Adult Survivors of Childhood Cancer: Health Management

Karen Goddard
Conflicts of Interest

- None
Objectives

• Consider
  • Childhood cancer treatments and cure rates
    • Historical perspective
  • Late effects
    • Definition
    • Causes
    • Nature
      • Physical
        • Organ function
        • Second cancers
      • Psychological
  • Screening
  • Prevention
  • Health care implications
  • How can we best support survivorship?
Published in 1978

The Private Worlds of Dying Children

Myra Bluebond-Langner
Survival Rates

Childhood cancer survival

Proportion surviving after 2 years [%]

Year of Diagnosis

- M. Hodgkin
- Wilms Tumour
- Acute lymphoblastic Leukemia
- Non-Hodgkin Lymphoma
- Ewing Sarcoma
- Osteosarcoma
- Rhabdomyosarcoma
- Malignant Germ Cell Tumours
- Neuroblastoma
- Brain Tumours
- Acute myeloid Leukemia

© 2003-2007, Genentech
Improvement related to:

- Multimodality approach:
  - Surgery
  - Systemic therapy (chemotherapy)
  - Radiation therapy
- Therapy intensification
  - Bone marrow transplant
  - Interval compression of chemotherapy
- Better supportive care during therapy
- Development of new targeted therapeutic agents
Incidence

- About 12,000 children in the US (between birth and 14 years of age) develop childhood cancer each year.
- In Canada 1310 patients diagnosed with cancer between the ages of 0 and 19 per year.
- 83% of these children will be long term survivors who have been cured of their disease.
- 20 to 30 years ago many children with cancer did not survive.
  - In 1950s less than 10% of childhood cancers were cured.
- Improvements due to:
  - Multimodality Rx
  - Therapy intensification
- In 2010 - estimated that 1:250 of the adult population in North America was a survivor of childhood cancer.
- In 2013 - 400,000 childhood cancer survivors in US.
Late Effects

• Definition:
  • “Side effects that occur more than 5 years after diagnosis”
• Problems with definition:
  • Etoposide related AML (short latency)
• Generally takes many years for late effects to develop
• How are these problems detected?
  • Follow up
    • Surveillance programs – clinic or mail contact
Late Effects

• Late effects include:
  • Physical problems
    • Organ damage
      • Development affected
      • High risk of late effects in adults treated for childhood cancer
    • Secondary tumors
  • Psychological problems
    • Depression, anxiety
Late Effects

Clinical Ascertainment of Health Outcomes Among Adults Treated for Childhood Cancer

Melissa M. Hudson, MD
Kirsten K. Ness, PT, PhD
James G. Gurney, PhD
Daniel A. Mulrooney, MD, MS
Wassim Chemaitilly, MD
Kevin R. Krull, PhD
Daniel M. Green, MD
Gregory T. Armstrong, MD, MSCE
Kerri A. Nottage, MD
Kendra E. Jones, MS
Charles A. Sklar, MD
Deo Kumar Srivastava, PhD
Leslie L. Robison, PhD

Importance Adult survivors of childhood cancer are known to be at risk for treatment-related adverse health outcomes. A large population of survivors has not been evaluated using a comprehensive systematic clinical assessment to determine the prevalence of chronic health conditions.

Objective To determine the prevalence of adverse health outcomes and the proportion associated with treatment-related exposures in a large cohort of adult survivors of childhood cancer.

Design, Setting, and Participants Presence of health outcomes was ascertained using systematic exposure–based medical assessments among 1713 adult (median age, 32 [range, 18-60] years) survivors of childhood cancer (median time from diagnosis, 25 [range, 10-47] years) enrolled in the St. Jude Lifetime Cohort Study since October 1, 2007, and undergoing follow-up through October 31, 2012.

Main Outcomes and Measures Age-specific cumulative prevalence of adverse outcomes by organ system.

