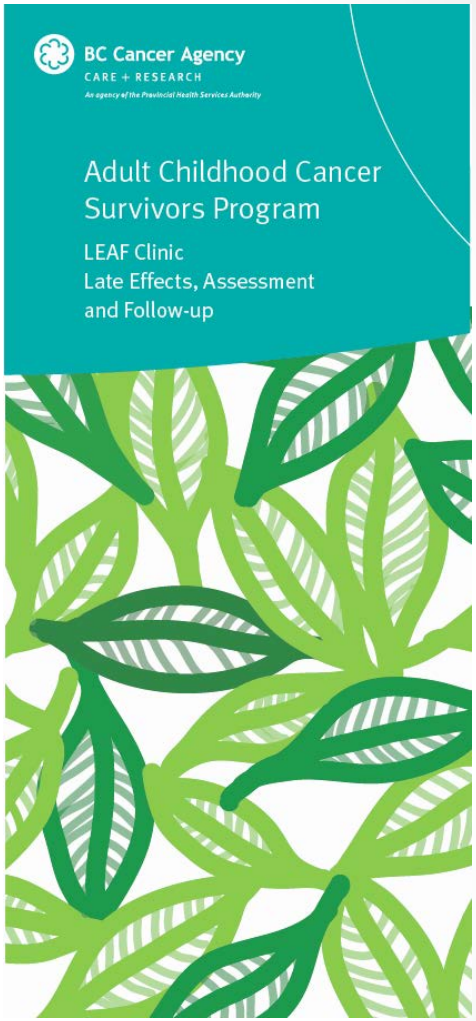
The Late Effects, Assessment & Follow-up (LEAF) Clinic



