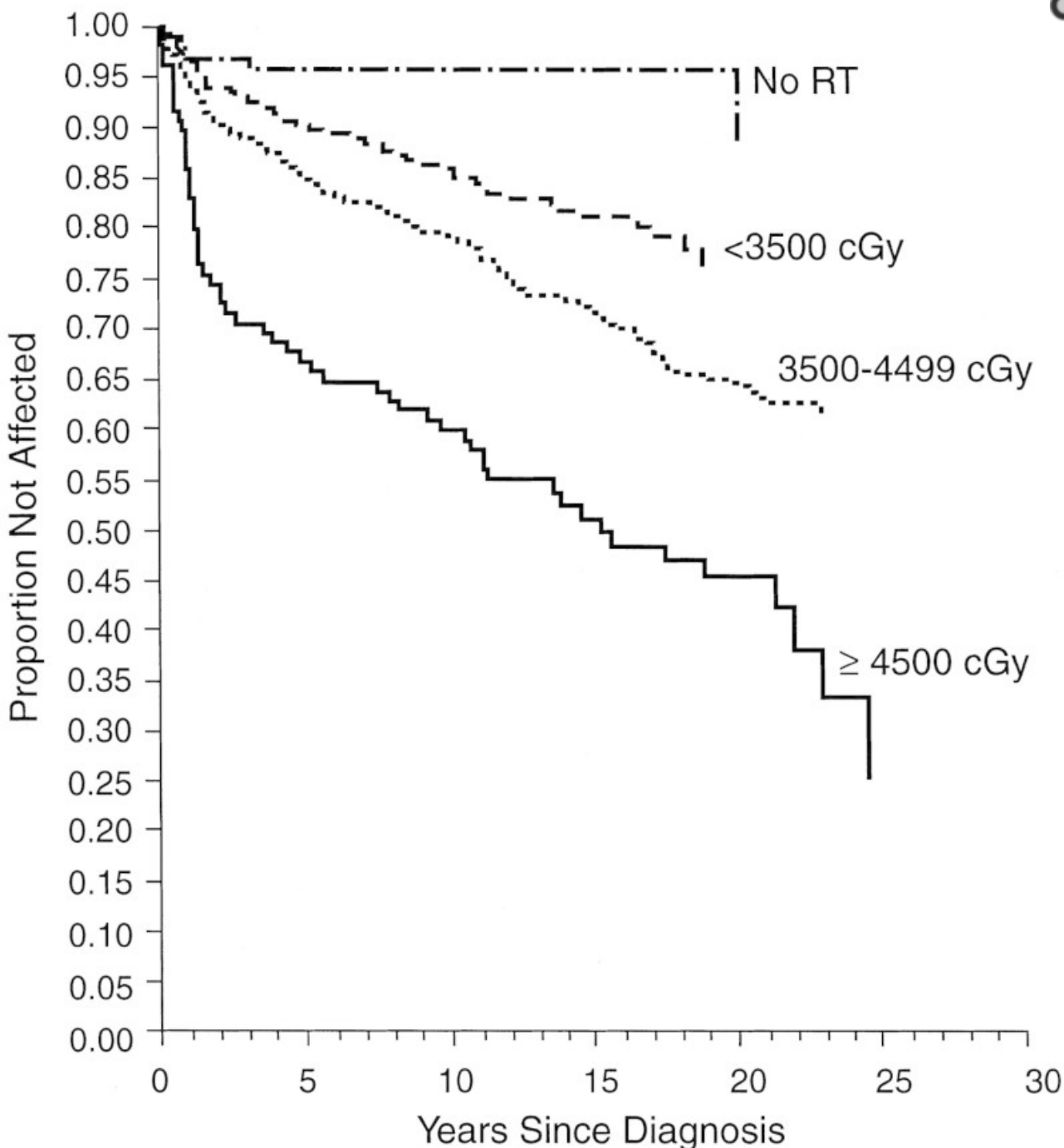
Figure 7. Probability of developing hypothyroidism according to radiation dose in 5-year survivors of childhood cancer. Data from the Childhood Cancer Survivor Study. Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L: Abnormalities of the Thyroid in Survivors of Hodgkin's Disease: Data from the Childhood Cancer Survivor Study. The Journal of Clinical Endocrinology and Metabolism 85 (9): 3227-3232, September 1, 2000. *Copyright 2000, The Endocrine Society*.

Thyroid nodules

Any radiation field that includes the thyroid is associated with an excess risk of thyroid neoplasms, which may be benign (usually adenomas) or malignant (most often differentiated papillary carcinoma).[4-8] The clinical manifestation of thyroid neoplasia among childhood cancer survivors ranges from asymptomatic, small, solitary nodules to large, intrathoracic goiters that compress adjacent structures. CCSS investigators performed a nested case-control study to evaluate the magnitude of risk for thyroid cancer over the therapeutic radiation dose range of pediatric cancers. The risk

of thyroid cancer increased with radiation doses up to 20 Gy to 29 Gy (odds ratio [OR], 9.8; 95% confidence interval [CI], 3.2–34.8), but declined at doses higher than 30 Gy, consistent with a cell-killing effect.[8]

The following factors are linked to an increased risk of thyroid nodule development:

- **Time from diagnosis, female gender, and radiation dose.** In a study of HL survivors, CCSS investigators identified time from diagnosis, female gender, and radiation dose of 25 Gy or more as significant risk factors for thyroid nodule development.[4] Based on a cohort of 3,254 2-year childhood cancer survivors treated before 1986 and monitored for 25 years, the risk of thyroid adenoma increased with the size of the radiation dose to the thyroid during childhood cancer treatment and plateaued at doses exceeding 10 Gy.[6]

- **Age at time of radiation therapy.** Based on the same cohort of 3,254 2-year childhood cancer survivors, the risk of thyroid adenoma per unit of radiation dose to the thyroid was higher if radiation therapy had been delivered before age 5 years; the risk was also higher in individuals who were younger than 40 years at the time of the study.[6] Younger age at radiation therapy has also been linked to an excess risk of thyroid carcinoma.[5-8]

- **Exposure to iodine I 131 metaiodobenzylguanidine (^{131}I-mIBG).** During childhood and adolescence, there is an increased incidence of developing thyroid nodules, and potentially thyroid cancer, for patients exposed to ^{131}I-mIBG. Children who have been treated with ^{131}I-mIBG should undergo lifelong monitoring, not only for thyroid function but also for the development of thyroid nodules and thyroid cancer.[9]

- **Chemotherapy.** Whereas the risk of thyroid cancer is known to be increased by exposure to radiation therapy and ^{131}I-mIBG, an increased risk of thyroid nodules and cancer has also been observed in association with chemotherapy, independent of radiation exposure.[5,6]
  In a pooled study of two cohorts of 16,757 survivors that included 187 patients with secondary thyroid cancer, treatments with alkylating agents, anthracyclines, or bleomycin were associated with a significantly increased risk of thyroid cancer in individuals not exposed to radiation therapy.[10] Defining the precise role of exposure to chemotherapy and developing risk prediction models for thyroid cancer in childhood cancer survivors based on demographic and treatment-related risk factors are areas of active research.[11]

Several investigations have demonstrated the superiority of ultrasound to clinical exam for detecting thyroid nodules and thyroid cancers and characterized ultrasonographic features of nodules that are more likely to be malignant.[12-14] However, primary screening for thyroid neoplasia (beyond physical exam with thyroid palpation) remains controversial because of the lack of data indicating a survival benefit and quality-of-life benefit associated with early detection and intervention. In fact, because these lesions tend to be indolent, are rarely life-threatening, and may clinically manifest many years after exposure to radiation, there are significant concerns regarding the costs and harms of overscreening. [15]

(Refer to the Subsequent Neoplasms section of this summary for information about subsequent thyroid cancers.)

Posttransplant thyroid dysfunction

Survivors of pediatric hematopoietic stem cell transplantation (HSCT) are at increased risk of thyroid dysfunction, with the risk being much lower (15%–16%) after fractionated total-body irradiation (TBI), as opposed to single-dose TBI (46%–48%). Non–TBI-containing regimens historically were not associated with an increased risk. However, in a report from the Fred Hutchinson Cancer Research Center, the increased risk of thyroid dysfunction did not differ between children receiving a TBI-based or busulfan-based regimen (P = .48).[16] Other high-dose therapies have not been studied.

Table 7. Thyroid Late Effects[a]

Predisposing Therapy	Endocrine/Metabolic Effects	Health Screening

Radiation impacting thyroid gland; thyroidectomy	Primary hypothyroidism	TSH level
Radiation impacting thyroid gland	Hyperthyroidism	Free T_4 level
		TSH level
Radiation impacting thyroid gland, including mIBG	Thyroid nodules	Thyroid exam
		Thyroid ultrasound

mIBG = metaiodobenzylguanidine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

TSH deficiency (central hypothyroidism) is discussed with late effects that affect the pituitary gland.

Pituitary Gland

Survivors of childhood cancer are at risk for a spectrum of neuroendocrine abnormalities, primarily because of the effect of radiation therapy on the hypothalamus. In addition, tumor development or surgical resection close to the hypothalamus and/or pituitary gland may induce direct anatomical damage to these structures and result in hypothalamic/pituitary dysfunction. Essentially all of the hypothalamic-pituitary axes are at risk.[17-20] Although the quality of the literature regarding pituitary endocrinopathy among childhood cancer survivors is often limited by retrospective data collection, small sample size, cohort selection and participation bias, heterogeneity in treatment approach, time since treatment, and method of ascertainment, the evidence linking this outcome with radiation therapy, surgery, and tumor infiltration is quite compelling because affected individuals typically present with metabolic and developmental abnormalities early in follow-up.

Central diabetes insipidus

Central diabetes insipidus may herald the diagnosis of craniopharyngioma, suprasellar germ cell tumor, or Langerhans cell histiocytosis.[21-23] In these conditions, diabetes insipidus may occur as an isolated pituitary deficiency, although additional pituitary hormone deficiencies may develop with tumor progression. More commonly, however, diabetes insipidus occurs in the context of panhypopituitarism caused by the presence of a tumor in close proximity to the sellar region or as a consequence of surgical procedures undertaken for local tumor control.

Central diabetes insipidus has not been reported as a late effect of cranial irradiation in childhood cancer survivors.

Anterior pituitary hormone deficiency

Deficiencies of anterior pituitary hormones and major hypothalamic regulatory factors are common late effects among survivors treated with cranial irradiation. In a study of 1,713 adult survivors of childhood cancers and brain tumors (median age, 32 years) monitored in a single institution (median follow-up duration, 25 years), the prevalence of hypothalamic-pituitary axis disorders was 56.4% in individuals exposed to cranial radiation therapy at doses of 18 Gy or more.[20] Among 748 childhood cancer survivors treated with cranial irradiation and observed for a mean of 27.3 years, the estimated point prevalence for anterior pituitary hormone deficiency was 46.5% for growth hormone deficiency (GHD), 10.8% for luteinizing/follicle stimulating hormone deficiency, 7.5% for thyroid-stimulating hormone deficiency, and 4% for adrenocorticotropin deficiency; the cumulative incidence increased with follow-up.[24] The six anterior pituitary hormones and their major hypothalamic regulatory factors are outlined in Table 8.

Table 8. Anterior Pituitary Hormones and Major Hypothalamic Regulatory Factors

Pituitary Hormone	Hypothalamic Factor	Hypothalamic Regulation of the Pituitary Hormone

Growth hormone (GH)	Growth hormone–releasing hormone	+
	Somatostatin	−
Prolactin	Dopamine	−
Luteinizing hormone (LH)	Gonadotropin-releasing hormone	+
Follicle-stimulating hormone (FSH)	Gonadotropin-releasing hormone	+
Thyroid-stimulating hormone (TSH)	Thyroid-releasing hormone	+
	Somatostatin	−
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone	+
	Vasopressin	+

(−) = inhibitory; (+) = stimulatory.

Growth hormone deficiency (GHD)

GHD is the earliest hormonal deficiency associated with cranial radiation therapy in childhood cancer survivors. The risk increases with radiation dose and time since treatment. GHD is sensitive to low doses of radiation. Other hormone deficiencies require higher doses, and their time to onset is much longer than for GHD.[25] The prevalence in pooled analysis was found to be approximately 35.6%.[26]

GHD is commonly observed in these long-term survivors because of radiation doses used in the treatment of childhood brain tumors. Approximately 60% to 80% of irradiated pediatric brain tumor patients who received doses higher than 30 Gy will have impaired serum growth hormone (GH) response to provocative stimulation, usually within 5 years of treatment. The dose-response relationship has a threshold of 18 Gy to 20 Gy; the higher the radiation dose, the earlier that GHD will occur after treatment.

- A study of conformal radiation therapy (CRT) in children with central nervous system (CNS) tumors indicates that GH insufficiency can usually be demonstrated within 12 months of radiation therapy, depending on hypothalamic dose-volume effects.[27]

- In a report featuring data from 118 patients with localized brain tumors who were treated with radiation therapy, peak GH was modeled as an exponential function of time after CRT and mean radiation dose to the hypothalamus. The average patient was predicted to develop GHD with the following combinations of time after CRT and mean dose to the hypothalamus: 12 months and more than 60 Gy; 36 months and 25 Gy to 30 Gy; and 60 months and 15 Gy to 20 Gy. A cumulative dose of 16.1 Gy to the hypothalamus would be considered the mean radiation dose required to achieve a 50% risk of GHD at 5 years (TD50/5).[28]
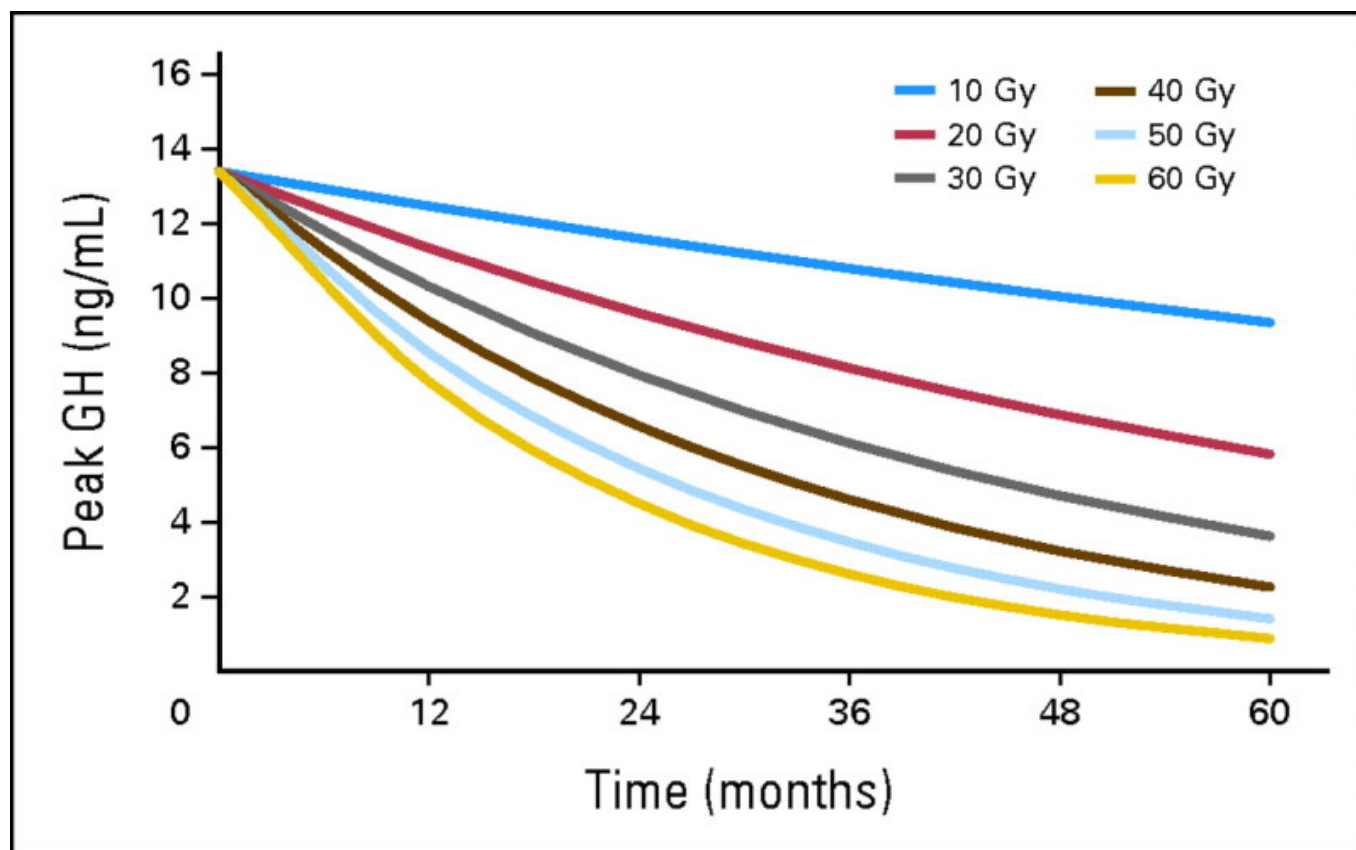
Figure 8. Peak growth hormone (GH) according to hypothalamic mean dose and time after start of radiation. According to equation 2, peak GH = exp{2.5947 + time × [0.0019 − (0.00079 × mean dose)]}. Thomas E. Merchant, Susan R. Rose, Christina Bosley, Shengjie Wu, Xiaoping Xiong, and Robert H. Lustig, Growth Hormone Secretion After Conformal Radiation Therapy in Pediatric Patients With Localized Brain Tumors, Journal of Clinical Oncology, volume 29, issue 36, pages 4776-4780. Reprinted with permission. © (2011) American Society of Clinical Oncology. All rights reserved.