Results Using clinical criteria, the crude prevalence of adverse health outcomes was highest for pulmonary (abnormal pulmonary function, 65.2% [95% CI, 60.4%-69.8%]), auditory (hearing loss, 62.1% [95% CI, 55.8%-68.2%]), endocrine or reproductive (any endocrine condition, such as hypothalamic-pituitary axis disorders and male germ cell dysfunction, 62.0% [95% CI, 59.5%-64.6%]), cardiac (any cardiac condition, such as heart valve disorders, 56.4% [95% CI, 53.5%-59.2%]), and neurocognitive (neurocognitive impairment, 48.0% [95% CI, 44.9%-51.0%]) function,

Curative therapy for pediatric malignancies has produced a growing population of adults formerly treated for...
Late Effects

• At age 45 years:
  • 95.5% cumulative prevalence of any chronic health condition
  • 80.5% (95% CI, 73.0%-86.6%) for a serious/disabling or life-threatening chronic condition
Survivors at Risk
Researchers followed more than 1,700 adults who had been treated for cancer as children and found that those who had received certain types of treatment were very likely to develop certain health problems later in life.

**Adult condition: Breast cancer**
Childhood treatment: Radiation to the breast (females only)

**Heart-valve disorder**
Radiation to the heart

**Pituitary dysfunction**
Radiation to the hypothalamus-pituitary

**Hearing loss**
Radiation to the ear or exposure to cisplatin or carboplatin

Sources: St. Jude Children’s Research Hospital; JAMA

The Wall Street Journal
Incidence

- Significant long term risk for any child who has RT
  - 8-10% risk of second malignancies within 20 years
  - 5-20 X greater than general population (Friedman et al. Pediatric Clin North Am 2002)
- **Childhood Cancer Survivor Study**
- 30-year cumulative incidence rates for all CCS:
  - All second neoplasms
    - 20.5% (95% CI, 19.1%–21.8%).
  - Malignant second neoplasms (excluding non-melanoma skin cancer
    - 7.9% (95% CI, 7.2%–8.5%).
  - Non Malignant second neoplasms
    - 9.1% (95% CI, 8.1%–10.1%).
    - Meningioma
      - 3.1% (95% CI, 2.5%–3.8%).
- This is a 6X increased risk of secondary neoplasms among cancer survivors, compared with the general population.
Incidence

- Childhood Cancer Survivor Study
  - 30 year cumulative incidence of second malignancy = 9%

---

Fig 1. Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At the 30-year follow-up, the cumulative incidence of SMNs and NMSC continues to increase with time since 5 years after diagnosis of primary childhood cancer.
Organs at Risk

- Central nervous system
- Orbit
- Hearing
- Peripheral Nervous system
- Endocrine
- GU system
- Respiratory
- Gastro-intestinal
- Musculoskeletal
- Reproductive organs
- Cardiovascular
- Skin
Tumor Related Damage

• Invasion into and pressure on different structures
  • Wilms tumor
    • One kidney usually completely destroyed by disease and has to be removed
Tumor Related Damage

- **Craniopharyngioma** tumor growth and cyst expansion leads to compression of:
  - Optic apparatus
    - Blindness
  - Pituitary
    - Endocrinopathy
Surgery Related Damage

- Surgery
  - Prime modality for local control
- Lymph node dissection
  - Lymphedema
- Splenectomy
  - Life threatening infection
    - Pneumococcal vaccine
    - Medic Alert bracelet
Chemotherapy Related Damage

- Chemotherapy prime modality for systemic control
- Depends on agent and sensitivity of target organs
  - Adriamycin – cardiomyopathy
  - Cisplatin – nephrotoxicity and hearing loss
  - Alkylating agents – infertility and second cancers
  - Vincristine and peripheral neuropathy
Radiation Therapy (RT)

• In children (unlike adults) affects normal growth/development
• Severity of late effects depends on:
  • Age at the time of therapy
  • Total dose given
  • Fractionation
  • Region treated:
    • Some organs more sensitive and easily damaged
    • Amount of normal tissue treated
• Concurrent chemotherapy can sensitize normal tissues
• Underlying genetic problems:
  • Radio-genomics
Determining the Risk

- Adult survivors of childhood cancer may be at:
  - Low risk
    - Many patients treated for leukemia
    - No radiation therapy
    - Combination low dose chemotherapy
  - Intermediate risk
    - More intensive chemotherapy
  - High risk
    - Intensive chemotherapy (including alkylating agents and adriamycin)
    - Any previous history of radiation therapy
Determining the Risk