Kristin Goddard

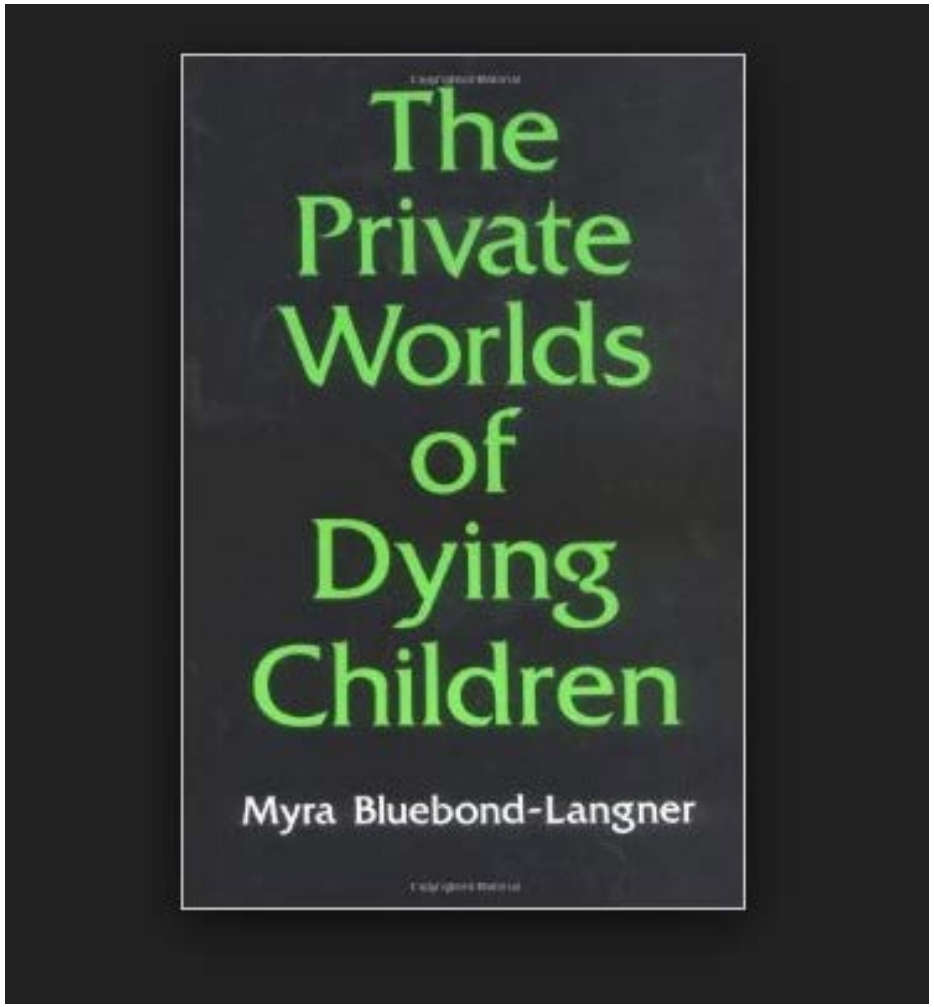
Conflicts of Interest

- None
- No disclosures to make

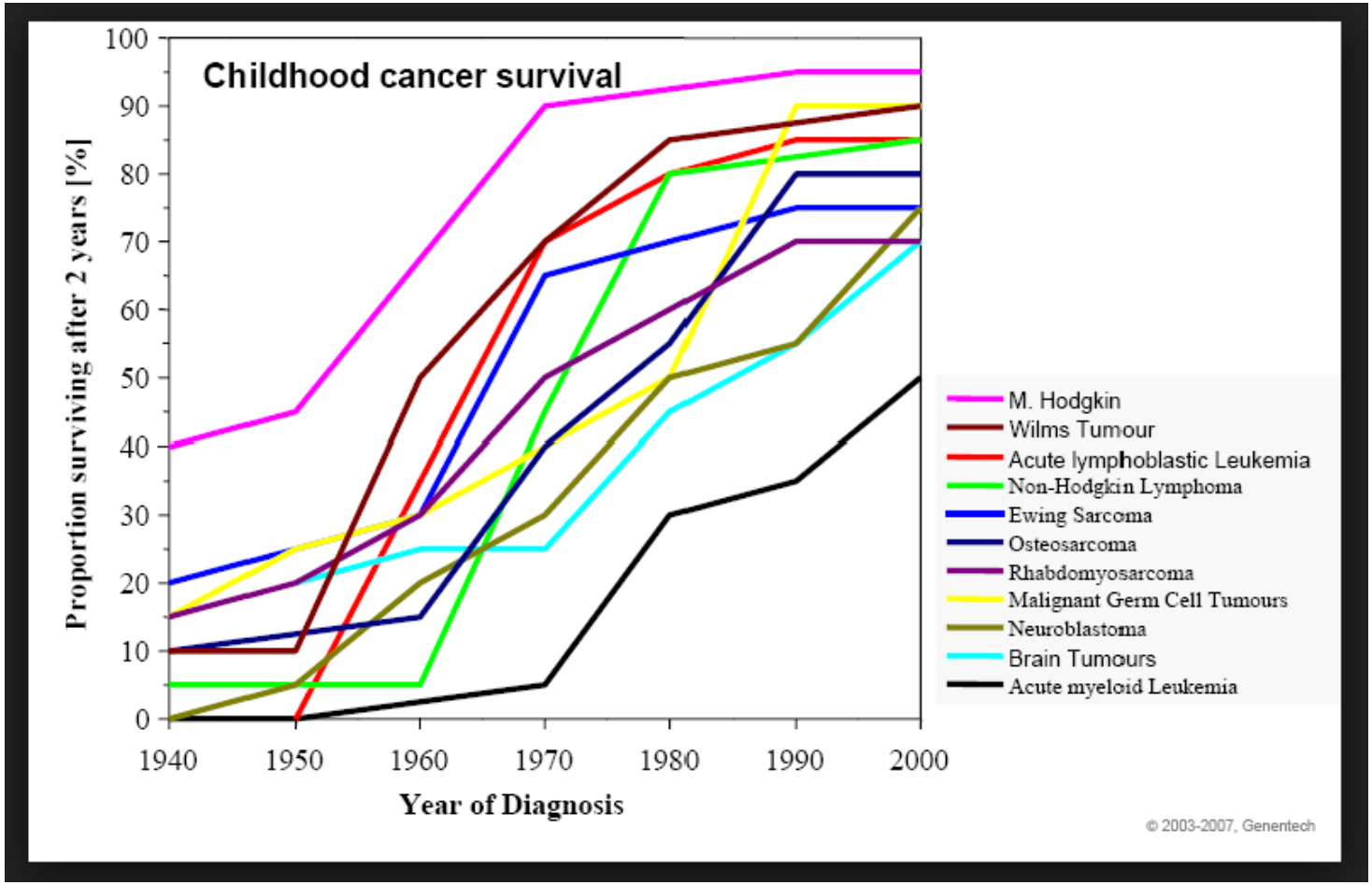
Objectives

- Consider
  - The definition of late effects
    - Etiology and incidence of chronic health problems in adult childhood cancer survivors (ACCS)
    - Nature
      - Physical
        - Organ function
        - Second cancers
      - Psychological
  - Factors which determine the severity of late effects
  - Current international recommendations regarding screening and prevention
  - The function of the new LEAF clinic
    - Who works in the clinic and what our roles are
    - How to contact us and refer patients