Children treated with CNS-directed therapy for leukemia are also at increased risk of GHD. Results from selected studies of childhood acute lymphocytic leukemia (ALL) survivors are as follows:

- One study evaluated 127 patients with ALL treated with 24 Gy, 18 Gy, or no cranial radiation therapy. The change in height, compared with population norms expressed as the standard deviation score (SDS), was significant for all three groups, with a dose response of -0.49 ± 0.14 for the group that did not receive radiation therapy, -0.65 ± 0.15 for the group that received 18 Gy of radiation therapy, and -1.38 ± 0.16 for the group that received 24 Gy of radiation therapy.[29]

- Another study found similar results in 118 ALL survivors treated with 24 Gy of cranial radiation, in which 74% had SDS of -1 or higher and the remainder had scores of -2 or higher.[30]

- Survivors of childhood ALL who are treated with chemotherapy alone are also at increased risk for adult short stature, although the risk is highest for those treated with cranial and craniospinal radiation therapy at a young age. [31] In this cross-sectional study, attained adult height was determined among 2,434 ALL survivors participating in the CCSS.

  - All survivor treatment exposure groups (chemotherapy alone and chemotherapy with cranial or craniospinal radiation therapy) had decreased adult height and an increased risk of adult short stature (height SDS < -2), compared with siblings (P < .001).

> Compared with siblings, the risk of short stature for survivors treated with chemotherapy alone was elevated (OR, 3.4; 95% CI, 1.9–6.0).
>
> - Among survivors, significant risk factors for short stature included diagnosis of ALL before puberty, higher-dose cranial radiation therapy (≥20 Gy vs. <20 Gy), any radiation therapy to the spine, and female gender.

- The impact of chemotherapy alone on growth in 67 survivors treated with contemporary regimens for ALL was statistically significant at -0.59 SD. The loss of growth potential did not correlate with GH status in this study, further highlighting the participation of other factors in the growth impairments observed in this population.[32]

Children who undergo HSCT with TBI have a significant risk of both GHD and the direct effects of radiation on skeletal development. The risk is increased with single-dose TBI as opposed to fractionated TBI, pretransplant cranial irradiation, female gender, and posttreatment complications such as graft-versus-host disease (GVHD).[33-35] Regimens containing busulfan and cyclophosphamide appear to increase risk in some studies,[35,36] but not others.[37] Hyperfractionation of the TBI dose markedly reduces risk in patients who have not undergone pretransplant cranial irradiation for CNS leukemia prophylaxis or therapy.[38]

The late effects that occur after HSCT have been studied and reviewed by the Late Effect Working Party of the European Group for Blood and Marrow Transplantation. Among 181 patients with aplastic anemia, leukemias, and lymphomas who underwent HSCT before puberty, the following results were observed:[39,40]

- An overall decrease in final height-SDS value was found, compared with height at transplant and genetic height. The mean loss of height is estimated to be approximately 1 height-SDS (6 cm), compared with the mean height at time of HSCT and mean genetic height.

- The type of transplantation, GVHD, and GH or steroid treatment did not influence final height.

- TBI (single-dose radiation therapy more than fractionated-dose radiation therapy), male gender, and young age at transplant were found to be major factors for long-term height loss. Most patients (140 of 181) reached adult height within the normal range of the general population.

GHD replacement therapy provides the benefit of optimizing height outcomes among children who have not reached skeletal maturity. Treatment with recombinant GH (rGH) replacement therapy is generally delayed until 12 months after successful completion of cancer or brain tumor treatments and after a multidisciplinary discussion involving the prescribing pediatric endocrinologist, the primary oncologist, and other providers selected by the patient or family. Safety concerns pertaining to the use of rGH in childhood cancer survivors have primarily been related to the mitogenic potential of the GH stimulating tumor growth in a population with an increased risk of second neoplasms.[41] Most studies that report these outcomes, however, are limited by selection bias and small sample size.

The following study results have been reported in survivors who did or did not receive treatment with GH:

- One study evaluated 361 GH-treated cancer survivors enrolled in the CCSS and compared risk of recurrence, risk of subsequent neoplasm, and risk of death among survivors who did and did not receive treatment with GH.[42]

  - The RR of disease recurrence was 0.83 (95% CI, 0.37–1.86) for GH-treated survivors. GH-treated subjects were diagnosed with 15 subsequent neoplasms, all solid tumors, for an overall RR of 3.21 (95% CI, 1.88–5.46), mainly because of a small excess number of subsequent neoplasms observed in survivors of acute leukemia.[42] With prolonged follow-up, the elevation of subsequent cancer risk due to GH diminished.[43]

  - Compared with survivors not treated with GH, those who were treated had a twofold excess risk of developing a subsequent neoplasm (RR, 2.15; 95% CI, 1.33–3.47; $P < .002$); meningiomas were the most commonly

observed (9 of 20 tumors).

- A review of existing data suggests that treatment with GH is not associated with an increased risk of CNS tumor progression or recurrence, or new or recurrent leukemia.[44]

- A recent study from the CCSS reported specifically on the risk of subsequent CNS neoplasms after a longer period of follow-up. The adjusted rate ratio of meningioma and gliomas in GH-treated survivors of CNS tumors was 1.0 (95% CI, 0.6–1.8; *P* = .94) when compared with CNS tumor survivors who were not treated with GH, thus indicating negligible differences between the two groups for this particular risk.[45]

In general, the data addressing subsequent malignancies should be interpreted with caution given the small number of events.[41,42]

Disorders of luteinizing hormone (LH) and follicle-stimulating hormone (FSH): Central precocious puberty and LH/FSH deficiency

Pubertal development can be adversely affected by cranial radiation therapy. Doses higher than 18 Gy can result in central precocious puberty, while doses higher than 30 Gy to 40 Gy may result in LH and FSH deficiency.[46]

Central precocious puberty

Central precocious puberty is defined by the onset of pubertal development before age 8 years in girls and 9 years in boys as a result of the premature activation of the hypothalamic-pituitary-gonadal axis. Aside from the adjustment and psychosocial challenges associated with early pubertal development, precocious puberty can lead to the rapid closure of the skeletal growth plates and short stature. This deleterious effect can be further potentiated by GHD.[47] The increased growth velocity induced by pubertal development can mask concurrent GHD with seemingly normal growth velocity; this occurrence may mislead care providers. It is also important to note that the assessment of puberty cannot be performed using testicular volume measurements in boys exposed to chemotherapy or direct radiation to the testes, given the toxic effect of these treatments on germ cells and repercussions on gonadal size. The staging of puberty in males within this population relies on the presence of other signs of virilization, such as the presence of pubic hair and the measurement of plasma testosterone levels.[47]

Central precocious puberty has been reported in some children receiving cranial irradiation in doses of 24 Gy or higher. Earlier puberty and earlier peak height velocity, however, have been observed in girls treated with 18 Gy of cranial radiation therapy.[48,49] The impact of central precocious puberty on linear growth can be ascertained by assessing the degree of skeletal maturation (or bone age) using an x-ray of the left hand.[50]

When appropriate, delaying the progression of puberty relies on the use of various gonadotropin-releasing hormone agonist preparations, an approach that has been shown to improve growth prospects—especially when other pituitary abnormalities, including GHD, are concurrently treated.[51]

LH/FSH deficiency

LH/FSH deficiency (also referred to as hypogonadotropic hypogonadism) can manifest through pubertal delay, arrested puberty, or symptoms of decreased sex hormone production, depending on age and pubertal status at the time of diagnosis. With higher doses of cranial radiation therapy (>35 Gy), deficiencies in LH/FSH can be seen, with a cumulative incidence of 10% to 20% at 5 to 10 years posttreatment.[52,53] The treatment of LH/FSH deficiency relies on sex-hormone replacement therapy adjusted to age and pubertal status.

TSH deficiency

TSH deficiency (also referred to as central hypothyroidism) in survivors of childhood cancer can have profound clinical consequences and be underappreciated. Symptoms of central hypothyroidism (e.g., asthenia, edema, drowsiness, and

skin dryness) may have a gradual onset and go unrecognized until thyroid replacement therapy is initiated. In addition to delayed puberty and slow growth, hypothyroidism may cause fatigue, dry skin, constipation, increased sleep requirement, and cold intolerance. Individuals with TSH deficiency have low plasma free T_4 levels and either low or *inappropriately normal* TSH levels.

Radiation dose to the hypothalamus in excess of 42 Gy is associated with an increased risk of developing TSH deficiency (44% ± 19% for dose of ≥42 Gy and 11% ± 8% for dose of <42 Gy).[54] It occurs in as many as 65% of survivors of brain tumors, 43% of survivors of childhood nasopharyngeal tumors, 35% of bone marrow transplant recipients, and 10% to 15% of leukemia survivors.[55,56]

Mixed primary and central hypothyroidism can also occur and reflects separate injuries to the thyroid gland and the hypothalamus (e.g., radiation injury to both structures). TSH values may be elevated and, in addition, the secretory dynamics of TSH are abnormal, with a blunted or absent TSH surge or a delayed peak response to TSH-releasing hormone (TRH).[57] In a study of 208 childhood cancer survivors referred for evaluation of possible hypothyroidism or hypopituitarism, mixed hypothyroidism was present in 15 patients (7%).[57] Among patients who received TBI (fractionated total doses of 12–14.4 Gy) or craniospinal radiation therapy (fractionated total cranial doses higher than 30 Gy), 15% had mixed hypothyroidism. In one study of 32 children treated for medulloblastoma, 56% developed hypothyroidism, including 38% with primary hypothyroidism and 19% with central hypothyroidism.[58]

Thyroid hormone replacement therapy using levothyroxine represents the mainstay of treatment of TSH deficiency. The dose of levothyroxine needs to be adjusted solely using plasma free T_4 levels; the levels of TSH are expected to remain low during therapy, given the central nature of this deficiency.

Adrenal-corticotropin (ACTH) deficiency

ACTH deficiency is less common than other neuroendocrine deficits but should be suspected in patients who have a history of brain tumor (regardless of therapy modality), cranial radiation therapy, GHD, or central hypothyroidism. [25,54,59-61] Although uncommon, ACTH deficiency can occur in patients treated with intracranial radiation doses of less than 24 Gy and has been reported to occur in fewer than 3% of patients after chemotherapy alone.[61] The diagnosis should be suspected when low plasma levels of morning cortisol are measured (a screening cortisol level collected at 8 a.m. that is 10 mcg/dl or more is reassuring for ACTH sufficiency, whereas a value of 5 mcg/dl or lower is suspicious for insufficiency). Confirmation is necessary using dynamic testing such as the low-dose ACTH stimulation test.[60] Because of the substantial risk of central adrenal insufficiency among survivors treated with cranial radiation doses exceeding 30 Gy to the hypothalamic-pituitary axis, endocrine monitoring with periodic dynamic testing as clinically indicated is recommended for this high-risk group.

Patients with partial ACTH deficiency may have only subtle symptoms unless they become ill. Illness can disrupt these patients' usual homeostasis and cause a more severe, prolonged, or complicated course than expected. As in complete ACTH deficiency, incomplete or unrecognized ACTH deficiency can be life-threatening during concurrent illness.

The treatment of ACTH deficiency relies on replacement with hydrocortisone, including stress dosing in situations of illness to adjust to the body's physiologically increased need for glucocorticoids.

Hyperprolactinemia

Hyperprolactinemia has been described in patients who received radiation therapy to the hypothalamus in doses higher than 50 Gy or who underwent surgery that disrupted the integrity of the pituitary stalk. Primary hypothyroidism may lead to hyperprolactinemia as a result of hyperplasia of thyrotrophs and lactotrophs, presumably due to TRH hypersecretion. The prolactin response to TRH is usually exaggerated in these patients.[25,62]

In general, hyperprolactinemia may result in delayed puberty, galactorrhea, menstrual irregularities, loss of libido, hot flashes, infertility, and osteopenia. However, hyperprolactinemia resulting from cranial radiation therapy is rarely

symptomatic and, given its frequent associations with hypogonadism (both central and primary), rarely requires treatment.

Table 9. Pituitary Gland Late Effects[a]

Predisposing Therapy	Endocrine/Metabolic Effects	Health Screening
Radiation impacting hypothalamic-pituitary axis	Growth hormone deficiency	Assessment of nutritional status
		Height, weight, BMI, Tanner stage[b]
Radiation impacting hypothalamic-pituitary axis	Precocious puberty	Height, weight, BMI, Tanner stage[b]
		FSH, LH, estradiol, or testosterone levels
Radiation impacting hypothalamic-pituitary axis	Gonadotropin deficiency	History: puberty, sexual function
		Exam: Tanner stage[b]
		FSH, LH, estradiol or testosterone levels
Radiation impacting hypothalamic-pituitary axis	Central adrenal insufficiency	History: failure to thrive, anorexia, episodic dehydration, hypoglycemia, lethargy, unexplained hypotension
		Endocrine consultation for those with radiation dose ≥30 Gy
Radiation impacting hypothalamic-pituitary axis	Hyperprolactinemia	History/exam: galactorrhea
		Prolactin level
Radiation impacting hypothalamic-pituitary axis	Overweight/obesity	Height, weight, BMI
		Blood pressure
	Components of metabolic syndrome (abdominal obesity, hypertension, dyslipidemia, impaired glucose metabolism)	Fasting blood glucose level and lipid profile
Radiation impacting hypothalamic-pituitary axis	Central hypothyroidism	TSH[c] free thyroxine (free T_4) level

BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

[b]Testicular volume measurements are not reliable in the assessment of pubertal development in boys exposed to chemotherapy or direct radiation to the testes.

[c]Appropriate only at diagnosis. TSH levels are not useful for follow-up during replacement therapy.

Testis and Ovary

Testicular and ovarian hormonal functions are discussed in the Late Effects of the Reproductive System section of this summary.

Metabolic Syndrome

An increased risk of metabolic syndrome or its components has been observed among cancer survivors. The evidence for this outcome ranges from clinically manifested conditions that are self-reported by survivors to retrospectively assessed data in medical records and hospital registries to systematic clinical evaluations of clinically well-characterized cohorts. Studies have been limited by cohort selection and participation bias, heterogeneity in treatment approach, time since treatment, and method of ascertainment. Despite these limitations, compelling evidence indicates that metabolic syndrome is highly associated with cardiovascular events and mortality. Definitions of metabolic syndrome are evolving but generally include a combination of central (abdominal) obesity with at least two or more of the following features:

- Hypertension.

- Atherogenic dyslipidemia (elevated triglycerides, reduced high-density lipoprotein [HDL] cholesterol).

- Abnormal glucose metabolism (fasting hyperglycemia, hyperinsulinism, insulin resistance, diabetes mellitus type 2).[63]

Long-term survivors of ALL, especially those treated with cranial radiation therapy, may have a higher prevalence of some potentially modifiable risk factors for cardiovascular disease such as impaired glucose tolerance or overt diabetes mellitus, dyslipidemia, hypertension, and obesity.[64-70] The contribution of modifiable risk factors associated with metabolic syndrome to the risk of major cardiac events suggests that survivors are good candidates for targeted screening and lifestyle counseling regarding risk-reduction measures.[71]

Several studies have provided support for the potential benefits of lifestyle modifications in reducing cardiovascular disease risk.

- Survivors participating in the St. Jude Lifetime Cohort study who were adherent to a heart-healthy lifestyle had a lower risk of metabolic syndrome. Females (RR, 2.4; 95% CI, 1.7–3.3) and males (RR, 2.2; 95% CI, 1.6–3.0) in the cohort who did not follow recommended dietary and physical activity guidelines had a more than twofold excess risk of having clinical features of the metabolic syndrome.[72]

- In a CCSS investigation evaluating the impact of exercise on cardiovascular disease risk among survivors of HL, vigorous exercise was associated with a lower risk of cardiovascular events in a dose-dependent manner, independent of cardiovascular risk profile and treatment. Survivors who were adherent to national vigorous intensity exercise guidelines had a 51% reduction in the risk of any cardiovascular event compared with those not meeting the guidelines.[73]

Results of selected studies describing the metabolic syndrome in childhood cancer cohorts include the following:

- In a study of 784 childhood long-term ALL survivors (median age, 31.7 years; median follow-up duration, 26.1 years), the prevalence of metabolic syndrome was 33.6%, which was significantly higher than that in a cohort of age-, sex-, and race-matched controls (N = 777) from the National Health and Nutrition Examination Survey (RR, 1.43; 95% CI, 1.22–1.69). Risk factors associated with metabolic syndrome in this study included older age and past exposures to cranial radiation therapy. Components of metabolic syndrome with significantly higher prevalence in ALL survivors than in controls included obesity, insulin resistance, hypertension, and decreased HDL levels.[69]

- In a European cohort of 184 adult survivors of childhood leukemia (81.5% had ALL; median age, 21.2 years; median follow-up duration, 15.4 years), the prevalence of metabolic syndrome was 9.2%. In this study, exposure to TBI was found to be significantly associated with metabolic syndrome, with significant associations between TBI and hypertriglyceridemia, and low HDL and impaired fasting glucose.[70]

Abdominal irradiation is an additional risk factor for metabolic syndrome. Survivors of developmental or embryonal tumors treated with abdominal irradiation are also at an increased risk of developing components of metabolic syndrome. In a prospective study of 164 long-term survivors (median follow-up time, 26 years), nephroblastoma (OR, 5.2) and neuroblastoma (OR, 6.5) survivors had more components of metabolic syndrome than did controls. Compared with nonirradiated survivors, survivors treated with abdominal irradiation had higher blood pressure, triglycerides, low-density lipoprotein (LDL) cholesterol, and total fat percentage, which were assessed by dual-energy x-ray absorptiometry.[74]

Abnormal glucose metabolism

Abdominal radiation therapy and TBI in the context of HSCT are increasingly recognized as independent risk factors for diabetes mellitus in childhood cancer survivors.[65,70,74-78]

- A single-center cohort study of 532 adult (median age, 25.6 years) long-term (median follow-up time, 17.9 years) survivors observed that treatment but not genetic variation was strongly associated with the occurrence of the components of metabolic syndrome. Metabolic syndrome was more frequent in cranially (23.3%, P = .002) and abdominally (23.4%, P = .009) irradiated survivors than in nonirradiated survivors (10.0%).[77]

- In a cross-sectional study evaluating cardiovascular risk factors and insulin resistance in a clinically heterogeneous cohort of 319 childhood cancer survivors 5 or more years since diagnosis and 208 sibling controls, insulin resistance was significantly higher in survivors treated with cisplatin plus cranial irradiation (92% brain tumors) and in those who received steroids but no cisplatin (most leukemia survivors), compared with siblings.[79] Insulin resistance did not differ between survivors treated with surgery alone and siblings. Among survivors, analysis of individual chemotherapy agents failed to find associations with cardiovascular risk factors or insulin resistance. However, compared with siblings, nearly all chemotherapeutic agents, when examined individually, seemed to be associated with a high cardiovascular risk profile, characterized by lower total lean body mass, higher percentage fat mass, and insulin resistance.