- Assess for each patient:
  - Original diagnosis
  - Radiation therapy:
    - Region treated
    - Amount given
  - Chemotherapy
    - Which drug?
    - Quantity given
      - For example, adriamycin
  - Drug administration
    - For example, Cyclophosphamide and Mesna
  - Comorbidities
    - Concurrent illness
    - Underlying genetic problems
      - Li-Fraumeni
Clinical case 1

- 35 year old man treated at the age of 7 for high risk acute lymphoblastic leukemia
- Chemotherapy included:
  - Adriamycin
  - IV and IT Methotrexate
- Prophylactic, low dose cranial radiation therapy (18 Gy in 10#)
Health Risks

• Neuro-cognitive
  • Mild cognitive dysfunction
  • Depression and post traumatic stress syndrome

• Endocrine
  • Hypothyroidism

• Metabolic syndrome
  • Hypertension
  • Obesity
  • Hyperlipidemia
  • Diabetes

• Cardiomyopathy

• Secondary tumors
  • Skin cancers (generally basal cell cancers)
  • Thyroid cancer (and multinodular goitre)
  • Meningioma
  • Malignant brain tumor (very small risk)

• Increased risk of stroke and vascular disease
Clinical Case 2

• 40 years old male with a history of medulloblastoma treated with craniospinal radiation therapy at the age of 7.
  • Higher dose of radiation therapy
  • More extensive treatment fields
• He was also given concurrent chemotherapy which included cisplatin and an alkylating agent.
Craniospinal RT:

- **Multiple late effects:**
Musculoskeletal

- Bone/Muscle/soft tissues
  - “Hypoplasia” – reduced growth within the RT field
Endocrinopathy

- Pituitary dysfunction
  - GH
  - TSH
  - FSH & LH
  - ACTH
- Thyroid damage
  - Primary Hypothyroidism
Metabolic Syndrome

• Associated with treatment for childhood cancer
• Cranial radiation therapy and TBI (whole body RT prior to transplant) significantly increase the risk

• Etiology
  • Poorly understood post chemotherapy alone
  • Radiation therapy:
    • Hypothalamic effect
    • Radiation therapy to pancreas

• Characterized by:
  • Central obesity
  • Hypertension
  • Hyperlipidemia
  • Diabetes
Neurocognitive Problems

- Long term IQ in pediatric brain tumor patients depends on age at the time of therapy:
- Age at time of therapy for medulloblastoma:
  - 1–5 years:
    - Mean IQ of 72
    - 50% of patients had scores less than 80
  - 6–10 years
    - Mean IQ of 93
    - 14% had IQ scores of less than 80
  - Children 11-15 years
    - Mean IQ of 107
    - 9% had IQ scores of less than 80
Other CNS Problems

- Brain
  - Developmental delay
    - Poor short term memory
    - Poor executive function
- Seizures
- Cerebrovascular events
  - Vascular malformations
  - Early aging of small blood vessels
  - Thrombotic and haemorrhagic
Hearing Loss

• Radiation Therapy:
  • Conductive: wax build up
  • Sensorineural: direct damage to cochlea

• Chemotherapy:
  • Sensorineural
  • Cisplatin causes high frequency hearing loss
    • Sensory hair cells in the cochlea
Visual Problems

- Cataracts
Second Neoplasm

A second cancer or second malignant neoplasm (SMN) is defined as a histologically distinct second cancer that develops after the first.

Definition: (ICD-O)
- Tumor in new location and not from direct spread or metastasis of the primary cancer
- Tumor in the same location as the primary cancer but of different histological type
Thyroid cancer
Radiation induced Meningioma

- **RT induced meningioma**
  - Multiple
  - Atypical
  - More likely to recur after surgery
Skin Cancer

- Increased risk of cancers in previous radiation therapy field
  - Basal cell carcinoma
  - Melanoma

Skin Cancer Information

What Is Skin Cancer?

Skin cancer is the uncontrolled growth of abnormal skin cells. It occurs when unrepaired DNA damage to skin cells (most often caused by ultraviolet radiation from sunshine or tanning beds) triggers mutations, or genetic defects, that lead the skin cells to multiply rapidly and form malignant tumors.