Published in 1978

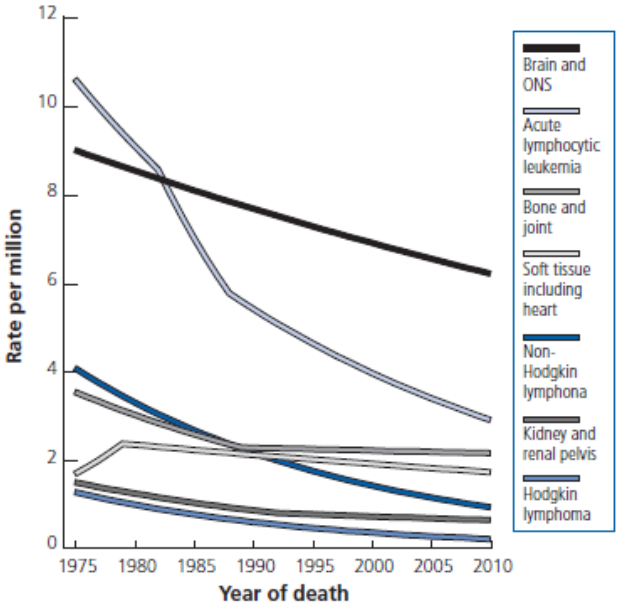


Survival Rates



U.S. Mortality and Survival Rates

Figure 3. Trends in Pediatric Cancer Mortality Rates by Site, Ages 0-19, 1975-2010



ONS = Other nervous system.

Note: Lines are fitted trends based on Joinpoint analyses.

Average annual percent change (APC) for cancers with significant trends during most recent period: ALL (-3.1 during 1988-2010), brain (-1.1 during 1975-2010), NHL (-4.1 during 1975-2010), soft tissue (-1.0 during 1979-2010), kidney (-1.2 during 1992-2010), HL (-4.9 during 1975-2010).

Source: National Center for Health Statistics, Centers for Disease Control and Preventaion.

American Cancer Society, Surveillance Research, 2014

Table 4. Pediatric Cancer Five-year Observed Survival Rates for Two Time Periods, Ages 0-19

	Year of Diagnosis 1975-79 %	2003-09* %
All ICCC sites	63	83
Leukemia	48	84
Acute lymphocytic leukemia	57	90
Acute myeloid leukemia	21	64
Lymphomas and reticuloendothelial neoplsams	72	91
Hodgkin lymphoma	87	97
Non-Hodgkin lymphoma	47	85
Brain and CNS	59	75
Ependymoma	37	81
Astrocytoma	69	85
Medulloblastoma	47	70
Neuroblastoma and ganglioneuroblastoma	54	79
Retinoblastoma	92	99
Wilms tumor	75	90
Hepatic tumors	25	74
Bone tumors	49	73
Osteosarcoma	45	71
Ewing sarcoma	42	72
Rhabdomyosarcoma	49	64
Testicular germ cell tumors	74	96
Ovarian germ cell tumors	75	94
Thyroid carcinoma	99	98
Melanoma	83	95

ICCC=International classification of childhood cancers.

CNS=Central nervous system.

*Cases were followed through 2010.

Note: Does not include benign and borderline brain tumors.

Source: Surveillance, Epidemiology, and End Results (SEER) program, 9 SEER registries, National Cancer Institute.

American Cancer Society, Surveillance Research, 2014

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 2014 - estimated that 1: 530 of the adult population (ages 20 to 39) in North America was a survivor of childhood cancer
- In 2013 - 400,000 childhood cancer survivors in US

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Survivorship

- **Cancer survivor:**
  - One who remains alive and continues to function during and after overcoming a serious hardship or life-threatening disease.
  - In cancer, a person is considered to be a survivor from the time of diagnosis until the end of life.

Survivorship

There are millions of people in the United States who are cancer survivors. Many say that they felt they had lots of support during their treatment, but once it ended, it was hard to make a transition to a new way of life. It was like entering a whole new world where they had to adjust to new feelings, new problems and different ways of looking at the world.

A New Normal

Adjusting to physical and emotional changes after cancer treatment and tips on coping with fear of recurrence.