- In a European multicenter cohort of 2,520 childhood cancer survivors (median follow-up duration, 28 years), significant associations were found between diabetes mellitus and increasing doses of radiation therapy to the tail of the pancreas. These data support the contribution of radiation-induced islet cell injury to impairments of glucose homeostasis in this population.[78]

- In a report from the CCSS that compared 8,599 childhood cancer survivors to 2,936 randomly selected sibling controls, and after adjustment for age, body mass index (BMI), and several demographic factors, the risk of diabetes mellitus was 1.8 times higher in survivors (95% CI, 1.3–2.5; P < .001). Significant associations were found between diabetes mellitus and young age at diagnosis (0–4 years), the use of alkylating agents and abdominal radiation therapy or TBI. Also, survivors were significantly more likely to be receiving medication for hypertension, dyslipidemia, and/or diabetes mellitus than were sibling controls.[80]

Table 10. Metabolic Syndrome Late Effects[a]

Predisposing Therapy	Potential Late Effects	Health Screening
Total-body irradiation	Components of metabolic syndrome (abdominal obesity, hypertension, dyslipidemia, impaired glucose metabolism)	Height, weight, BMI, blood pressure
		Labs: fasting glucose and lipids

BMI = body mass index.

a

"Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Obesity and Being Overweight

To date, the primary cancer groups recognized with an increased incidence of treatment-related obesity are ALL [81-90] and CNS tumor [17,18] survivors treated with cranial radiation therapy.[91,92] In addition, craniopharyngioma survivors have a substantially increased risk of extreme obesity because of the tumor location and the hypothalamic damage resulting from surgical resection.[93-98]

In addition to treatment factors, lifestyle factors and medication use can also contribute to the risk of obesity. CCSS investigators reported the following independent risk factors for obesity in childhood cancer survivors:[99]

- Cancer diagnosed at ages 5 to 9 years (RR, 1.12; 95% CI, 1.01–1.24).

- Abnormal physical functioning (RR, 1.19; 95% CI, 1.06–1.33).

- Hypothalamic/pituitary radiation dose of 20 Gy to 30 Gy (RR, 1.17; 95% CI, 1.05–1.3; $P = .01$).

- Specific antidepressant use (paroxetine) (RR, 1.29; 95% CI, 1.08–1.54).

Survivors who adhered to the U.S. Centers for Disease Control and Prevention guidelines for vigorous physical activity (RR, 0.90; 95% CI, 0.82–0.97; $P = .01$) and who had a medium amount of anxiety (RR, 0.86; 95% CI, 0.75–0.99; $P = .04$) had a lower risk of obesity.[99]

The development of obesity after cranial radiation therapy is multifactorial and includes the following:[87,100,101]

- GHD.

- Leptin sensitivity.

- Reduced levels of physical activity and energy expenditure.

Body composition alterations after childhood ALL

Moderate-dose cranial radiation therapy (18–24 Gy) among ALL survivors is associated with obesity, particularly in females treated at a young age.[66,84,87,102] Female adult survivors of childhood ALL who were treated with cranial radiation therapy of 24 Gy before age 5 years are four times more likely to be obese than are women who have not been treated for a cancer.[84] In addition, women treated with 18 Gy to 24 Gy cranial radiation therapy before age 10 years have a substantially greater rate of increase in their BMI through their young adult years than do women who were treated for ALL with only chemotherapy or women in the general population.[87] It appears that these women also have a significantly increased visceral adiposity and associated insulin resistance.[103,104] These outcomes are attenuated in males.

ALL therapy regimens are associated with increases in BMI shortly after completion of therapy, and possibly with a higher risk of obesity in the long term.[88-90,105,106] Several studies have reported that survivors of childhood ALL treated with chemotherapy alone also exhibit long-term changes in body composition, with relative increases in body fat [104,107-109] and visceral adiposity in comparison to lean mass.[103] These changes cannot be detected if BMI alone is used in the assessment of metabolic risk in this population. A cohort study of 365 adult survivors of ALL (149 treated with cranial radiation therapy and 216 treated without cranial radiation therapy) that compared body composition, energy balance, and fitness to age-, sex-, and race-matched peers disclosed that female survivors who were not exposed to cranial irradiation had comparable body composition values to that of peers. However, waist circumference, waist-to-height ratio, and total and percent fat mass were higher among male survivors and cranial radiation–exposed female survivors than among comparison group members. Survivors of both sexes exposed to cranial radiation therapy had

higher BMI and percent body fat than did survivors not exposed to cranial radiation therapy. Although survivors who did not receive cranial radiation therapy had energy balance similar to the matched peer group, they had significantly higher measures of impaired fitness (impaired flexibility, peripheral sensorimotor deficits, proximal muscle weakness, and poor exercise tolerance). These results suggest that elimination of cranial radiation from ALL therapy has improved, but not eliminated, adverse body composition outcomes and underscores the importance of attention to interventions to preserve function in this group as they age.[110]

In contrast, in a report from the CCSS, adult survivors of childhood ALL treated with chemotherapy alone did not have significantly higher rates of obesity than did sibling controls,[84] nor were there differences in BMI changes between these groups after a subsequent period of follow-up that averaged 7.8 years.[87] Results from the CCSS, however, were based on self-reported height and weight measurements. Likewise, COG investigators also did not observe an increased risk of being overweight and obese based on BMI measurements in 269 patients with standard-risk ALL (age, 3.5 years at diagnosis and 13.3 years at follow-up) compared with peers without cancer. Again, these variable outcomes likely relate to the use of BMI as the metric for abnormal body composition, which does not adequately assess visceral adiposity that can contribute to metabolic risk in this population.[111]

Body composition alterations after treatment for CNS tumors

Among brain tumor survivors treated with higher doses of cranial radiation therapy, only females treated at a younger age appear to be at increased risk for obesity.[112]

Body composition alterations after hematopoietic cell transplantation

Survivors of childhood cancer treated with TBI in preparation for an allogeneic HSCT have increased measures of body fatness (percent fat) while often having a normal BMI.[75,113] Longitudinal decline in BMI related to substantial decrease in lean mass has been observed among survivors of hematological malignancies treated with allogeneic HSCT. This finding was largely attributable to TBI conditioning and severity of chronic GVHD.[114]

Body composition and frailty

Young adult childhood cancer survivors have a higher-than-expected prevalence of frailty, a phenotype characterized by low muscle mass, self-reported exhaustion, low energy expenditure, slow walking speed, and weakness. The frailty phenotype increases in prevalence with aging, and has been associated with excess risk of mortality and onset of chronic conditions. Ongoing research aims to elucidate the pathophysiology of frailty and develop/test interventions to prevent or reverse this condition.[115]

Table 11. Body Composition Late Effects[a]

Predisposing Therapy	Potential Late Effects	Health Screening
Cranial radiation therapy	Overweight/obesity	Height, weight, BMI, blood pressure
		Labs: fasting glucose and lipids

BMI = body mass index.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for endocrine and metabolic syndrome late effects information, including risk factors, evaluation, and health counseling.

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Late Effects of the Immune System

Late effects of the immune system have not been well studied, especially in survivors treated with contemporary therapies. Reports published about long-term immune system outcomes are limited by retrospective data collection, small sample size, cohort selection and participation bias, heterogeneity in treatment approach, time since treatment, and method of ascertainment.

Asplenia

Surgical or functional splenectomy increases the risk of life-threatening invasive bacterial infection:[1]

- Although staging laparotomy is no longer standard practice for pediatric Hodgkin lymphoma, patients from earlier time periods have ongoing risks.[2,3]

- Children may be rendered asplenic by radiation therapy to the spleen in doses greater than 30 Gy.[4,5] Low-dose involved-field radiation therapy (21 Gy) combined with multiagent chemotherapy did not appear to adversely affect splenic function, as measured by pitted red blood cell assays.[5] No other studies of immune status after radiation therapy are available.

- Functional asplenia (with Howell-Jolly bodies, reduced splenic size and blood flow) after hematopoietic stem cell transplantation (HSCT) has been attributed to graft-versus-host disease (GVHD).

Individuals with asplenia, regardless of the reason for the asplenic state, have an increased risk of fulminant bacteremia, especially associated with encapsulated bacteria, which is associated with a high mortality rate. The risk of bacteremia is higher in younger children than in older children, and this risk may be greater during the years immediately after splenectomy. Fulminant septicemia, however, has been reported in adults up to 25 years after splenectomy.

Bacteremia may be caused by the following organisms:

- *Streptococcus pneumoniae*. The most common pathogen that causes bacteremia in children with asplenia.

- Other *streptococci*.

- *Haemophilus influenzae* type b (Hib).

- *Neisseria meningitidis*.

- *Escherichia coli*; *Staphylococcus aureus*.

- Gram-negative bacilli, such as the *Salmonella* species, the *Klebsiella* species, and *Pseudomonas aeruginosa*.

Individuals with functional or surgical asplenia are also at increased risk of fatal malaria and severe babesiosis.

Posttherapy management

Clinicians should consider and encourage the administration of inactivated vaccines (e.g., influenza) and vaccines made of purified antigens (e.g., pneumococcus), bacterial components (e.g., diphtheria-tetanus-pertussis), or genetically engineered recombinant antigens (e.g., hepatitis B) in all cancer and transplant survivors according to recommended doses and schedules.[6-8]

Two primary doses of quadrivalent meningococcal conjugate vaccine should be administered 2 months apart to children with asplenia, from age 2 years through adolescence, and a booster dose should be administered every 5 years.[9] (Refer to the Scheduling Immunizations section of the Red Book for more information.) However, the efficacy of

meningococcal vaccines in children with asplenia has not been established. (Refer to the Meningococcal Infections section of the Red Book for more information.) No known contraindication exists to giving these vaccines at the same time as other required vaccines, in separate syringes, at different sites.

Pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV) are indicated at the recommended age for all children with asplenia. Following the administration of the appropriate number of doses of PCV13, PPSV23 should be administered starting at age 24 months. A second dose should be administered 5 years later. For children aged 2 to 5 years with a complete PCV7 series who have not received PCV13, a supplemental dose of PCV13 should be administered. For asplenic individuals aged 6 to 18 years who have not received a dose of PCV13, a supplemental dose of PCV13 should be considered.[10] (Refer to the Pneumococcal Infections section of the Red Book for more information.) Hib immunization should be initiated at age 2 months, which is recommended for otherwise healthy young children and for all previously unimmunized children with asplenia.[10] (Refer to the Scheduling Immunizations section of the Red Book for more information.)

Daily antimicrobial prophylaxis against pneumococcal infections is recommended for many children with asplenia, regardless of their immunization status. Although the efficacy of antimicrobial prophylaxis has been proven only in patients with sickle cell anemia, other children with asplenia at particularly high risk, such as children with malignant neoplasms or thalassemia, should also receive daily chemoprophylaxis. In general, antimicrobial prophylaxis (in addition to immunization) should be considered for all children with asplenia younger than 5 years and for at least 1 year after splenectomy.

The age at which chemoprophylaxis is discontinued is often an empiric decision. On the basis of a multicenter study, prophylactic penicillin can be discontinued at age 5 years in children with sickle cell disease who are receiving regular medical attention and who have not had a severe pneumococcal infection or surgical splenectomy. The appropriate duration of prophylaxis is unknown for children with asplenia attributable to other causes. Some experts continue prophylaxis throughout childhood and into adulthood for particularly high-risk patients with asplenia.

Table 12. Spleen Late Effects[a]

Predisposing Therapy	Immunologic Effects	Health Screening/Interventions
Radiation impacting spleen; splenectomy; HSCT with currently active GVHD	Asplenia/hyposplenia; overwhelming post-splenectomy sepsis	Blood cultures during febrile episodes (T >38.5°C); empiric antibiotics
HSCT with any history of chronic GVHD	Immunologic complications (secretory IgA deficiency, hypogammaglobulinemia, decreased B cells, T cell dysfunction, chronic infections [e.g., conjunctivitis, sinusitis, and bronchitis associated with chronic GVHD])	History: chronic conjunctivitis, chronic sinusitis, chronic bronchitis, recurrent or unusual infections, sepsis
		Exam: attention to eyes, nose/sinuses, and lungs

GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; IgA = immunoglobulin A; T = temperature.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Refer to the Centers for Disease Control and Prevention (CDC) *Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients* for more information on posttransplant immunization.

Humoral immunity

Although the immune system appears to recover from the effects of active chemotherapy and radiation therapy, there is some evidence that lymphoid subsets may not always normalize. Innate immunity, thymopoiesis, and DNA damage responses to radiation were shown to be abnormal in survivors of childhood leukemia.[11] Antibody levels to previous vaccinations are also reduced in patients off therapy for acute lymphoblastic leukemia for at least 1 year,[12,13] suggesting persistence of abnormal humoral immunity [14] and a need for revaccination in such children. Many survivors of childhood cancer will remain susceptible to vaccine-preventable infections.

While there is a paucity of data regarding the benefits of administering active immunizations in this population, reimmunization is necessary to provide protective antibodies. The recommended reimmunization schedule will depend on previously received vaccinations and on the intensity of therapy.[15,16] In some children who received intensive treatment, consideration may be given to evaluating the antibodies against common vaccination antigens to determine the need for revaccination. (Refer to the Scheduling Immunizations section of the Red Book for more information.)

Immune status is also compromised after HSCT, particularly in association with GVHD.[17] In a prospective, longitudinal study of 210 survivors treated with allogeneic HSCT, antibody responses lasting for more than 5 years after immunization were observed in most patients for tetanus (95.7%), rubella (92.3%), poliovirus (97.9%), and, in diphtheria-tetanus-acellular pertussis (DTaP) recipients, diphtheria (100%). However, responses to pertussis (25.0%), measles (66.7%), mumps (61.5%), hepatitis B (72.9%), and diphtheria in tetanus-diphtheria (Td) recipients (48.6%) were less favorable. Factors associated with vaccine failure include older age at immunization; lower CD3, CD4, or CD19 count; higher immunoglobulin M concentration; positive recipient cytomegalovirus serology; negative titer before immunization; history of acute or chronic GVHD; and radiation conditioning.[18]

Follow-up recommendations for transplant recipients have been published by the major North American and European transplant groups, the CDC, and the Infectious Diseases Society of America.[19,20]

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for immune system late effects information including risk factors, evaluation, and health counseling.

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Late Effects of the Musculoskeletal System

The musculoskeletal system of growing children and adolescents is vulnerable to the cytotoxic effects of cancer therapies, including surgery, chemotherapy, and radiation therapy. Documented late effects include the following:

- Bone and joint (abnormal bone and/or muscle growth) problems.

- Deformity and functional loss associated with amputation/limb-sparing surgery, joint contracture, osteoporosis/fractures, and osteonecrosis.

- Changes in body composition (obesity and loss of lean muscle mass).

While these late effects are discussed individually, it is important to remember that the components of the musculoskeletal system are interrelated. For example, hypoplasia to a muscle group can negatively affect the function of the long bones and the resultant dysfunction can subsequently lead to disuse and osteoporosis.