What to Look for

- Actinic Keratosis
- Basal Cell
- Dysplastic Nevi
- Melanoma
- Squamous Cell
Colorectal Cancer (CRC)

- 2-3% risk of CRC 30–40 years after treatment for childhood cancer and increasing.
- Associated with abdominal radiation therapy
- Risk is proportional to dose and volume of RT
  - Increased by 70% with each 10-Gy increase in RT dose.
  - Increased RT volume increased risk (group 1 OR, 1.5; P < .001; group 2 OR, 1.8; P < .001).
- Alkylating agent exposure associated with 8.8X increased risk of secondary CRC.
Hodgkin Lymphoma

- Treated with:
  - Combination chemotherapy
    - Adriamycin
    - Alkylating agents
    - Bleomycin
  - Radiation therapy (RT) to neck and chest.
- Splenectomy common over 20 years ago
Hodgkin Lymphoma: Long-term Health Risks

- Heart damage
  - Cardiomyopathy (Adriamycin)
  - Coronary artery disease
  - Valvular stenosis
- Stroke
  - Carotid artery disease
- Pulmonary fibrosis (RT and Bleomycin)
- Spinal arthritis and osteoporosis
- Thyroid disease
  - Multinodular goiter
  - Hypothyroidism
- Infertility related to chemotherapy
- Overwhelming sepsis and immune compromise
- Second cancers:
  - Thyroid
  - Skin
  - Lung (smokers)
- **Breast cancer in females**
Breast Cancer

- Commonest solid tumor among female survivors of Hodgkin lymphoma
- Moderately high-dose mediastinal RT
  - Scatter to adjacent (breast) tissue
- Adolescent girls most at risk
Breast Cancer

• After treatment for Hodgkin lymphoma in adolescence
  • 37X risk of breast cancer
  • Bilateral disease more common
  • Increased risk:
    • Over 12 years of age at diagnosis
    • Higher dose of RT

History

• History of previous illness and therapy critical to understanding risks and organizing appropriate screening
• Generate a “care plan”
Screening

• Generally, follow up care depends on “risk category”
  • High risk: Hospital based and family practitioner
  • Low risk: Family practitioner

• Survivorship Care Plan:
  • Coordinated post-treatment plan
  • Built by survivor’s oncology team
  • Includes
    • Summary of the survivor’s treatment
    • Direction for future care

• Screening recommendations: COG Long Term FU Guidelines
Screening

- Screening guidelines available
  - Children’s Oncology Group

Health Link
Healthy living after treatment of childhood cancer

Thyroid Problems after Childhood Cancer

Some people who were treated for cancer during childhood may develop endocrine (hormone) problems as a result of changes in the function of a complex system of glands known as the endocrine system.

What is the endocrine system?
The endocrine system is a group of glands that regulate many body functions including growth, puberty, energy level, urine production, and stress response. Glands of the endocrine system include the pituitary, hypothalamus, thyroid, adrenals, pancreas, ovaries (in females), and testes (in males). The hypothal-
Breast Cancer Screening

Health Link
Healthy living after treatment of childhood cancer

Breast Cancer Following Treatment for Childhood Cancer: Are You at Risk?

You have successfully been treated for cancer during childhood or adolescence and are now moving forward with your life—so the last thing you want to be reminded about is the risk of developing another cancer during adulthood. For a variety of reasons, the risk of cancer increases for everyone as they age. Depending on the specific treatment you received for childhood cancer, you may be at increased risk for developing breast cancer. It is important to understand that risk, so that you can take steps to protect your health.