In memoriam

Ellen Stovall

1946-2016

NCCS
NATIONAL COALITION FOR CANCER SURVIVORSHIP

WE ADVOCATE FOR QUALITY CANCER CARE FOR ALL INDIVIDUALS TOUCHED BY CANCER

BC CANCER

Survivorship

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

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

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

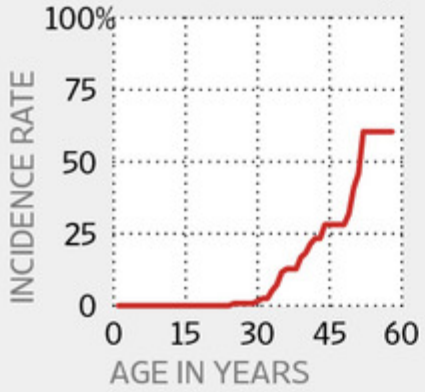
- At age 45 years:
  - 95.5% cumulative prevalence of any chronic health condition
  - 80.5% (95% CI, 73.0%-86.6%) for a serious/disabling or life-threatening chronic condition

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.

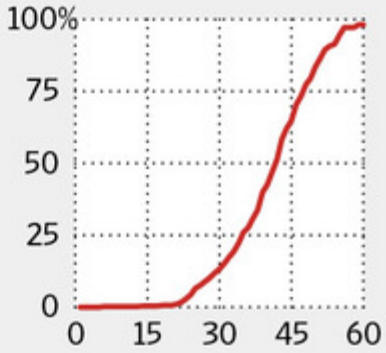
Adult condition: Breast cancer

Childhood treatment: Radiation to the breast (females only)



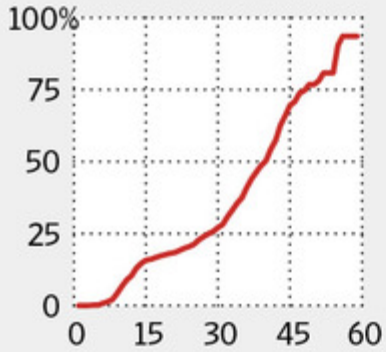
Heart-valve disorder

Radiation to the heart



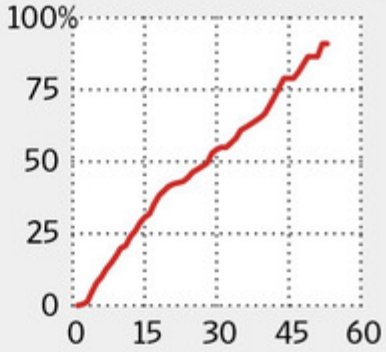
Pituitary dysfunction

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

Aging and Risk of Late Effects

- ACCS who reached age 35 years without a previous grade 3 or 4 condition
  - 25.9% experienced a subsequent grade 3 to 5 health condition within next 10 years

Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study

Gregory T. Armstrong ✉, Toana Kawashima, Wendy Leisenring, Kayla Stratton, Marilyn Stovall, Melissa M. Hudson, Charles A. Sklar, Leslie L Robison, Kevin C. Oeffinger

Gregory T. Armstrong, Melissa M. Hudson, Leslie L Robison, St Jude Children's Research Hospital, Memphis, TN; Toana Kawashima, Wendy Leisenring, Kayla Stratton, Fred Hutchinson Cancer Research Center, Seattle, WA; Marilyn Stovall, The University of Texas MD Anderson Cancer Center, Houston, TX; Charles A. Sklar, Kevin C. Oeffinger, Memorial Sloan-Kettering Cancer Center, New York, NY.

Causes of LEs

- Tumor related
- Patient related
  - Genetic factors
- Treatment related
  - Surgery
  - Chemotherapy
  - Radiation therapy

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 threating infection
    - Pneumococcal vaccine
    - Medic Alert bracelet