The major strength of the published literature documenting musculoskeletal late effects among children and adolescents treated for cancer is that most studies have clearly defined outcomes and exposures. However, many studies are observational and cross-sectional or retrospective in design. Single-institution studies are common, and for some outcomes, only small convenience cohorts have been described. Thus, it is possible that studies either excluded patients with the most severe musculoskeletal effects because of death or inability to participate in follow-up testing, or oversampled those with the most severe musculoskeletal late effects because these patients were accessible because they returned for complication-related follow-up. Additionally, some of the results reported in adult survivors of childhood cancer may not be relevant to patients currently being treated because the delivery of anticancer modalities, particularly radiation therapy, has changed over the years in response to documented toxicities.[1,2]

Bone and Joint

Abnormal bone growth

Radiation to the head and brain

In an age- and dose-dependent fashion, radiation can inhibit normal bone and muscle maturation and development. Radiation to the head (e.g., cranial, orbital, infratemporal, or nasopharyngeal radiation therapy) can cause craniofacial abnormalities, particularly in children treated before age 5 years or with radiation doses of 20 Gy or more.[3-7] Soft tissue sarcomas such as orbital rhabdomyosarcoma and retinoblastoma are two of the more common cancer groups treated with these radiation fields. Often, in addition to the cosmetic impact of the craniofacial abnormalities, there can be related dental and sinus problems.

Cranial radiation therapy damages the hypothalamic-pituitary axis in an age- and dose-response fashion, and can result in growth hormone deficiency (GHD).[8,9] If untreated during the growing years, and sometimes, even with appropriate treatment, it leads to a substantially lower final height. Patients with a central nervous system tumor [8,10] or acute lymphoblastic leukemia (ALL) [11-13] treated with 18 Gy or more of cranial radiation therapy are at highest risk. Also, patients treated with total-body irradiation (TBI), particularly single-fraction TBI, are at risk of GHD.[14-17] In addition, if the spine is also irradiated (e.g., craniospinal radiation therapy for medulloblastoma or early ALL therapies in the 1960s), growth can be affected by two separate mechanisms—GHD and direct damage to the spine.

Radiation to the spine and long bones

Radiation therapy can also directly affect the growth of the spine and long bones (and associated muscle groups) and can cause premature closure of the epiphyses, leading to the following:[18-24]

- Short stature.

- Asymmetric growth (scoliosis/kyphosis).

- Limb-length discrepancy.

Orthovoltage radiation therapy, commonly used before 1970, delivered high doses of radiation to bone and was commonly associated with subsequent abnormalities in bone growth. However, even with contemporary radiation therapy, if a solid tumor is located near an epiphysis or the spine, alterations in normal bone development can be difficult to avoid.

The effects of radiation therapy administered to the spine on stature in survivors of Wilms tumor have been assessed.

- In the National Wilms Tumor Study (NWTS), studies 1 through 4, stature loss in 2,778 children was evaluated. [19] Repeated height measurements were collected during long-term follow-up. The effects of radiation dosage, age at treatment, and chemotherapy on stature were analyzed using statistical models that accounted for the normal variation in height with gender and advancing age. Predictions from the model were validated by descriptive analysis of heights measured at ages 17 to 18 years for 205 patients. For those younger than 12 months at diagnosis who received more than 10 Gy, the estimated adult-height deficit was 7.7 cm when contrasted with the nonradiation therapy group. For those who received 10 Gy, the estimated trunk shortening was 2.8 cm or less. Among those whose height measurements in the teenage years were available, patients who received more than 15 Gy of radiation therapy were 4 to 7 cm shorter on average than their nonirradiated counterparts, with a dose-response relationship evident. Chemotherapy did not confer additional risk.

- The effect of radiation therapy on the development of scoliosis has also been re-evaluated. In a group of 42 children treated for Wilms tumor from 1968 to 1994, scoliosis was seen in 18 patients, with only one patient needing orthopedic intervention.[25] Median time to development of scoliosis was 102 months (range, 16–146 months). A clear dose-response relationship was seen; children treated with lower dosages (<24 Gy) of radiation had a significantly lower incidence of scoliosis than those who received more than 24 Gy of radiation. There was also a suggestion that the incidence was lower in patients who received 10 to 12 Gy, the dosages currently used for Wilms tumor, although the sample size was small.

Osteoporosis/fractures

Maximal peak bone mass is an important factor influencing the risk of osteoporosis and fracture associated with aging. Treatment-related factors that affect bone mineral loss include the following:

- Chemotherapy. Methotrexate has a cytotoxic effect on osteoblasts, resulting in a reduction of bone volume and formation of new bone.[26,27] This effect may be exacerbated by the chronic use of corticosteroids, another class of agents routinely used in the treatment of hematological malignancies and in supportive care for a variety of pediatric cancers.

- Radiation therapy. Radiation-related endocrinopathies, such as GHD or hypogonadism, may contribute to ongoing bone mineral loss.[28,29]

- Suboptimal nutrition and physical inactivity may further predispose to deficits in bone mineral accretion.

Most of our knowledge about cancer and treatment effects on bone mineralization has been derived from studies of children with ALL.[26,30] In this group, the leukemic process, and possibly vitamin D deficiency, may play a role in the alterations in bone metabolism and bone mass observed at diagnosis.[31] Antileukemic therapy causes further bone mineral density loss,[32] which has been reported to normalize over time [33,34] or to persist for many years after completion of therapy.[35,36] Clinical factors predicting higher risk of low bone mineral density include treatment with high cumulative doses of methotrexate (>40 g/m^2), high cumulative doses of corticosteroids (>9 g/m^2), cranial radiation therapy, and use of more potent glucocorticoids like dexamethasone.[35,37-39]

Clinical assessment of bone mineral density in adults treated for childhood ALL indicates that most bone mineral deficits normalize over time after discontinuing osteotoxic therapy. Very low bone mineral density was relatively uncommon in a cohort of 845 adult survivors of childhood ALL evaluated at a median age of 31 years, with only 5.7% and 23.8% demonstrating bone mineral density z-scores consistent with osteoporosis and osteopenia, respectively. Cranial radiation dose of 24 Gy or greater, but not cumulative methotrexate or prednisone equivalent doses, was associated with a twofold elevated risk of bone mineral density z-scores of -1 or lower. In a subset of 400 survivors with longitudinal bone mineral density evaluations, bone mineral density z-scores tended to improve from adolescence to young adulthood.[39]

Bone mineral density deficits that are likely multifactorial in etiology have been reported in allogeneic hematopoietic cell transplant recipients conditioned with TBI.[40,41] French investigators observed a significant risk for lower femoral

bone mineral density among adult survivors of childhood leukemia treated with hematopoietic stem cell transplantation (HSCT) who had gonadal deficiency.[42] Hormonal therapy has been shown to enhance bone mineral density of adolescent girls diagnosed with hypogonadism after HSCT.[43][Level of evidence: 3iiiC]

Despite disease- and treatment-related risks of bone mineral density deficits, the prevalence of self-reported fractures among Childhood Cancer Survivor Study (CCSS) participants was lower than that reported by sibling controls. Predictors of increased prevalence of fracture by multivariable analyses included the following:[44]

- Among female survivors, increasing age at follow-up, white race, methotrexate treatment, and balance difficulties.

- Among male survivors, smoking history and white race.

Radiation-induced fractures can occur with doses of radiation of 50 Gy or greater, as is often used in the treatment of Ewing sarcoma of the extremity.[45,46]

Osteonecrosis

Osteonecrosis (also known as aseptic or avascular necrosis) is a rare, but well-recognized skeletal complication observed predominantly in survivors of pediatric hematological malignancies treated with corticosteroids.[47-49] The prevalence of osteonecrosis has varied from 1% to 22% based on the study population, treatment protocol, method of evaluation, and time from treatment.[49-55] The condition is characterized by death of one or more segments of bone that most often affects weight-bearing joints, especially the hips and knees. Longitudinal cohort studies have identified a spectrum of clinical manifestations of osteonecrosis, ranging from asymptomatic, spontaneously-resolving imaging changes to painful progressive articular collapse requiring joint replacement.[56,57] Symptomatic osteonecrosis characterized by pain, joint swelling, and reduced mobility typically presents during the first 2 years of therapy, particularly in patients with ALL. These symptoms may improve over time, persist, or progress in the years after completion of therapy. In one series, 60% of patients continued to have symptoms at a median follow-up of 4.9 years after diagnosis of osteonecrosis. [58] Surgical procedures, including core decompression, osteotomy and joint replacements, are sometimes performed in those with persistently severe symptoms.[58]

Factors that increase the risk of osteonecrosis include the following:

- **Exposure to corticosteroids, and possibly methotrexate and concurrent asparaginase.** The most important treatment factor associated with the development of osteonecrosis is prolonged exposure to corticosteroids, which is typical in regimens used for ALL, non-Hodgkin lymphoma, and HSCT.[52,55,59,60] Osteonecrosis risk may be related to type of corticosteroid, with some studies in patients with ALL indicating increased risk with the use of dexamethasone compared with prednisone.[61] Corticosteroid dosing schedule also appears to impact the risk of developing osteonecrosis. In the Children's Oncology Group (COG) 1961 trial for newly diagnosed high-risk ALL, patients were randomly assigned to receive either continuous (daily) dexamethasone or an alternate-week schedule of dexamethasone during the delayed intensification phase; the alternate-week schedule was associated with a lower incidence of osteonecrosis.[49] In addition to corticosteroids, exposure to methotrexate and concurrent asparaginase may contribute to the development of osteonecrosis.[62]

- **Hematopoietic cell transplantation (HCT) conditioning and course.** In a large case-control study that evaluated risk factors for osteonecrosis using data from the Center for International Blood and Marrow Transplant Research, lower risks of osteonecrosis were seen in patients with nonmalignant diseases and in those who had received reduced-intensity conditioning regimens for malignant diseases compared with patients receiving myeloablative regimens for malignant diseases.[63] Several studies have reported an increased risk of osteonecrosis in association with chronic graft-versus-host disease (GVHD).[53,59,63]

- **Age at time of diagnosis or transplant.** Several studies have demonstrated that age at diagnosis (or at time of transplant) is a significant independent predictor of osteonecrosis.[49,50,59 ,55,58,61,63] Osteonecrosis is

significantly more common in older children and adolescents than in younger children. In the COG-1961 trial for high-risk ALL, the 5-year cumulative incidence of symptomatic osteonecrosis was 1.0% for patients aged 1 to 9 years, 9.9% for patients aged 10 to 15 years, and 20% for patients aged 16 to 21 years ($P < .0001$).[49]

- **Race.** Osteonecrosis also occurs more frequently in whites than in blacks.[60,64]

- **Genetic factors.** Genetic factors influencing antifolate and glucocorticoid metabolism have also been linked to excess risk of osteonecrosis among survivors.[60] St. Jude Children's Research Hospital investigators observed an almost sixfold (odds ratio, 5.6; 95% confidence interval, 2.7–11.3) risk of osteonecrosis among survivors with polymorphism of the *ACP1* gene, which regulates lipid levels and osteoblast differentiation.[54]

Studies evaluating the influence of gender on the risk of osteonecrosis have yielded conflicting results, with some suggesting a higher incidence in females [56,58,64] that has not been confirmed by others.[48,56]

Osteochondroma

Osteochondromas are benign boney protusions that can be spontaneous or associated with radiation therapy. They generally occur as a single lesion, however multiple lesions may develop in the context of hereditary multiple osteochondromatosis.[65] Approximately 5% of children undergoing myeloablative stem cell transplantation will develop osteochondroma, which most commonly presents in the metaphyseal regions of long bones.[65] A large Italian study reported a 6.1% cumulative risk of developing osteochondroma at 15 years posttransplant, with increased risk associated with younger age at transplant (≤3 years) and use of TBI.[66] Osteochondromas have been reported in patients with neuroblastoma who received local radiation therapy, anti-GD2 monoclonal antibody therapy, and isotretinoin. They occurred at a median of 8.2 years from diagnosis and the cumulative incidence rate was 4.9% at 10 years from diagnosis among 362 patients younger than 10 years. In this series, most of the osteochondromas were unrelated to radiation and had features characteristic of benign developmental osteochondroma. The pathogenic role for chemotherapy, anti-GD2 monoclonal antibody therapy, or isotretinoin in the development of osteochondroma remains speculative.[67] Growth hormone therapy may influence the onset and pace of growth of osteochondromas.[17,68]

Because malignant degeneration of these lesions is exceptionally rare, clinical rather than radiological follow-up is most appropriate.[69] Surgical resection is only necessary when the lesion interferes with joint alignment and movement.[70]

Amputation and limb-sparing surgery

Amputation and limb-sparing surgery prevent local recurrence of bone tumors by removal of all gross and microscopic disease. If optimally executed, both procedures accomplish an *en bloc* excision of tumor with a margin of normal uninvolved tissue. The type of surgical procedure, the primary tumor site, and the age of the patient affect the risk of postsurgical complications.[30] Complications in survivors treated with amputation include prosthetic fit problems, chronic pain in the residual limb, phantom limb pain, and bone overgrowth.[71,72] While limb-sparing surgeries may offer a more aesthetically pleasing outcome, complications have been reported more frequently in survivors who underwent these procedures than in those treated with amputation. Complications after limb-sparing surgery include non-union, pathologic fracture, aseptic loosening, limb-length discrepancy, endoprosthetic fracture, and limited joint range of motion.[71,73] Occasionally, refractory complications develop after limb-sparing surgery and require amputation.[74,75]

A number of studies have compared functional outcomes after amputation and limb-sparing surgery, but results have been limited by inconsistent methods of functional assessment and small cohort sizes. Overall, data suggest that limb-sparing surgery results in better function than amputation, but differences are relatively modest.[71,75] Similarly, long-term quality of life outcomes among survivors undergoing amputation and limb sparing procedures have not differed substantially.[74] A longitudinal analysis of health status among extremity sarcoma survivors in the CCSS indicates an association between lower extremity amputation and increasing activity limitations with age, and an association between upper extremity amputation and lower educational attainment.[76]

Joint contractures

HCT with any history of chronic GVHD is associated with joint contractures.[77-79]

Table 13. Bone and Joint Late Effects[a]

Predisposing Therapy	Musculoskeletal Effects	Health Screening
Radiation impacting musculoskeletal system	Hypoplasia; fibrosis; reduced/uneven growth (scoliosis, kyphosis); limb length discrepancy	Exam: bones and soft tissues in radiation fields
Radiation impacting head and neck	Craniofacial abnormalities	History: psychosocial assessment, with attention to: educational and/or vocational progress, depression, anxiety, posttraumatic stress, social withdrawal
		Head and neck exam
Radiation impacting musculoskeletal system	Radiation-induced fracture	Exam of affected bone
Methotrexate; corticosteroids (dexamethasone, prednisone); radiation impacting skeletal structures; HSCT	Reduced bone mineral density	Bone mineral density test (DXA or quantitative CT)
Corticosteroids (dexamethasone, prednisone)	Osteonecrosis	History: joint pain, swelling, immobility, limited range of motion
		Musculoskeletal exam
Radiation with impact to oral cavity	Osteoradionecrosis	History/oral exam: impaired or delayed healing after dental work, persistent jaw pain or swelling, trismus
Amputation	Amputation-related complications (impaired cosmesis, functional/activity limitations, residual limb integrity, chronic pain, increased energy expenditure)	History: pain, functional/activity limitations
		Exam: residual limb integrity
		Prosthetic evaluation
Limb-sparing surgery	Limb-sparing surgical complications (functional/activity limitations, fibrosis, contractures, chronic infection, chronic pain, limb length discrepancy, increased energy expenditure, prosthetic malfunction [loosening, non-union, fracture])	History: pain, functional/activity limitations
		Exam: residual limb integrity
		Radiograph of affected limb
		Orthopedic evaluation
HSCT with any history of chronic GVHD	Joint contracture	Musculoskeletal exam

CT = computed tomography; DXA = dual-energy x-ray absorptiometry; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation.

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¯Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for musculoskeletal system late effects information, including risk factors, evaluation, and health counseling.

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Late Effects of the Reproductive System

Surgery, radiation therapy, or chemotherapy that negatively affects any component of the hypothalamic-pituitary axis or gonads may compromise reproductive outcomes in childhood cancer survivors. Evidence for this outcome in childhood cancer survivors is limited by studies characterized by small sample size, cohort selection and participation bias, cross-sectional assessment, heterogeneity in treatment approach, time since treatment, and method of ascertainment. In particular, the literature is deficient regarding hard outcomes of reproductive potential (e.g., semen analysis in men, primordial follicle count in women) and outcomes after contemporary risk-adapted treatment approaches.

The risk of infertility is generally related to the tissues or organs involved by the cancer and the specific type, dose, and combination of cytotoxic therapy.

- Orchiectomy or oophorectomy performed for the management of pediatric germ cell tumors may reduce germ cell numbers.

- Alkylating agents and similar DNA interstrand cross-linking agents are the primary chemotherapeutic agents used in the treatment of pediatric cancers that are associated with a high risk of infertility. Factors influencing the risk of gonadal injury in children treated with alkylating agent chemotherapy include the following:

  - Cumulative dose.

  - The specific alkylating agent.

  - The length of treatment.

  - Age at treatment.

  - Gender.

- The risk of radiation injury to the hypothalamic-pituitary axis or gonads is related to the treatment volume, total dose, fractionation schedule, and age at treatment.

In addition to anticancer therapy, age at treatment, and gender, it is likely that genetic factors influence the risk of permanent infertility. It should be noted that pediatric cancer treatment protocols often prescribe combined-modality therapy; thus, the additive effects of gonadotoxic exposures may need to be considered in assessing reproductive potential. Detailed information about the specific cancer treatment modalities including specific surgical procedures, the type and cumulative doses of chemotherapeutic agents, and radiation treatment volumes and doses are needed to

estimate risks for gonadal dysfunction and infertility.

Testis

Cancer treatments that may impair testicular and reproductive function include the following:

- Surgery (orchiectomy, retroperitoneal lymph node dissection, extensive pelvic dissection).