What are the risk factors?
Screening

• Screening not possible for all late effects
  • Some radiation induced malignancies such as sarcomas and malignant brain tumors
Prevention

Information about late effects critical for prevention:
• Initial therapy
  • Give treatments which are less likely to cause long-term damage
    • Avoid or reduce radiation therapy
    • Targeted therapy
      • We don’t know about the late effects of these agents yet
• Tailored therapy
  • Genomic studies to identify people more likely to develop side effects
Prevention

• Information/education
  • Childhood cancer survivors
    • Know to seek advice
  • Health care professionals
    • Do the correct investigations
Prevention

• Lifestyle:
  • Diet
  • Exercise
  • Smoking
  • Sun/UV exposure
Cancer Survivors Who Stay Active Live Longer
By GRETCHEN REYNOLDS  MAY 16, 2012 12:01 AM  81 Comments
Prevention is Complex

- Risk of cerebrovascular disease:
  - Radiation therapy (RT)
    - Dose, fractionation and area treated
  - Chemotherapy at time of RT
  - Genetic factors
  - Endocrinopathy
    - GH deficiency
  - Metabolic syndrome
    - Hyperlipidemia
    - Hypertension
    - Diabetes
  - Lifestyle
    - Smoking and exercise
  - Genetic factors
  - Prophylactic aspirin
    - Hemorrhagic and thrombotic
  - **Publication just accepted:**
    - A cross-sectional cohort study of cerebrovascular disease and late effects after radiation therapy for craniopharyngioma

---

**Clinical Investigation: Central Nervous System Tumor**

**Long-Term Outcomes and Complications in Patients With Craniopharyngioma: The British Columbia Cancer Agency Experience**

Andrea C. Lo, MD, A. Fuchsia Howard, PhD, Alan Nichol, MD, FRCPC, Keerat Sidhu, BSc, Farah Abdulsatar, BSc, Haroon Hasan, BSc, and Karen Goddard, MD, FRCPC

*Department of Radiation Oncology, British Columbia Cancer Agency Vancouver Centre; Department of Surgery, University of British Columbia, and School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada*

Received Nov 5, 2013, and in revised form Jan 9, 2014. Accepted for publication Jan 16, 2014.
Psychosocial

• Post-traumatic stress syndrome
  • Anxiety
  • Depression

• Many brain tumor survivors:
  • Need very modified school curriculum
  • Rely on permanent disability pension:
    • Differences across the province and between different provinces regarding available programs
      • Access to vocational/recreational rehab
  • Drug costs covered by parents benefits plan
  • Other costs not covered:
    • Hearing aids
Impact on Life

- Huge range of late effects:
  - Low risk:
    - Many (but not all) previous lymphoma and leukemia patients
    - Function very well
    - Minimal risk for long-term health problems
  - High risk:
    - Any RT, high dose chemotherapy including alkylating agents and anthracylines
    - Some leukemia patients, brain tumors and solid tumors (e.g. sarcomas)
    - Lives may be “devastated”
- Long term health care:
  - Counseling
  - Screening/Surveillance for late effects
ASCO May 2015

- Analysis of more than 34,000 participants in the Childhood Cancer Survivor Study (CCSS)
- Mortality at 15 years after diagnosis
  - 12.4% if treated in 1970s
  - 6% if treated in 1990s

Changes in Pediatric Cancer Treatments Yield Reduced Late Mortality

June 1, 2015
Survivorship Program

• Provincial survivorship program essential
  • Medical care
    • Detect and monitor for late effects
      • Screening
      • Coordinate specialist and primary care
  • Psychosocial support
    • Family counseling
    • Close links with rehab programs
    • Wellness program focusing on diet, exercise and mental wellbeing
  • Education
    • Primary and specialist care
    • Families and survivors
  • Research
    • Collaborative program focusing on how to reduce the risk of late effects and improve survivor’s quality of life
Resources

• COG: [Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers](#)
Resources

• National Cancer Institute:
Resources

**Pediatric Oncology Education Materials**

---

**Late Effects**

**General Overview**

On average approximately 10,400 North American children (between birth and 14 years of age) develop childhood cancer each year and these numbers seemingly increase annually.

More than 80% of these children will be long term survivors who have been cured of their disease. This was very different 20 to 30 years ago, when many children did not survive.

In general, cure rates have been improved by using:

- Multiple treatment modalities
  - Radiation therapy (RT)
  - Chemotherapy
  - Surgery
- Therapy intensification (using higher total doses of chemotherapy over a shorter period of time)
- Improved supportive care
What didn’t kill me made me Stronger
The End

• Thank you!
• kgoddard@bccancer.bc.ca