Chemotherapy Related Damage

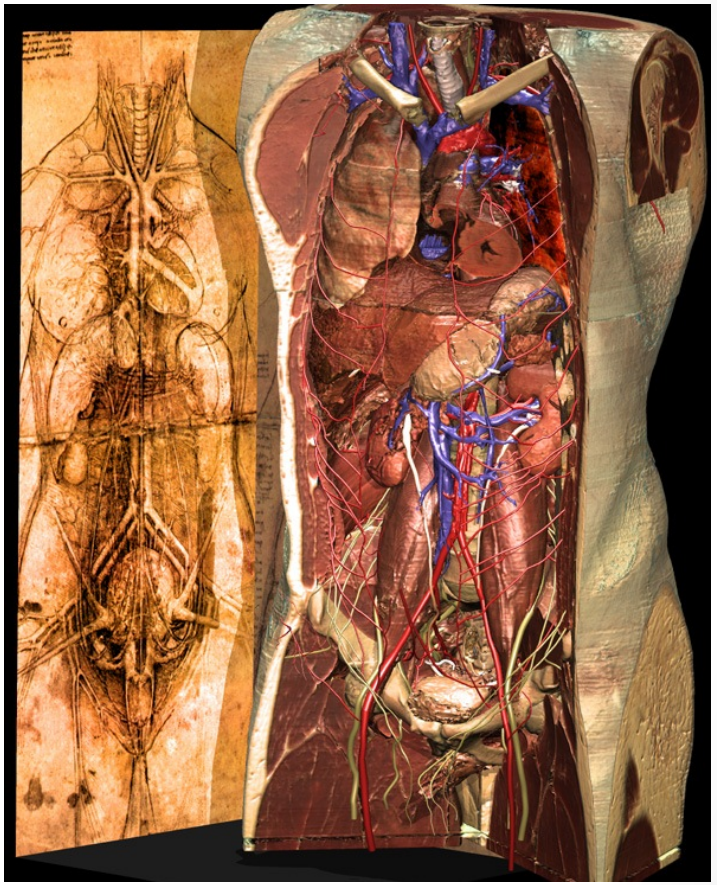
- Chemotherapy prime modality for systemic control
- Depends on agent and sensitivity of target organs
  - Adriamycin: Cardiomyopathy
  - Cisplatin: Nephrotoxicity and hearing loss
  - Alkylating agents: Infertility and second cancers
  - Vincristine: Peripheral neuropathy
  - Bleomycin: Pulmonary fibrosis

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:
    - Ataxia-telangectasia
    - Radio-genomics