- Radiation therapy (exposing the hypothalamic-pituitary axis or testes).

- Chemotherapy (alkylating agents and similar DNA interstrand cross-linking agents such as procarbazine).

- Hematopoietic stem cell transplantation (HSCT).

Surgery affecting testicular function

Patients who undergo unilateral orchiectomy for testicular torsion may have subnormal sperm counts at long-term follow-up.[1,2] Retrograde ejaculation is a frequent complication of bilateral retroperitoneal lymph node dissection performed on males with testicular neoplasms,[3,4] and impotence may occur after extensive pelvic dissections to remove a rhabdomyosarcoma of the prostate.[5]

Radiation affecting testicular function

Among men treated for childhood cancer, the potential for gonadal injury exists if radiation treatment fields include the pelvis, gonads, or total body. The germinal epithelium is more sensitive to radiation injury than are the androgen-producing Leydig cells. A decrease in sperm counts can be seen 3 to 6 weeks after irradiation, and depending on the dosage, recovery may take 1 to 3 years. The germinal epithelium is damaged by much lower dosages (<1 Gy) of radiation than are Leydig cells (20–30 Gy). Irreversible germ cell failure may occur with fractionated radiation doses of greater than 2 Gy to 4 Gy.[6] Administration of higher radiation doses, such as 24 Gy, which was used for the treatment of testicular relapse of acute lymphoblastic leukemia (ALL), results in both germ cell failure and Leydig cell dysfunction.[7]

Radiation injury to Leydig cells is related to the dose delivered and age at treatment. Testosterone production may be normal in prepubertal boys treated with less than 12 Gy fractionated testicular irradiation, but elevated plasma concentrations of luteinizing hormone observed in this group suggest subclinical injury. Gonadal failure typically results when prepubertal boys are treated with more than 20 Gy of radiation to the testes; androgen therapy is required for masculinization. Leydig cell function is usually preserved in sexually mature male patients if radiation doses do not exceed 30 Gy. Although available data suggest that Leydig cells are more vulnerable when exposed to radiation before puberty, confounding factors, such as the age at testing and the effects of both orchiectomy and chemotherapy, limit the reliability of this observation.[8]

Chemotherapy affecting testicular function

Cumulative alkylating agent (e.g., cyclophosphamide, mechlorethamine, dacarbazine) dose is an important factor in estimating the risk of testicular germ cell injury, but limited studies are available that correlate results of semen analyses in clinically well-characterized cohorts.[9] In general, Leydig cell function is preserved, but germ cell failure is common in men treated with high cumulative doses of cyclophosphamide (7,500 mg/m^2 or more) and more than 3 months of combination alkylating agent therapy. Most studies suggest that prepubertal males are not at lower risk for chemotherapy-induced testicular damage than are postpubertal patients.[10-13]

Studies of testicular germ cell injury, as evidenced by oligospermia or azoospermia, after alkylating agent administration with or without radiation therapy, have reported the following:

- **Cyclophosphamide:**

Male survivors of non-Hodgkin lymphoma who received a cumulative cyclophosphamide dose of greater than 9.5 g/m^2 and underwent pelvic radiation therapy were at increased risk for failure to recover spermatogenesis.[14]

- In survivors of Ewing sarcoma and soft tissue sarcoma, treatment with a cumulative cyclophosphamide dose of greater than 7.5 g/m^2 was correlated with persistent oligospermia or azoospermia.[15]

- Cyclophosphamide doses exceeding 7.5 g/m^2 and ifosfamide doses exceeding 60 g/m^2 produced oligospermia or azoospermia in most exposed individuals.[16-18]

- A small cohort study reported normal semen quality in adult long-term survivors of childhood ALL treated with 0 to 10 g/m^2 of cyclophosphamide and cranial irradiation, whereas no spermatozoa were detected in semen samples from survivors treated with more than 20 g/m^2 of cyclophosphamide.[19]

- Treatment with a cyclophosphamide equivalent dose of less than 4 g/m^2 results in infrequent azoospermia or oligospermia, with 88.6% of 31 men treated being normospermic.[20]

- Spermatogenesis was present in 67% of 15 men who received 200 mg/kg of cyclophosphamide before undergoing HSCT for aplastic anemia.[21]

- **Dacarbazine:**

  - The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) produced oligospermia or azoospermia in adults frequently during the course of treatment. However, recovery of spermatogenesis occurred after treatment was completed, in contrast to the experience reported after treatment with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP).[22]

- **Alkylating agent plus procarbazine:**

  - Most studies suggest that combination chemotherapy with an alkylating agent and procarbazine causes severe damage to the testicular germinal epithelium that is irreversible at high cumulative doses.[10,23-26]

  - Azoospermia occurred less frequently in adults after treatment with two, rather than six, cycles of MOPP.[27]

  - Elevation of the basal follicle-stimulating hormone (FSH) level, reflecting impaired spermatogenesis, was less frequent among patients receiving two courses of vincristine, procarbazine, prednisone, and doxorubicin (OPPA) than among those who received two courses of OPPA in combination with two or more courses of cyclophosphamide, vincristine, procarbazine and prednisone (COPP).[28]

Testicular function after HSCT

The risk of gonadal dysfunction and infertility related to conditioning with total-body irradiation (TBI), high-dose alkylating agent chemotherapy, or both is substantial. Because transplantation is often undertaken for relapsed or refractory cancer, previous treatment with alkylating agent chemotherapy or hypothalamic-pituitary axis or gonadal radiation therapy may confer additional risks. Age at treatment also influences the risk of gonadal injury. Young boys and adolescents treated with high-dose cyclophosphamide (200 mg/kg) will generally maintain Leydig cell function and testosterone production, but germ cell failure is common. After TBI conditioning, most male patients retain their ability to produce testosterone but will experience germ cell failure.[29]

Recovery of gonadal function

Recovery of gonadal function after cytotoxic chemotherapy and radiation therapy is possible. Dutch investigators used inhibin B as a surrogate marker of gonadal function in a cross-sectional, retrospective study of 201 male survivors of

childhood cancer, with a median follow-up of 15.7 years (range, 5–37 years) from diagnosis. The median inhibin B level among the cohort increased based on serial measurements performed over a median of 3.3 years (range, 0.7–11.3 years). The probability of recovery of the serum inhibin B level was significantly influenced by baseline inhibin B level, but not age at diagnosis, age at study evaluation, interval between discontinuation of treatment and study evaluation, gonadal irradiation, and alkylating agent dose score. These results suggest that recovery can occur but not if inhibin B is already at a critically low level.[30]

Inhibin B and FSH levels are correlated with sperm concentration and often used to estimate the presence of spermatogenesis; however, limitations in the specificity and positive predictive value of these tests have been reported. [31] Hence, male survivors should be advised that semen analysis is the most accurate assessment of adequacy of spermatogenesis.

Ovary

Cancer treatments that may impair ovarian function/reserve include the following:

- Surgery (oophorectomy).

- Radiation therapy (exposing the hypothalamic-pituitary axis or ovaries).

- Chemotherapy (alkylating agents, similar DNA interstrand cross-linking agents like procarbazine).

- HSCT.

Surgery affecting ovarian function

Oophorectomy performed for the management of germ cell tumors may reduce ovarian reserve. Contemporary treatments utilize fertility-sparing surgical procedures combined with systemic chemotherapy to reduce this risk.[32]

Radiation affecting ovarian function

In women treated for childhood cancer, the potential for primary gonadal injury exists if treatment fields involve the lumbosacral spine, abdomen, pelvis, or total body. The frequency of ovarian failure after abdominal radiation therapy is related to both the age of the woman at the time of irradiation and the radiation therapy dose received by the ovaries. The ovaries of younger individuals are more resistant to radiation damage than are those of older women because of their greater complement of primordial follicles.

Whole-abdomen irradiation at doses of 20 Gy or greater is associated with the highest risk of ovarian dysfunction. Seventy-one percent of women in one series failed to enter puberty, and 26% had premature menopause after receiving whole-abdominal radiation therapy doses of 20 Gy to 30 Gy.[33] Other studies reported similar results in women treated with whole-abdomen irradiation [34] or craniospinal irradiation [35,36] during childhood.

Chemotherapy affecting ovarian function

Ovarian function may be impaired after treatment with combination chemotherapy that includes an alkylating agent and procarbazine. In general, girls maintain gonadal function at higher cumulative alkylating agent doses than do boys. Most female childhood cancer survivors who are treated with risk-adapted combination chemotherapy retain or recover ovarian function. However, the risk of acute ovarian failure and premature menopause is substantial if treatment includes combined-modality therapy with alkylating agent chemotherapy and abdominal or pelvic radiation therapy or dose-intensive alkylating agents for myeloablative conditioning before HSCT.[37-40]
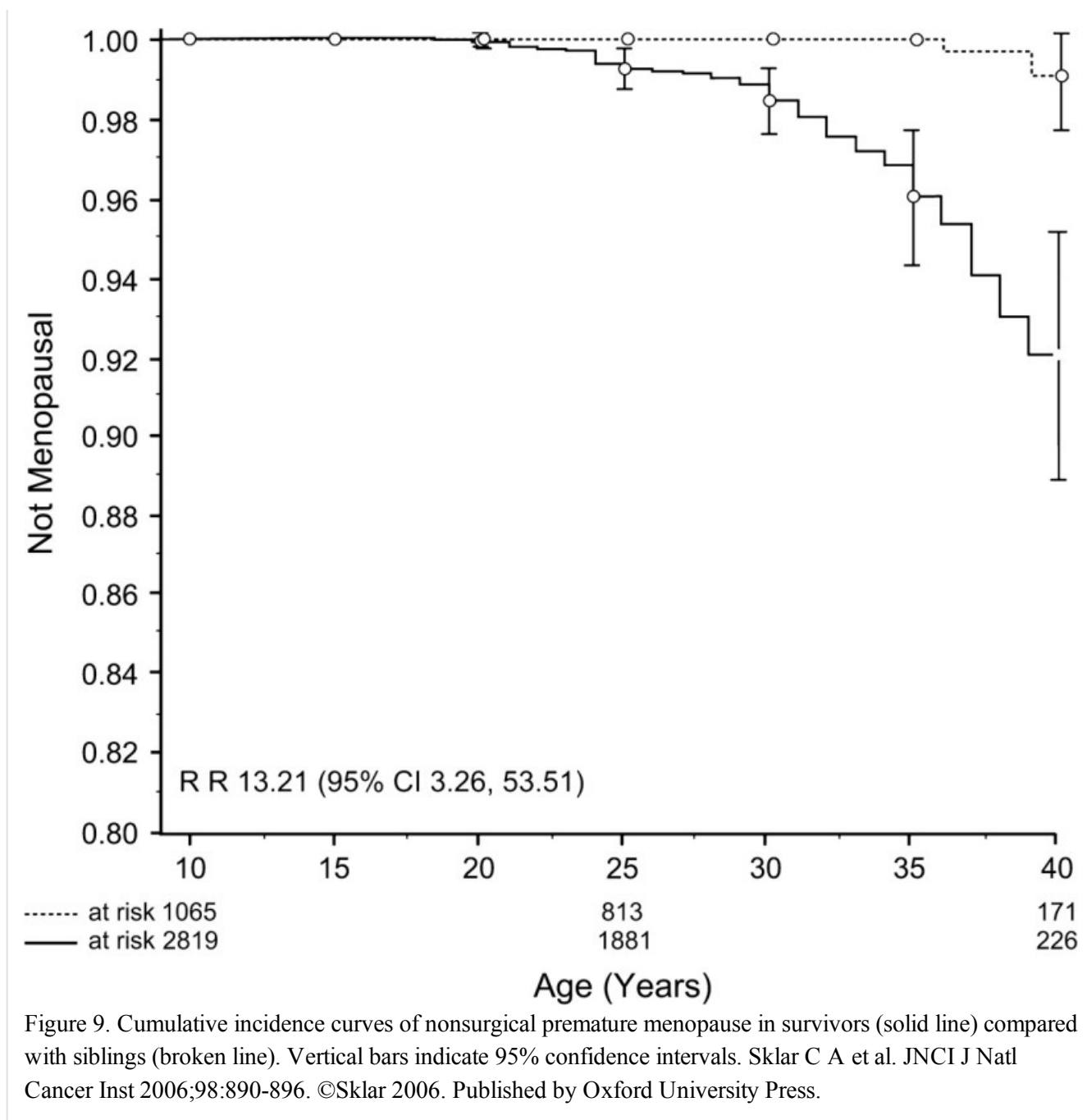
Premature ovarian failure

Premature ovarian failure is well documented in childhood cancer survivors, especially in women treated with both an alkylating agent and abdominal radiation therapy.[37,41,42] Studies have associated the following factors with an

increased rate of premature ovarian failure (acute ovarian failure and premature menopause):

- Age at the time of treatment and attained age.

- Increasing doses of abdominal-pelvic radiation therapy.

- Exposure to alkylating agents and/or procarbazine.

- Oophorectomy.

The presence of apparently normal ovarian function at the completion of chemotherapy should not be interpreted as evidence that no ovarian injury has occurred. Studies of acute ovarian failure and premature menopause have observed the following:

- Of 3,390 eligible participants in the Childhood Cancer Survivor Study (CCSS), 215 (6.3%) developed acute ovarian failure (defined as never having menses or ceased having menses within 5 years of diagnosis). Survivors with acute ovarian failure were older (aged 13–20 years vs. aged 0–12 years) at cancer diagnosis and more likely to have been diagnosed with Hodgkin lymphoma or to have received abdominal or pelvic radiation therapy than were survivors without acute ovarian failure.[38] Of survivors who developed acute ovarian failure, 75% had received abdominal-pelvic radiation therapy. Radiation doses to the ovary of at least 20 Gy were associated with the highest rate of acute ovarian failure, with over 70% of such patients developing acute ovarian failure. In a multivariable logistic regression model, increasing doses of ovarian radiation, exposure to procarbazine at any age, and exposure to cyclophosphamide at ages 13 to 20 years were independent risk factors for acute ovarian failure. [38]

- A total of 126 childhood cancer survivors and 33 control siblings who participated in the CCSS developed premature menopause, defined as cessation of menses before 40 years. The cumulative incidence of nonsurgical premature menopause was substantially higher for survivors than for siblings (8% vs. 0.8%; relative risk [RR], 13.21; 95% confidence interval [CI], 3.26–53.51; $P < .001$).[37] A multiple Poisson regression model showed that risk factors for nonsurgical premature menopause included attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent dose score, and a diagnosis of Hodgkin lymphoma. For survivors who were treated with alkylating agents plus abdominal-pelvic radiation therapy, the cumulative incidence of nonsurgical premature menopause approached 30%.[37]

Figure 9. Cumulative incidence curves of nonsurgical premature menopause in survivors (solid line) compared with siblings (broken line). Vertical bars indicate 95% confidence intervals. Sklar C A et al. JNCI J Natl Cancer Inst 2006;98:890-896. ©Sklar 2006. Published by Oxford University Press.

- A French cohort study of 1,109 female survivors of childhood solid cancer identified the following as risk factors for nonsurgical menopause:[42]

    o Exposure to and dose of alkylating agents, especially during adolescence.

    o Radiation dose to the ovaries.

    o Oophorectomy.

Women treated with alkylating agents after the onset of puberty, either alone (RR, 9; 95% CI, 2.7–28; P = .0003) or associated with even a low dose of radiation to the ovaries (RR, 29; 95% CI, 8–108; P < .0001), had the highest risk ratio for nonsurgical menopause. Unilateral oophorectomy was associated with a 7-year-earlier age at menopause. The overall rate of nonsurgical menopause by age 40 years was only 2.1% and substantially lower than the CCSS and European Organization for Research and Treatment of Cancer cohort studies that include survivors of hematological malignancies.[42]

- In Europe, survivors of Hodgkin lymphoma treated between the ages 15 years and 40 years and who were not receiving hormonal contraceptives were surveyed for the occurrence of premature ovarian failure. In 460 women, premature ovarian failure was mainly influenced by alkylating chemotherapy use with a linear dose relationship between alkylating chemotherapy and premature ovarian failure occurrence. Premature ovarian failure risk increased by 23% per year of age at treatment. In women treated without alkylating chemotherapy before age 32 years and at age 32 years or older, cumulative premature ovarian failure risks were 3% and 9%, respectively. If menstruation returned after treatment, cumulative premature ovarian failure risk was independent of age at treatment. Among women who ultimately developed premature ovarian failure, 22% had one or more children after treatment, compared with 41% of women without premature ovarian failure who had one or more children after treatment. This report indicates that women with proven fertility after treatment can still face infertility problems at a later stage.[41]

Ovarian function after HSCT

The preservation of ovarian function among women treated with HSCT is related to age at treatment, receipt of pretransplant alkylating agent chemotherapy and abdominal-pelvic radiation therapy, and transplant conditioning regimen.[39,43] Studies of ovarian function among women treated with HSCT have observed the following:

- Girls and young women conditioned with TBI or busulfan-based regimens appear to be at equally high risk of declining ovarian function and premature menopause compared with patients conditioned with cyclophosphamide only.[39] All women who received high-dose (50 mg/kg/day x 4 days) cyclophosphamide before HSCT for aplastic anemia developed amenorrhea after transplantation. In one series, 36 of 43 women with aplastic anemia conditioned with cyclophosphamide (200 mg/kg) had recovery of normal ovarian function 3 to 42 months after transplantation, including all of the 27 patients who were between ages 13 and 25 years at the time of HSCT.[40]

- TBI is especially damaging when given in a single fraction.[39] Most postpubertal women who receive TBI before HSCT develop amenorrhea. In one series, recovery of normal ovarian function occurred in only 9 of 144 patients and was highly correlated with age at time of radiation therapy in patients younger than 25 years.[40]

- Among women with leukemia, cranial irradiation before transplantation further decreased the possibility of retaining ovarian function.[39]

Fertility

Infertility remains one of the most common life-altering treatment effects experienced by long-term childhood survivors. Pediatric cancer cohort studies demonstrate the impact of cytotoxic therapy on reproductive outcomes. CCSS investigations have elucidated factors contributing to subfertility among childhood cancer survivors. Fertility was evaluated among the 6,224 male CCSS participants aged 15 to 44 years who were not surgically sterile. They were less likely to sire a pregnancy than siblings (hazard ratio [HR] 0.56; 95% CI, 0.49–0.63).[44]

Treatment factors associated with significantly lower rates of siring a pregnancy include the following:[45]

- Radiation dose greater than 0.75 Gy to the testes (HR, 0.12; 95% CI, 0.02–0.61).

- Higher cyclophosphamide equivalent dose.

  - ≥ 4 g/m^2 to < 8 g/m^2: HR, 0.72; 95% CI, 0.55–0.95.

  - ≥ 8 g/m^2 to < 12 g/m^2: HR, 0.49; 95% CI, 0.36–0.68.

  - ≥ 12 g/m^2 to < 16 g/m^2: HR, 0.37; 95% CI, 0.24–0.57.

  - ≥ 16 g/m^2 to < 20 g/m^2: HR, 0.53; 95% CI, 0.34–0.8.

2

- ≥ 20 g/m⁻: HR, 0.17; 95% CI, 0.10–0.29.

Fertility was evaluated among the 5,149 female CCSS participants and 1,441 female siblings of CCSS participants, aged 15 to 44 years. The RR for ever being pregnant was 0.81 (95% CI, 0.73–0.90; $P < .001$), compared with female siblings. In multivariate models among survivors only, those who received a hypothalamic-pituitary radiation dose of greater than 30 Gy (RR, 0.61; 95% CI, 0.44–0.83) or an ovarian/uterine radiation dose of greater than 5 Gy were less likely to have ever been pregnant (RR, 0.56 for 5–10 Gy; 95% CI, 0.37–0.85; RR, 0.18 for >10 Gy; 95% CI, 0.13–0.26). A summed alkylating agent dose score of 3 (RR, 0.72; 95% CI, 0.58–0.90; $P = .003$) or 4 (RR, 0.65; 95% CI, 0.45–0.96; $P = .03$) was associated with lower observed risk of pregnancy, compared with those with no alkylating agent exposure.[46] A follow-up study of the same cohort demonstrated impaired fertility in female survivors who received modest doses (22–27 Gy) of hypothalamic-pituitary radiation and no or very low doses (<0.1 Gy) of ovarian radiation, providing support for the contribution of the role of luteal phase deficiency to infertility in some women.[47]

Fertility may be impaired by factors other than the absence of sperm and ova. Conception requires delivery of sperm to the uterine cervix, patency of the fallopian tubes for fertilization to occur, and appropriate conditions in the uterus for implantation. [3,4,48]

- Retrograde ejaculation occurs with a significant frequency in men who undergo bilateral retroperitoneal lymph node dissection.[3,4]

- Uterine structure may be affected by abdominal irradiation. A study demonstrated that uterine length was significantly shorter in ten women with ovarian failure who had been treated with whole-abdomen irradiation. Endometrial thickness did not increase in response to hormone replacement therapy in three women who underwent weekly ultrasound examination. No flow was detectable with Doppler ultrasound through either uterine artery of five women, and through one uterine artery in three additional women.[48]

Reproduction

For survivors who maintain fertility, numerous investigations have evaluated the prevalence of and risk factors for pregnancy complications in adults treated for cancer during childhood. Pregnancy complications including hypertension, fetal malposition, fetal loss/spontaneous abortion, preterm labor, and low birth weight have been observed in association with specific diagnostic and treatment groups.[44,46,49-57]

- In a study of 4,029 pregnancies among 1,915 women followed in the CCSS, there were 63% live births, 1% stillbirths, 15% miscarriages, 17% abortions, and 3% unknown or in gestation. Risk of miscarriage was 3.6-fold higher in women treated with craniospinal irradiation and 1.7-fold higher in those treated with pelvic irradiation. Chemotherapy exposure alone did not increase risk of miscarriage. Survivors were less likely to have live births, more likely to have medical abortions, and more likely to have low-birth-weight babies than were siblings.[46]

- In the National Wilms Tumor Study, records were obtained for 1,021 pregnancies of more than 20 weeks duration. In this group, there were 955 single live births. Hypertension complicating pregnancy, early or threatened labor, malposition of the fetus, lower birth weight (<2,500 g), and premature delivery (<36 weeks) were more frequent among women who had received flank irradiation, in a dose-dependent manner.[58]

- Another CCSS study evaluated pregnancy outcomes of partners of male survivors. Among 4,106 sexually active males, 1,227 reported they sired 2,323 pregnancies, which resulted in 69% live births, 13% miscarriages, 13% abortions, and 5% unknown or in gestation at the time of analysis. Compared with partners of male siblings, there was a decreased incidence of live births (RR, 0.77), but no significant differences of pregnancy outcome by treatment.[44]

- Results from a Danish study confirm the association of uterine irradiation with spontaneous abortion, but not other

types of abortion. Thirty-four thousand pregnancies were evaluated in a population of 1,688 female survivors of childhood cancer in the Danish Cancer Registry. The pregnancy outcomes of survivors, 2,737 sisters, and 16,700 comparison women in the population were identified. No significant differences were seen between survivors and comparison women in the proportions of live births, stillbirths, or all types of abortions combined. Survivors with a history of neuroendocrine or abdominal radiation therapy had an increased risk of spontaneous abortion. Thus, the pregnancy outcomes of survivors were similar to those of comparison women with the exception of spontaneous abortion.[49]

- In a retrospective cohort analysis from the CCSS of 1,148 men and 1,657 women who had survived cancer, there were 4,946 pregnancies. Irradiation of the testes in men and pituitary gland in women and chemotherapy with alkylating drugs were not associated with an increased risk of stillbirth or neonatal death. Uterine and ovarian irradiation significantly increased the risk of stillbirth and neonatal death at doses higher than 10 Gy. For girls treated before menarche, irradiation of the uterus and ovaries at doses as low as 1 Gy to 2.49 Gy significantly increased the risk of stillbirth or neonatal death.[56]

- Most pregnancies reported by HSCT survivors and their partners result in live births. In female HSCT survivors who were exposed to TBI, there appears to be an increased risk of preterm delivery of low-birth-weight infants. Female HSCT survivors are at higher risk of needing Cesarean sections than are the normal population (42% vs. 16%). [57]

- Preservation of fertility and successful pregnancies may occur after HSCT, although the conditioning regimens that include TBI, cyclophosphamide, and busulfan are highly gonadotoxic. One study evaluated pregnancy outcomes in a group of females treated with HSCT. Among 708 women who were postpubertal at the time of transplant, 116 regained normal ovarian function and 32 became pregnant. Among 82 women who were prepubertal at the time of transplant, 23 had normal ovarian function and nine became pregnant. Of the 72 pregnancies in these 41 women, 16 occurred in those treated with TBI and 50% resulted in early termination. Among the 56 pregnancies in women treated with cyclophosphamide without either TBI or busulfan, 21% resulted in early termination. There were no pregnancies among the 73 women treated with busulfan and cyclophosphamide, and only one retained ovarian function.[59]

Fertility preservation

Progress in reproductive endocrinology has resulted in the availability of several options for preserving or permitting fertility in patients about to receive potentially toxic chemotherapy or radiation therapy.[60] For males, cryopreservation of spermatozoa before treatment is an effective method to circumvent the sterilizing effect of therapy. Although pretreatment semen quality in patients with cancer has been shown to be less than that noted in healthy donors, the percentage decline in semen quality and the effect of cryodamage to spermatozoa from patients with cancer is similar to that of normal donors.[61,62] For those unable to bank sperm, newer technologies such as testicular sperm extraction may be an option. Further micromanipulative technologic advances such as intracytoplasmic sperm injection and similar techniques may be able to render sperm extracted surgically, or even poor-quality cryopreserved spermatozoa from cancer patients, capable of successful fertilization.[63]

For females, the most successful assisted-reproductive techniques depend on harvesting and banking the postpubertal patient's oocytes and cryopreserving unfertilized oocytes or embryos before gonadotoxic therapy.[64] Options for prepubertal patients are limited to investigational ovarian tissue cryopreservation for later autotransplantation, which may be offered to girls with nonovarian, nonhematologic cancers.[65]

Offspring of childhood cancer survivors

For childhood cancer survivors who have offspring, there is concern about congenital anomalies, genetic disease, or risk of cancer in the offspring. Children of cancer survivors are not at significantly increased risk for congenital anomalies

stemming from their parents' exposure to mutagenic cancer treatments, as supported by the following observations:

- A retrospective cohort analysis of validated cases of congenital anomalies among 4,699 children of 1,128 male and 1,627 female participants of the CCSS showed no significant associations between gonadal radiation therapy or cumulative exposure to alkylating agents and congenital anomalies in offspring.[66]

- In a report of 2,198 offspring of adult survivors treated for childhood cancer between 1945 and 1975 compared with 4,544 offspring of sibling controls, there were no differences in the proportion of offspring with cytogenetic syndromes, single-gene defects, or simple malformations. There was similarly no effect of type of childhood cancer treatment on the occurrence of genetic disease in the offspring. A population-based study of 2,630 live-born offspring of childhood cancer survivors versus 5,504 live-born offspring of the survivors' siblings found no differences in proportion of abnormal karyotypes or incidence of Down syndrome or Turner syndrome between survivor and sibling offspring.[67]

- In the same population-based cohort, survivors treated with abdominal radiation therapy and/or alkylating agents did not have an increased risk of offspring with genetic disease, compared with survivors not exposed to these agents.[68]

- In a study of 5,847 offspring of survivors of childhood cancers treated in five Scandinavian countries, in the absence of a hereditary cancer syndrome (such as hereditary retinoblastoma), there was no increased risk of cancer.[69] Data from the five-center study also indicated no excess risk of single-gene disorders, congenital malformations, or chromosomal syndromes among the offspring of former patients compared with the offspring of siblings.[70]

- In a study that evaluated pregnancy outcomes in 19,412 allogeneic and 17,950 autologous transplant patients, European Group for Blood and Marrow Transplantation investigators did not observe an increased risk of birth defects, developmental delay, or cancer among offspring of male and female HSCT recipients.[57]

(Refer to the PDQ summary on Sexuality and Reproductive Issues for more information about sexuality and reproductive issues and cancer patients.)

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for reproductive late effects information including risk factors, evaluation, and health counseling.

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Late Effects of the Respiratory System

Specific chemotherapeutic agents, thoracic radiation therapy, pulmonary/chest wall surgery, and hematopoietic stem cell transplantation (HSCT) can compromise respiratory function in long-term survivors of childhood cancer. The effects of early lung injury from cancer treatment may be exacerbated by the decline in lung function associated with normal aging, other comorbid chronic health conditions, or smoking. The quality of current evidence regarding this outcome is limited by retrospective data collection, small sample size, cohort selection and participation bias, description of outcomes following antiquated treatment approaches, and variability in time since treatment and method of ascertainment.

The true prevalence or incidence of pulmonary dysfunction in childhood cancer survivors is not clear. For children treated with HSCT, there is significant clinical disease. Evidence for this outcome in childhood cancer survivors is limited by studies characterized by small sample size, cohort selection and participation bias, cross-sectional assessment, heterogeneity in treatment approach, time since treatment, and method of ascertainment. Notably, no large cohort studies have been performed with clinical evaluations coupled with functional and quality-of-life assessments.

Results from selected cohort studies featuring long-term pulmonary function outcomes include the following:

- An analysis of self-reported pulmonary complications of 12,390 survivors of common childhood malignancies has been reported by the Childhood Cancer Survivor Study.[1] This cohort includes children treated with both conventional and myeloablative therapies. Compared with siblings, survivors had an increased relative risk (RR) of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen therapy, abnormal chest wall, exercise-induced shortness of breath, and bronchitis, with RRs ranging from 1.2 to 13.0 (highest for lung fibrosis and lowest for bronchitis). The 25-year cumulative incidence of lung fibrosis was 5% for those who received chest radiation therapy and less than 1% for those who received pulmonary toxic chemotherapy.

- The incidence of self-reported pulmonary dysfunction among a subset of adults in the same cohort treated for central nervous system malignancies with craniospinal irradiation (per 1,000 person-years) was 9.1 (95% confidence interval, 7.8–10.6) for emphysema/obliterative bronchiolitis and more than 3.0 for asthma, chronic cough, and need for extra oxygen. High rates of late onset pulmonary dysfunction occurring more than 5 years after diagnosis were also observed.[2]

- Dutch investigators reported outcomes of 193 childhood cancer survivors evaluated by pulmonary function testing at a median follow-up of 18 years after diagnosis. Pulmonary function impairment (Common Terminology Criteria for Adverse Events grade 2 or higher) was identified in 85 patients (44.0%) and included obstructive deficits (2.1%), restrictive deficits (17.6%), and decreased carbon monoxide diffusion capacity (39.9%). Multivariate logistic regression models showed that, compared with bleomycin treatment only, treatment with radiation therapy, radiation therapy combined with bleomycin, and radiation therapy combined with surgery were associated with the highest risk of pulmonary function impairment.[3]

- In a longitudinal study evaluating the magnitude and trajectory of pulmonary dysfunction among 121 childhood cancer survivors (median time from diagnosis to last evaluation, 17.1 years) treated with potentially pulmonary-toxic therapy (e.g., bleomycin, busulfan, pulmonary radiation therapy), survivors were significantly more likely to have restrictive and diffusion defects than were healthy controls.[4] Age younger than 16 years at diagnosis and exposure to more than 20 Gy of chest radiation were associated with increased odds of restrictive defects, whereas female gender and chest radiation dose were associated with diffusion abnormalities. Decline in pulmonary function over time was largely related to changes in diffusion capacity. The odds of decline in diffusion function over time showed a fourfold increase among females and 24-fold increase among survivors treated with more than 20 Gy of chest radiation. Compared with survivors with normal diffusion, those with diffusion defects were significantly more likely to be symptomatic and have poorer health-related quality-of-life scores, with decreases in the domains of physical functioning, role limitation as a result of physical health, and low energy/increased fatigue.

Respiratory complications following radiation therapy

Radiation therapy that exposes the lung parenchyma can result in pulmonary dysfunction related to reduced lung volume, impaired dynamic compliance, and deformity of both the lung and chest wall. The potential for chronic pulmonary sequelae is related to the radiation dose administered, the volume of lung irradiated, and the fractional radiation therapy doses.[5] Combined-modality therapy including radiation therapy and pulmonary toxic chemotherapy or thoracic/chest wall surgery increases the risk of pulmonary function impairment.[3]

Chronic pulmonary complications reported after treatment for pediatric malignancies include restrictive or obstructive chronic pulmonary disease, pulmonary fibrosis, and spontaneous pneumothorax.[6] These sequelae are uncommon after contemporary therapy, which most often results in subclinical injury that is detected only by imaging or formal pulmonary function testing.

Pulmonary outcomes reported from selected cohort studies treated with thoracic radiation therapy include the following:

- In a study of 48 survivors of pediatric malignant solid tumors with a median follow-up of 9.7 years after median whole-lung radiation doses of 12 Gy (range, 10.5–18 Gy), only nine patients (18.8%) reported respiratory symptoms. However, abnormalities in forced vital capacity, forced expiratory volume in 1 second, total lung capacity, and diffusion capacity were common (58%–73%). Focal-boost radiation therapy was also significantly associated with additional abnormalities.[7] Reducing the size of the daily radiation fractions (e.g., from 1.8 Gy per day to 1.5 Gy per day) decreases this risk.[8,9]

- For survivors of pediatric Hodgkin lymphoma, the prevalence of pulmonary symptoms using contemporary involved-field techniques is reported to be low. However, they still exhibit substantial subclinical dysfunction.[10]

- Changes in lung function have been reported in children treated with whole-lung radiation therapy for metastatic Wilms tumor. A dose of 12 Gy to 14 Gy reduced total lung capacity and vital capacity to about 70% of predicted values, and even lower if the patient had undergone thoracotomy.[8,9]

- Administration of bleomycin alone can produce pulmonary toxicity and, when combined with radiation therapy, can heighten radiation reactions. Chemotherapeutic agents such as doxorubicin, dactinomycin, and busulfan are radiomimetic agents and can reactivate latent radiation damage.[8,9,11]

Respiratory complications following chemotherapy

Chemotherapy agents with potential pulmonary toxic effects commonly used in the treatment of pediatric malignancies include bleomycin, busulfan, and the nitrosoureas (carmustine and lomustine). These agents induce lung damage on their own or potentiate the damaging effects of radiation to the lung. Combined-modality therapy including pulmonary toxic chemotherapy and thoracic radiation therapy or thoracic/chest wall surgery increases the risk of pulmonary

function impairment.[5] Outcomes observed among cohorts treated with pulmonary toxic chemotherapy include the following:

- The development of bleomycin-associated pulmonary fibrosis with permanent restrictive disease is dose dependent, usually occurring at doses greater than 200 U/m^2 to 400 U/m^2, higher than those used in treatment protocols for pediatric malignancies.[11-13]

- More current pediatric regimens for Hodgkin lymphoma using radiation therapy and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) have shown a significant incidence of asymptomatic pulmonary dysfunction after treatment, which appears to improve with time.[14-16] However, grades 3 and 4 pulmonary toxicity has been reported in 9% of children receiving 12 cycles of ABVD followed by 21 Gy of radiation.[13]

- ABVD-related pulmonary toxic effects may result from fibrosis induced by bleomycin or radiation recall pneumonitis related to administration of doxorubicin.