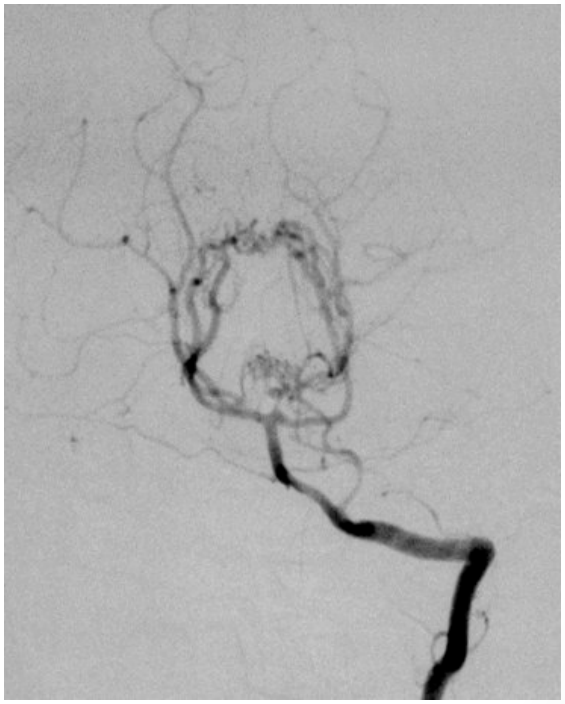
Organs at Risk

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



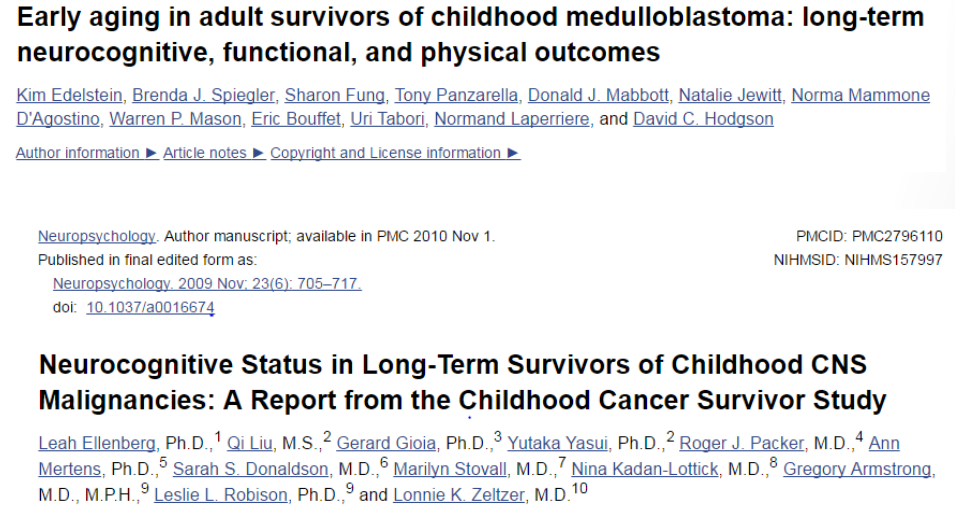
CNS

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



CNS: Brain Tumors

- Long-term cognitive function in pediatric brain tumor patients
  - Expect a 10 to 20-point decline in age-adjusted intelligence quotient (IQ) scores compared to the population norms within the first 5 to10 years
  - Depends on:
    - Age at the time of RT
    - RT volume of irradiated brain
    - RT Dose
    - VP shunt



Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes

Kim Edelstein, Brenda J. Spiegler, Sharon Fung, Tony Panzarella, Donald J. Mabbott, Natalie Jewitt, Norma Mammone D'Agostino, Warren P. Mason, Eric Bouffet, Uri Tabori, Normand Laperriere, and David C. Hodgson

Author information ► Article notes ► Copyright and License information ►

Neuropsychology. Author manuscript; available in PMC 2010 Nov 1.
Published in final edited form as:
Neuropsychology. 2009 Nov; 23(6): 705–717.
doi: 10.1037/a0016674

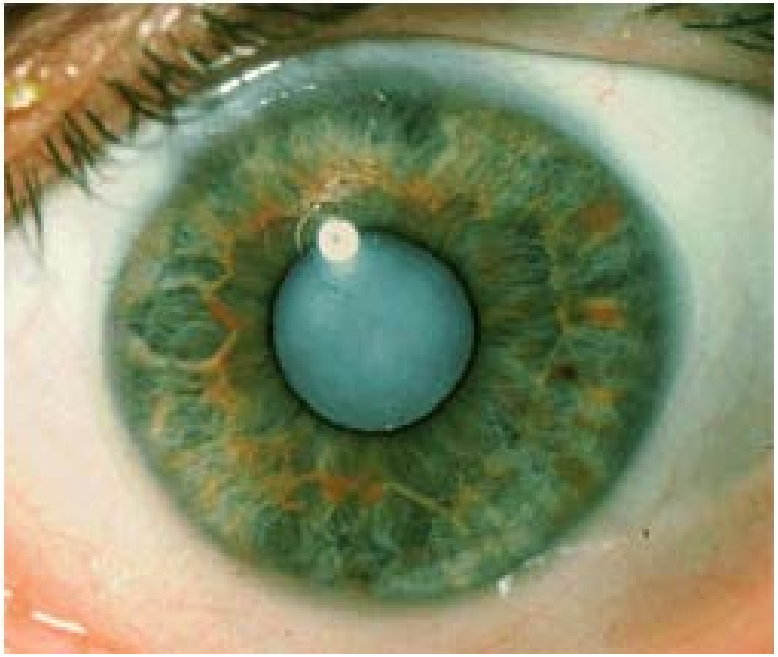
PMCID: PMC2796110
NIHMSID: NIHMS157997

Neurocognitive Status in Long-Term Survivors of Childhood CNS Malignancies: A Report from the Childhood Cancer Survivor Study

Leah Ellenberg, Ph.D.,[1] Qi Liu, M.S.,[2] Gerard Gioia, Ph.D.,[3] Yutaka Yasui, Ph.D.,[2] Roger J. Packer, M.D.,[4] Ann Mertens, Ph.D.,[5] Sarah S. Donaldson, M.D.,[6] Marilyn Stovall, M.D.,[7] Nina Kadan-Lottick, M.D.,[8] Gregory Armstrong, M.D., M.P.H.,[9] Leslie L. Robison, Ph.D.,[9] and Lonnie K. Zeltzer, M.D.[10]

Eye

- Ocular complications common
  - Cranial nerve palsies
  - Glucocorticoid Rx
    - Cataracts
  - High dose RT:
    - Anterior chamber damage
    - Acute glaucoma
    - Painful red eye
    - Treated by enucleation
  - Low dose RT:
    - Cataracts