- Pulmonary veno-occlusive disease has been observed rarely and has been attributed to bleomycin chemotherapy. [17]

Respiratory complications associated with HSCT

Patients undergoing HSCT are at increased risk of pulmonary toxic effects related to the following:[18-20]

- Preexisting pulmonary dysfunction (e.g., asthma, pretransplant therapy).

- Conditioning regimens, including cyclophosphamide, busulfan, or carmustine.

- Total-body irradiation.

- Graft-versus-host disease (GVHD).

Although most survivors of transplant are not clinically compromised, restrictive lung disease may occur and has been reported to increase in prevalence with increasing time from HSCT, based on limited data from longitudinally followed cohorts.[21,22] Obstructive disease is less common, as is late onset pulmonary syndrome, which includes the spectrum of restrictive and obstructive disease. Bronchiolitis obliterans with or without organizing pneumonia, diffuse alveolar damage, and interstitial pneumonia may occur as a component of this syndrome, generally between 6 and 12 months posttransplant. Cough, dyspnea, or wheezing may occur with either normal chest x-ray or diffuse/patchy infiltrates; however, most patients are symptom free.[19,23,24]

Other factors associated with respiratory late effects

Additional factors contributing to chronic pulmonary toxic effects include superimposed infection, underlying pneumonopathy (e.g., asthma), respiratory toxic effects, chronic GVHD, and the effects of chronic pulmonary involvement by tumor or reaction to tumor. Lung lobectomy during childhood appears to have no significant impact on long-term pulmonary function,[25] but the long-term effect of lung surgery for children with cancer is not well defined.

Pulmonary complications may also be exacerbated by smoking cigarettes or other substances. While smoking rates in survivors of childhood cancer tend to be lower than the general population, it is still important to prevent initiation of smoking and promote cessation in this distinct population.[26]

Pulmonary function evaluations of 433 adult childhood cancer survivors treated with pulmonary toxic modalities demonstrated significantly higher risk for pulmonary dysfunction among smokers compared to nonsmokers. Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) median values among current and former smokers were lower than those who had never smoked. Median FEV1/FVC values were lower among those who smoked less than 6 pack-years and those who smoked 6 pack-years or more compared with those who had never smoked suggesting

that survivors who are former or current smokers have an increased risk for future obstructive and restrictive lung disease.[27]

Table 14. Respiratory Late Effects[a]

Predisposing Therapy	Respiratory Effects	Health Screening/Interventions
Busulfan; carmustine (BCNU)/lomustine (CCNU); bleomycin; radiation impacting lungs; surgery impacting pulmonary function (lobectomy, metastasectomy, wedge resection)	Subclinical pulmonary dysfunction; interstitial pneumonitis; pulmonary fibrosis; restrictive lung disease; obstructive lung disease	History: cough, shortness of breath, dyspnea on exertion, wheezing
		Pulmonary exam
		Pulmonary function tests (including DLCO and spirometry)
		Chest x-ray
		Counsel regarding tobacco avoidance/smoking cessation
		In patients with abnormal pulmonary function tests and/or chest x-ray, consider repeat evaluation before general anesthesia
		Pulmonary consultation for patients with symptomatic pulmonary dysfunction
		Influenza and pneumococcal vaccinations
Hematopoietic cell transplantation with any history of chronic GVHD	Pulmonary toxicity (bronchiolitis obliterans, chronic bronchitis, bronchiectasis)	History: cough, shortness of breath, dyspnea on exertion, wheezing
		Pulmonary exam
		Pulmonary function tests (including DLCO and spirometry)
		Chest x-ray
		Counsel regarding tobacco avoidance/smoking cessation
		In patients with abnormal pulmonary function tests and/or chest x-ray, consider repeat evaluation before general anesthesia
		Pulmonary consultation for patients with symptomatic pulmonary dysfunction

		Influenza and pneumococcal vaccinations

DLCO = diffusing capacity of the lung for carbon monoxide; GVHD = graft-versus-host disease.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for respiratory late effects information including risk factors, evaluation, and health counseling.[28]

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Late Effects of the Special Senses

Hearing

Children treated for malignancies may be at risk for early- or delayed-onset hearing loss that can affect learning, communication, school performance, social interaction, and overall quality of life. Hearing loss as a late effect of therapy can occur after exposure to platinum compounds (cisplatin and carboplatin), cranial radiation therapy, or both. These therapeutic exposures are most common in the treatment of central nervous system (CNS) and non-CNS solid tumors. Children are more susceptible to otologic toxic effects from platinum agents than are adults.[1,2]

Risk factors associated with hearing loss include the following:

- Younger age at treatment.

- Higher cumulative dose of platinum-based chemotherapy.

- Exposure to cisplatin combined with myeloablative carboplatin.[3]

- CNS tumors.

- Concomitant cranial radiation therapy.

Hearing loss and platinum-based therapy

Platinum-related sensorineural hearing loss develops as an acute toxicity that is generally irreversible and bilateral. Hearing loss manifests initially in the high frequencies and progresses to the speech frequencies with increasing cumulative exposure. The prevalence of hearing loss has varied widely per series and is based on platinum treatment (e.g., platinum type, dose, infusion duration); host factors (e.g., age, genetic susceptibility, renal function); receipt of additional ototoxic therapy (cranial radiation therapy, aminoglycosides, loop diuretics), and the grading criteria used to report prevalence and severity of hearing loss.[4]

- Cisplatin-induced hearing loss involving the speech frequencies (500–2000 Hz) usually occurs with cumulative doses that exceed 400 mg/m^2 in pediatric patients.[3,5] Prolonging the duration of infusion or splitting the dose has been reported to reduce the risk of significant hearing loss.[6] Exposure to cisplatin combined with myeloablative carboplatin significantly increases the risk of severe hearing loss.[3] Otologic toxic effects after platinum chemotherapy have been reported to worsen years after completion of therapy.[7] Radiation therapy to the posterior fossa inclusive of the eighth cranial nerve (suggestive of damage to the cochlea at the end of therapy) increases the risk of late-onset hearing loss in survivors treated with cisplatin.[8]

- Carboplatin used in conventional (nonmyeloablative) dosing is typically not ototoxic.[9] However, delayed-onset hearing loss has been reported in specific populations. A single study of otologic toxic effects after non–stem cell transplant dosing of carboplatin for retinoblastoma reported that 8 of 175 children developed hearing loss. For seven of the eight children, the onset of the otologic toxic effects was delayed a median of 3.7 years.[10] Another study that evaluated audiological outcomes among 60 retinoblastoma survivors treated with nonmyeloablative systemic carboplatin and vincristine estimated a cumulative incidence of hearing loss of 20.3% at 10 years. Among the ten patients (17%) who developed sustained grade 3 or grade 4 hearing loss, nine were younger than 6 months at the start of chemotherapy. Younger age at the start of treatment was the only significant predictor of hearing loss; the cumulative incidence of hearing loss was 39% for patients younger than 6 months versus only 8.3% for patients aged 6 months and older.[11]

- The use of a carboplatin conditioning regimen for hematopoietic stem cell transplantation, particularly in combination with previous carboplatin or cisplatin therapy, may cause significant otologic toxic effects.[3,5]

Hearing loss and cranial radiation therapy

Cranial radiation therapy, when used as a single modality, may result in otologic toxic effects that may be gradual in onset, manifesting months to years after exposure. The *threshold dose* for auditory toxicity after radiation therapy alone is in the range of 35 to 45 Gy for children.[12] High-frequency sensorineural hearing loss is uncommon at cumulative radiation doses below 35 Gy, and is rarely severe below doses of 45 Gy.[13] The exception is for patients with supratentorial tumors and ventriculoperitoneal shunts, in whom doses below 30 Gy may be associated with intermediate frequency (1,000–2,000 Hz) hearing loss.[12,14] To reduce the risk of hearing loss, the average cochlear dose should not exceed 30 to 35 Gy, delivered over 6 weeks. Young patient age and presence of a brain tumor and/or hydrocephalus can increase susceptibility to hearing loss.

When used concomitantly with cisplatin, radiation therapy can substantially exacerbate the hearing loss associated with

platinum chemotherapy.[12,15-17] In a report from the Childhood Cancer Survivor Study (CCSS), 5-year survivors were at increased risk of problems with hearing sounds (relative risk [RR], 2.3), tinnitus (RR, 1.7), hearing loss requiring an aid (RR, 4.4), and hearing loss in one or both ears not corrected by a hearing aid (RR, 5.2), compared with siblings. Temporal lobe irradiation (>30 Gy) and posterior fossa irradiation (>50 Gy but also 30–49.9 Gy) were associated with these adverse outcomes. Exposure to platinum was associated with an increased risk of problems with hearing sounds (RR, 2.1), tinnitus (RR, 2.8), and hearing loss requiring an aid (RR, 4.1).[18]

Table 15. Auditory Late Effects[a]

Predisposing Therapy	Potential Auditory Effects	Health Screening/Interventions
Platinum agents (cisplatin, carboplatin); radiation impacting the ear	Otologic toxic effects; sensorineural hearing loss; tinnitus; vertigo; dehydrated ceruminosis; conductive hearing loss	History: hearing difficulties, tinnitus, vertigo
		Otoscopic exam
		Audiology evaluation
		Amplification in patients with progressive hearing loss
		Speech and language therapy for children with hearing loss
		Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss
		Educational accommodations (e.g., preferential classroom seating, FM amplification system, etc.)

FM = frequency modulated.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Orbital and Optic

Orbital complications are common after radiation therapy for retinoblastoma and after total-body irradiation (TBI) and in children with head and neck sarcomas and CNS tumors.

Retinoblastoma

For survivors of retinoblastoma, a small orbital volume may result from either enucleation or radiation therapy. Age younger than 1 year may increase risk, but this finding is not consistent across studies.[19,20] Progress has been made in the management of retinoblastoma, with better enucleation implants, intravenous chemoreduction, and intra-arterial chemotherapy in addition to thermotherapy, cryotherapy, and plaque radiation therapy. Longer follow-up is needed to assess the impact on vision in patients undergoing these more contemporary treatment modalities.[19,21,22] Previously, tumors located near the macula and fovea were associated with an increased risk of complications leading to vision loss, although treatment of these tumors with foveal laser ablation has shown promise in preserving vision.[23-26]

(Refer to the PDQ summary on Retinoblastoma Treatment for more information on the treatment of retinoblastoma.)

Rhabdomyosarcoma

Survivors of orbital rhabdomyosarcoma are at risk of dry eye, cataract, orbital hypoplasia, ptosis, retinopathy, keratoconjunctivitis, optic neuropathy, lid epithelioma, and impairment of vision after radiation therapy doses of 30 Gy to 65 Gy. The higher dose ranges (>50 Gy) are associated with lid epitheliomas, keratoconjunctivitis, lacrimal duct

atrophy, and severe dry eye. Retinitis and optic neuropathy may also result from doses of 50 Gy to 65 Gy and even at lower total doses if the individual fraction size is higher than 2 Gy.[27] Cataracts are reported after lower doses of 10 Gy to 18 Gy.[28-30]

(Refer to the PDQ summary on Childhood Rhabdomyosarcoma Treatment for more information on the treatment of rhabdomyosarcoma in children.)

Optic pathway glioma and craniopharyngioma

Survivors of optic pathway glioma and craniopharyngioma are also at risk of visual complications, resulting in part from tumor proximity to the optic nerve.

Longitudinal follow-up (mean, 9 years) of 21 patients with optic pathway gliomas indicated that before treatment, 81% of patients had reduced visual acuity, 81% had optic nerve pallor, and all had reduced visual evoked potentials in one or both eyes. Treatment arrested acuity loss for 4 to 5 years. Visual acuity was stable or improved in 33% of patients at last follow-up; however, it declined on average. Visual acuity at follow-up was related to tumor volume at initial presentation.[31]

In a study of 25 patients diagnosed with craniopharyngioma, 67% had visual complications at a mean follow-up of 11 years.[32] A retrospective review of 30 children with craniopharyngioma revealed that 19 patients had vision loss before surgery; 21 patients had postsurgical vision loss. Preoperative vision loss was predicative of postoperative vision loss. [33]

Treatment-specific effects

Survivors of childhood cancer are at increased risk for ocular late effects related to both glucocorticoid and radiation exposure to the eye. The CCSS reported that survivors who were 5 or more years from diagnosis were at increased risk for cataracts (RR, 10.8), glaucoma (RR, 2.5), legal blindness (RR, 2.6), double vision (RR, 4.1), and dry eye (RR, 1.9), compared with siblings. The dose of radiation to the eye is significantly associated with risk of cataracts, legal blindness, double vision, and dry eye, in a dose-dependent manner. Risk of cataracts was associated with a radiation dose of 30 Gy or more to the posterior fossa and temporal lobe and treatment with prednisone. The cumulative incidence of cataracts, double vision, dry eye, and legal blindness continued to increase up to 20 years after diagnosis for those who received more than 5 Gy to the eye.[34] The 15-year cumulative incidence of cataract was 4.5% among 517 survivors of childhood acute lymphoblastic leukemia (median, 10.9 years from diagnosis), systematically evaluated by slit lamp examination. CNS radiation therapy was the only treatment-related risk factor identified for cataract development, which occurred in 11.1% of irradiated survivors, compared with 2.8% of those who were not irradiated.[35]

Ocular complications, such as cataracts and dry-eye syndrome, are common after stem cell transplantation in childhood. Compared with patients treated with busulfan or other chemotherapy, patients treated with single-dose or fractionated TBI are at increased risk of cataracts. Risk ranges from approximately 10% to 60% at 10 years posttreatment, depending on the total dose and fractionation, with a shorter latency period and more severe cataracts noted after single fraction and higher dose or dose-rate TBI.[36-39] Patients receiving TBI doses of less than 40 Gy have a less than 10% chance of developing severe cataracts.[39] Corticosteroids and graft-versus-host disease may further increase risk.[36,40] The prevalence of cataracts, evaluated by serial slit lamp testing, among 271 participants (mean follow-up, 10.3 years) in the Leucémie Enfants Adolescents (LEA) program was 41.7%, with 8.1% requiring surgical intervention.[41] In this cohort, the cumulative incidence of cataracts among those treated with TBI increased over time from 30% at 5 years to 70.8% at 15 years and 78% at 20 years. The lack of a plateau in cataract incidence suggests that nearly all patients treated with TBI will develop cataracts as follow-up increases. In contrast, the 15-year cumulative incidence of cataracts was 12.5% among those conditioned with busulfan. Multivariable analysis identified high cumulative steroid dose as a potential cofactor with TBI for cataract risk. Epithelial superficial keratopathy has been shown to be more common if the patient was exposed to repeated high trough levels of cyclosporine A.[42]

a

Table 16. Ocular Late Effects

Predisposing Therapy	Ocular/Vision Effects	Health Screening/Interventions
Busulfan; corticosteroids; radiation impacting the eye	Cataracts	History: decreased acuity, halos, diplopia
		Eye exam: visual acuity, funduscopy
		Ophthalmology consultation
Radiation impacting the eye, including radioiodine (I-131)	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
		Eye exam: visual acuity, funduscopy
		Ophthalmology consultation
Hematopoietic cell transplantation with any history of chronic GVHD	Xerophthalmia (keratoconjunctivitis sicca)	History: dry eye (burning, itching, foreign body sensation, inflammation)
		Eye exam: visual acuity, funduscopy
Enucleation	Impaired cosmesis; poor prosthetic fit; orbital hypoplasia	Ocular prosthetic evaluation
		Ophthalmology

GVHD = graft-versus-host disease.

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for information on the late effects of special senses, including risk factors, evaluation, and health counseling.

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Late Effects of the Urinary System

Acute toxicity of the urinary system from cancer therapy is well known. Less is known about the genitourinary outcomes in long-term survivors.[1] The evidence for long-term renal injury in childhood cancer survivors is limited by

studies characterized by small sample size, cohort selection and participation bias, cross-sectional assessment, heterogeneity in time since treatment, and method of ascertainment. In particular, the inaccuracies of diagnosing chronic kidney dysfunction by estimating equations of glomerular dysfunction should be considered.[2] Cancer treatments predisposing to renal injury and/or high blood pressure later in life include chemotherapeutic drugs (cisplatin, carboplatin, ifosfamide, methotrexate), renal radiation therapy, and nephrectomy. The risk and the degree of renal dysfunction depend on type and intensity of therapy and interpretation of the studies is compromised by variability in testing.

Few large-scale studies have evaluated late renal-health outcomes and risk factors for renal dysfunction among survivors treated with potentially nephrotoxic modalities. In a large cross-sectional study of 1,442 childhood cancer survivors (median attained age, 19.3 years; median time from diagnosis, 12.1 years), Dutch investigators assessed the presence of albuminuria, hypomagnesemia, hypophosphatemia, and hypertension and estimated glomerular filtration rate (GFR) among survivors treated with ifosfamide, cisplatin, carboplatin, high-dose cyclophosphamide (>1 g/m^2 or more per course), or high-dose methotrexate (>1 g/m^2 or more per course), radiation therapy to the kidney region, total-body irradiation (TBI), or nephrectomy. At least one abnormality of renal function or hypertension was detected in 28.1% of survivors. History of nephrectomy (odds ratio [OR], 8.6; 95% confidence interval [CI], 3.4–21.4) had the strongest association with a GFR of less than 90 ml/min per 1.73 m^2. The prevalence of decreased GFR was highest among those treated with multimodality therapy including nephrectomy, nephrotoxic chemotherapy, and abdominal radiation therapy. Nearly 5% of these survivors had a GFR of less than 90 ml/min per 1.73 m^2. Abdominal irradiation was the only significant treatment-related risk factor for hypertension (OR, 2.5; 95% CI, 1.4–4.5).[3]

Therapy-related factors affecting the kidney

Cancer treatments predisposing to late renal injury and hypertension include the following:[4-6]

- **Nephrectomy.** Survivors of childhood cancer who have undergone nephrectomy are at risk for hyperfiltration injury. Compensatory hypertrophy of the remaining kidney typically occurs following nephrectomy, but over time, renal injury may manifest as reduced glomerular filtration, microalbuminuria and proteinuria, hypertension, and rarely, focal glomerulosclerosis leading to chronic renal failure. In a cross-sectional study of 1,442 5-year childhood cancer survivors (median 12.1 years from diagnosis), 28.1% of all survivors had at least one renal adverse effect with hypertension (14.8%) and albuminuria (14.5%) being the most prevalent. Survivors who had undergone nephrectomy had the highest risk for diminished renal function (OR, 8.6; 95% CI, 3.4–21.4).[3,5]

- **Chemotherapy.**

    - **Cisplatin.** Cisplatin can cause glomerular and tubular damage resulting in a diminished GFR and electrolyte wasting (particularly magnesium, calcium, and potassium). [7-9] Acute cisplatin-related nephrotoxicity has been reported in 30% to 100% of exposed children.[10] However, the prevalence of persistent renal dysfunction in long-term survivors appears to be considerably lower. Among 63 children treated with platinum agents, GFR was less than 60 ml/min/1.73 m^2 in 11% of children and hypomagnesemia requiring oral supplements in 7% of children at 10 years from completion of therapy. Among 651 sarcoma patients evaluated after cessation of antineoplastic therapy (median follow-up 2 years), hypomagnesemia occurred in 12.1% of patients after cisplatin therapy and in 15.6% after carboplatin therapy, compared with 4.5% who did not receive any platinum derivatives. In all groups, the frequency of hypomagnesemia decreased with ongoing follow-up, but serum magnesium remained lower in platinum-treated patients throughout the study period.[9,11]

    - **Carboplatin.** Carboplatin is a cisplatin analog and is less nephrotoxic than cisplatin. In a prospective, longitudinal, single-center, cohort study of children monitored for more than 10 years after cisplatin or carboplatin therapy, older age at treatment was found to be the major risk factor for nephrotoxicity, especially for patients receiving carboplatin, while cisplatin dose schedule and cumulative carboplatin dose were also important predictors of toxicity. Platinum nephrotoxicity did not change significantly over 10 years.[9] The

combination of carboplatin/ifosfamide may be associated with more renal damage than the combination of cisplatin/ifosfamide.[7-9] Additional follow-up in larger numbers of survivors treated with carboplatin (without other nephrotoxic agents and modalities) must be evaluated before potential renal toxicity can be better defined.

- **Ifosfamide.** Ifosfamide can also cause glomerular and tubular toxicity, with renal tubular acidosis, and Fanconi syndrome, a proximal tubular defect characterized by impairment of resorption of glucose, amino acids, phosphate, and bicarbonate. Ifosfamide doses greater than 60 g/m^2 to 100 g/m^2, age younger than 5 years at time of treatment, and combination with cisplatin and carboplatin increase the risk of ifosfamide-associated renal tubular toxicity.[12-14] A French study that evaluated the incidence of late renal toxicity after ifosfamide reported normal tubular function in 90% of pediatric cancer survivors (median follow-up of 10 years); 79% of the cancer survivors had normal GFR, and all had normal serum bicarbonate and calcium. Hypomagnesemia and hypophosphatemia were seen in 1% of cancer survivors. Glycosuria was detected in 37% of cancer survivors but was mild in 95% of cases. Proteinuria was observed in 12% of cancer survivors. In multivariate analysis, ifosfamide dose and interval from therapy were predictors of tubulopathy, and older age at diagnosis and interval from therapy were predictors of abnormal GFR.[14]

- **High-dose methotrexate.** High-dose methotrexate (1,000–33,000 mg/m^2) has been reported to cause acute renal dysfunction in 0% to 12.4% of patients. This has resulted in delayed elimination of the drug, but long-term renal sequelae have not been described.[5,15]

- **Radiation therapy.** Radiation therapy to the kidney can result in radiation nephritis or nephropathy after a latent period of 3 to 12 months. The kidney is relatively radiosensitive, with a tolerance dose of 20 Gy (5% complications in 5 years).[16] Doses of 18 Gy are considered unlikely to cause severe or chronic renal sequelae. In contrast, up to 50% of individuals treated with 20 Gy may develop glomerular dysfunction or hypertension within 20 years.[17] Specific quantitative data are sparse, but a study of 108 children treated for Wilms tumor who had undergone unilateral nephrectomy showed that 41% of children who received less than 12 Gy to the contralateral remaining kidney, 56% of children who received 12 Gy to 24 Gy, and 91% of children who received more than 24 Gy had a decreased creatinine clearance, defined as less than 63 mL/min/m^2.[18] In a report from the German Registry for the Evaluation of Side Effects after Radiation in Childhood and Adolescence (RISK consortium), 126 patients who underwent radiation therapy to parts of the kidneys for various cancers were evaluated. All patients also received potentially nephrotoxic chemotherapy. Whole-kidney volumes exposed to greater than 20 Gy (P = .031) or 30 Gy (P = .003) of radiation were associated with a greater risk for mild degrees of nephrotoxicity.[19]

  - Age at time of radiation therapy. Neonates appear to have an increased sensitivity to radiation therapy; doses of 12 Gy to 24 Gy at 1.25 Gy to 1.5 Gy per fraction to the entire kidney were associated with a decreased GFR. However, for older children, there is no convincing evidence that age at the time of radiation therapy is related to renal injury.[20]

  - Unilateral versus bilateral radiation therapy. In the National Wilms Tumor Study experience, renal failure was more common in children with bilateral tumors than in children with unilateral tumors.[21] The effects of radiation also depend on whether partial or whole-kidney radiation therapy is administered. Renal failure is rare after the administration of partial-volume radiation doses between 12 Gy and 27 Gy.[22] When certain agents such as cyclosporine and teniposide are not used, total-body irradiation doses of up to 13 Gy are associated with a less than 8% incidence of kidney toxicity.[23]

- **Hematopoietic stem cell transplantation (HSCT).** Chronic kidney disease is a long-term complication of HSCT that has been variably associated with acute kidney injury, lower pretransplant renal function, TBI, conditioning regimens such as fludarabine, graft-versus-host disease, and use of calcineurin inhibitors.[24-26] Most reports of

renal outcomes among long-term survivors of childhood cancer treated with HSCT are limited to descriptive outcomes of very small cohorts.

Refer to the Urinary System Late Effects section of the Childhood Hematopoietic Cell Transplantation summary for more information.

Genetic factors predisposing to renal dysfunction

Many childhood survivors of Wilms tumor who develop chronic renal failure have syndromes accompanying *WT1* mutations or deletions that predispose to renal disease. Data from the National Wilms Tumor Study Group and the U.S. Renal Data System indicate that the 20-year cumulative incidence of end-stage renal disease in children with unilateral Wilms tumor and Denys-Drash syndrome is 74%, 36% for those with WAGR (Wilms tumor, aniridia, genitourinary abnormalities, mental retardation) syndrome, 7% for male patients with genitourinary anomalies, and 0.6% for 5,347 patients with none of these conditions.[27] For patients with bilateral Wilms tumors, the incidence of end-stage renal disease is 50% for Denys-Drash syndrome, 90% for WAGR, 25% for genitourinary anomaly, and 12% for patients for all others.[27,28] End-stage renal disease in patients with WAGR and genitourinary anomalies tended to occur relatively late, and often during or after adolescence.[27]

Therapy-related bladder complications

Pelvic or central nervous system surgery, alkylator-containing chemotherapy including cyclophosphamide or ifosfamide, pelvic radiation therapy, and certain spinal and genitourinary surgical procedures have been associated with the following urinary bladder late effects:[29]

- **Chemotherapy.** The oxazophorine alkylating agents (cyclophosphamide and ifosfamide) and radiation therapy exposing the bladder have been implicated in the development of hemorrhagic cystitis. Chemotherapy-associated hemorrhagic cystitis presents as an acute toxicity and appears to be a rare persistent effect among clinically well characterized long-term survivor cohorts.[30,31] In a study of 6,119 children treated between 1986 and 2010 (mean age, 12.2 years ± 6.3 SD), 1.6% (n = 97) developed hemorrhagic cystitis, most of whom (75%) had severity scores of II or III (scale, I–IV). Patients with radiological evidence of renal or bladder calculi or tumors invading the bladder wall were excluded from the study. Older age, previous bone marrow or peripheral stem cell transplantation, and BK virus in the urine were risk factors for hemorrhagic cystitis and were associated with a higher severity score.[32]
Previous exposure to cyclophosphamide has been linked to risk of bladder carcinoma. An excess prevalence of bladder tumors has also been observed in survivors of specific diagnostic types (e.g., heritable retinoblastoma) supporting the contribution of genetic factors in the development of subsequent neoplasms.[33,34]

- **Radiation therapy.** Pelvic radiation therapy is also associated with an increased risk of hemorrhagic cystitis that may be either acute or chronic in presentation. The risk of radiation-induced hemorrhagic cystitis is greatest among survivors treated with radiation doses of more than 30 Gy to the whole bladder or more than 60 Gy to a portion of the bladder. Long-term bladder fibrosis and contracture may result as a sequelae of hemorrhagic cystitis or radiation therapy.[29]

- **Surgery.** Surgical procedures involving the lower genitourinary tract have the potential to impair normal function of the bladder and normal voiding mechanisms. Likewise, any cancer therapy or tumor infiltration that disrupts innervation of the bladder can have deleterious effects on bladder function that may manifest as impaired bladder storage, inability to void and/or incontinence.

Table 17. Kidney and Bladder Late Effects[a]

Predisposing Therapy	Renal/Genitourinary Effects	Health Screening
Cisplatin/carboplatin;	Renal toxicity (glomerular injury, tubular	Blood pressure

Ifosfamide	injury [renal tubular acidosis], Fanconi syndrome, hypophosphatemic rickets)	BUN, Creatinine, Na, K, Cl, CO_2, Ca, Mg, PO_4 levels
		Urinalysis
		Electrolyte supplements for patients with persistent electrolyte wasting
		Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency
Methotrexate; radiation impacting kidneys/urinary tract	Renal toxicity (renal insufficiency, hypertension)	Blood pressure
		BUN, Creatinine, Na, K, Cl, CO_2, Ca, Mg, PO_4 levels
		Urinalysis
		Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency
Nephrectomy	Renal toxicity (proteinuria, hyperfiltration, renal insufficiency)	Blood pressure
		BUN, Creatinine, Na, K, Cl, CO_2, Ca, Mg, PO_4 levels
		Urinalysis
		Discuss contact sports, bicycle safety (e.g., avoiding handlebar injuries), and proper use of seatbelts (i.e., wearing lapbelts around hips, not waist)
		Counsel to use NSAIDs with caution
		Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency
Nephrectomy; pelvic surgery; cystectomy	Hydrocele	Testicular exam
Cystectomy	Cystectomy-related complications (chronic urinary tract infections, renal dysfunction, vesicoureteral reflux, hydronephrosis, reservoir calculi, spontaneous neobladder perforation, vitamin B_{12}/folate/carotene deficiency [patients with ileal enterocystoplasty only])	Urology evaluation
		Vitamin B_{12} level
Pelvic surgery; cystectomy	Urinary incontinence; urinary tract obstruction	History: hematuria, urinary urgency/frequency, urinary incontinence/retention, dysuria, nocturia, abnormal urinary stream
		Counsel regarding adequate fluid intake, regular voiding, seeking

		medical attention for symptoms of voiding dysfunction or urinary tract infection, compliance with recommended bladder catheterization regimen
		Urologic consultation for patients with dysfunctional voiding or recurrent urinary tract infections
Cyclophosphamide/Ifosfamide; radiation impacting bladder/urinary tract	Bladder toxicity (hemorrhagic cystitis, bladder fibrosis, dysfunctional voiding, vesicoureteral reflux, hydronephrosis)	History: hematuria, urinary urgency/frequency, urinary incontinence/retention, dysuria, nocturia, abnormal urinary stream
		Urinalysis
		Urine culture, spot urine calcium/creatinine ratio, and ultrasound of kidneys and bladder for patients with microscopic hematuria (defined as ≥5 RBC/HFP on at least 2 occasions)
		Nephrology or urology referral for patients with culture-negative microscopic hematuria AND abnormal ultrasound and/or abnormal calcium/creatinine ratio
		Urology referral for patients with culture negative macroscopic hematuria

BUN = blood urea nitrogen; NSAIDs = nonsteroidal anti-inflammatory drugs; RBC/HFP = red blood cells per high-field power (microscopic exam).

[a]Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

Refer to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for urinary late effects information including risk factors, evaluation, and health counseling.

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Changes to This Summary (12/08/2015)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

General Information About Late Effects of Treatment for Childhood Cancer

Added text to state that an analysis of the Childhood Cancer Survivor Study (CCSS) and Surveillance, Epidemiology, and End Results (SEER) study evaluating conditional survival demonstrated a subsequent 5-year survival rate of 92% or higher among most diagnoses at 5 years, 10 years, 15 years, and 20 years. Among those who had survived at least 5 years from diagnosis, the probability of all-cause mortality in the next 10 years was 8.8% in the CCSS and 10.6% in the SEER study, with neoplasms accounting for cause of death in approximately 75% of survivors (cited Mertens et al. as reference 22).

Subsequent Neoplasms

Added text about the excess risk of subsequent neoplasms after the age of 40 years (cited Turcotte et al. as reference 3).

Added Chowdhry et al. as reference 20, Fidler et al. as reference 22, and Archer et al. as reference 70.

Late Effects of the Cardiovascular System

Added text about a collaborative study of North American and European pediatric cancer cohorts that evaluated the hazard ratio for clinical heart failure through age 40 years for doses of daunorubicin and doxorubicin (cited Feijen et al. as reference 28).

Added text to state that while these data suggest that dexrazoxane does protect the heart, there are not yet long-term data showing the impact of dexrazoxane on cardiac health (cited van Dalen et al. as reference 29).

Added text about the possible association between dexrazoxane and increased risk of second cancers (cited Chow et al. as reference 36).

Late Effects of the Central Nervous System

Added Khan et al. as reference 7.

Added text to state that radiation dose to specific subvolumes of the brain, including the temporal lobes and hippocampi, have been shown to significantly impact longitudinal intelligence quotients and academic achievement scores among children treated with craniospinal irradiation for medulloblastoma (cited Merchant et al. as reference 17).

Added Annett et al. as reference 49 and Iyer et al. as reference 54.

Added text about a cross-sectional study that evaluated neurologic morbidity and quality of life in 162 survivors of childhood acute lymphoblastic leukemia (ALL).

Added text about a CCSS study that evaluated psychological and neurocognitive function in 2,589 long-term cancer survivors who were diagnosed during adolescence and young adulthood (cited Prasad et al. as reference 86).

Late Effects of the Digestive System

Added text about a study from the CCSS that evaluated the incidence and risk of late-occurring intestinal obstruction requiring surgery in 12,316 5-year survivors and 4,023 siblings (cited Madenci et al. as reference 36 and level of evidence 3iiiC).

Late Effects of the Endocrine System

Added Li et al. as reference 14.

Late Effects of the Immune System

Added text to state that clinicians should consider and encourage the administration of inactivated vaccines and vaccines made of purified antigens, bacterial components, or genetically engineered recombinant antigens in all cancer and transplant survivors according to recommended doses and schedules (cited National Center for Immunization and Respiratory Diseases, Bridges et al., and Rubin et al. as references 6, 7, and 8, respectively).

Late Effects of the Musculoskeletal System

The Osteochondroma subsection was extensively revised.

Late Effects of the Respiratory System

Added text about a longitudinal study that evaluated the magnitude and trajectory of pulmonary dysfunction among 121 childhood cancer survivors treated with potentially pulmonary-toxic therapy (cited Armenian et al. as reference 4).

Late Effects of the Special Senses

Added text about the prevalence of cataracts, evaluated by serial slit lamp testing, among 271 participants in the Leucémie Enfants Adolescents (LEA) program (cited Horwitz et al. as reference 41).

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About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the late effects of treatment for childhood cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

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- be cited with text, or
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Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Late Effects of Treatment for Childhood Cancer are:

- Louis S. Constine, MD (James P. Wilmot Cancer Center at University of Rochester Medical Center)
- Melissa Maria Hudson, MD (St. Jude Children's Research Hospital)
- Nita Louise Seibel, MD (National Cancer Institute)

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