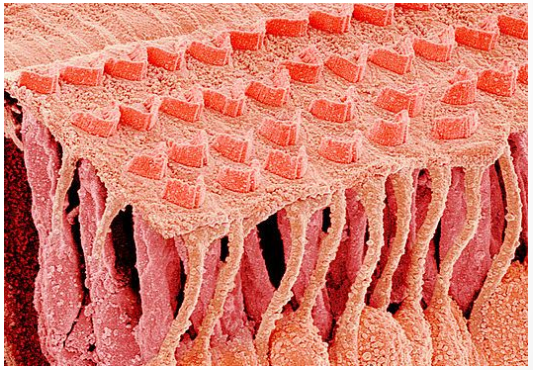


Ocular Late Effects in Childhood and Adolescent Cancer Survivors: A Report from the Childhood Cancer Survivor Study[a]

Kimberly F. Whelan,[1] Kayla Stratton,[2] Toana Kawashima,[2] John W. Waterbor,[3] Robert P. Castleberry,[1] Marilyn Stovall,[4] Charles A. Sklar,[5] Roger J. Packer,[6] Pauline Mitby,[7] Candice L. Aitken,[8] Julie Blatt,[9] Leslie L. Robison,[10] and Ann C. Mertens[11]

Hearing Loss

- Radiation Therapy:
  - Conductive: wax build up
  - Sensorineural (SNHL): direct damage to cochlea
    - SNHL (JCO study) present in 14% of pediatric brain tumor survivors
    - 12% needed hearing aids
    - Continued to deteriorate over time
- Chemotherapy:
  - Sensorineural
  - Cisplatin causes high frequency hearing loss
    - Sensory hair cells in the cochlea

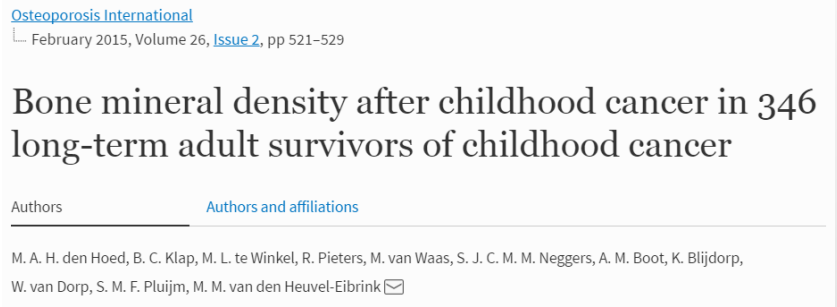


Hearing Loss in Patients Who Received Cranial Radiation Therapy for Childhood Cancer

Johnnie K. Bass ✉, Chia-Ho Hua, Jie Huang, Arzu Onar-Thomas, Kirsten K. Ness, Skye Jones, Stephanie White, Shaum P. Bhagat...

Bone Mineral Density

- Osteopenia common in adult survivors of childhood cancer
  - 45% in one large retrospective study
- Increased risk associated with
  - Intensive systemic chemotherapy
  - TBI as part of transplant preparative regimen
  - RT to spine (osteopenia especially severe within RT field)
  - Steroid therapy
  - Early menopause in female survivors
  - Reduced physical activity


Osteoporosis International
February 2015, Volume 26, Issue 2, pp 521–529

Bone mineral density after childhood cancer in 346 long-term adult survivors of childhood cancer

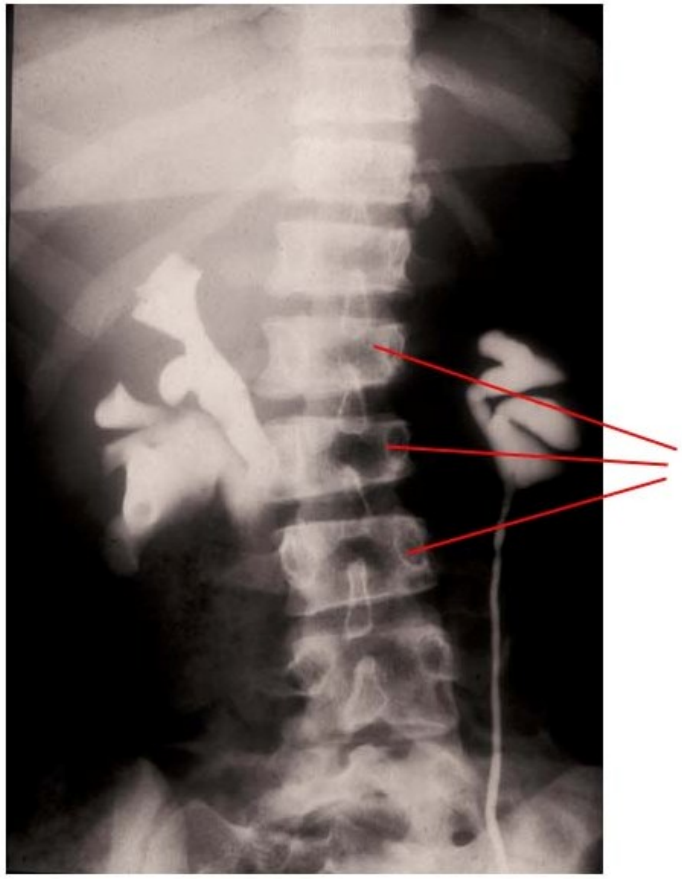
Authors Authors and affiliations

M. A. H. den Hoed, B. C. Klap, M. L. te Winkel, R. Pieters, M. van Waas, S. J. C. M. M. Neggers, A. M. Boot, K. Blijdorp, W. van Dorp, S. M. F. Pluijm, M. M. van den Heuvel-Eibrink

Musculoskeletal

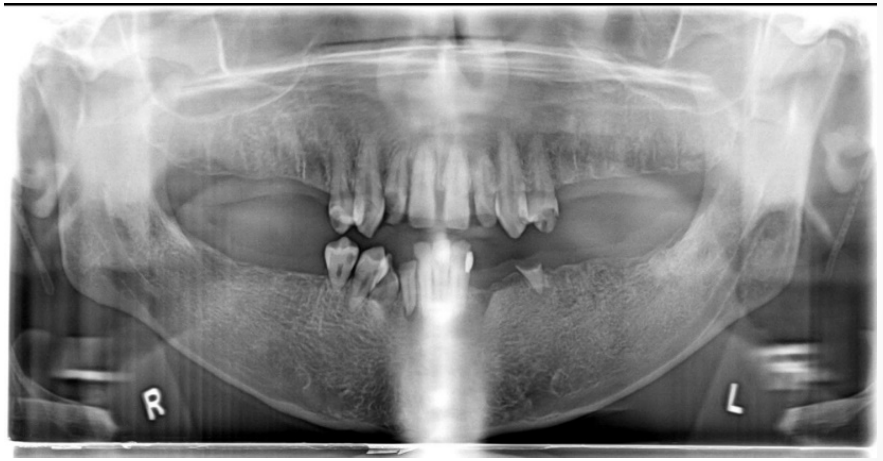
- Bone/Muscle/soft tissues
  - “Hypoplasia” – reduced growth within the RT field

Musculoskeletal



Dental Late Effects

- Chemotherapy:
  - Root and enamel development if given early in life
- Radiation therapy to mouth
  - Dental development
  - Trismus
  - Xerostomia
  - Dental decay
  - Osteoradionecrosis
    - After high dose RT
    - Then dental extraction
    - May need hyperbaric O2



A systematic review of dental late effects in survivors of childhood cancer

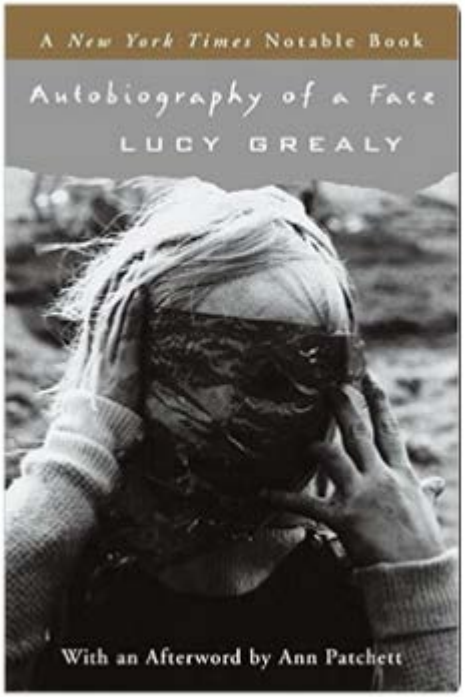
Prasad L. Gawade PhD, Melissa M. Hudson MD, Sue C. Kaste DO, Joseph P. Neglia MD, MPH, Louis S. Constine MD, Leslie L. Robison PhD, Kirsten K. Ness PT, PhD ✉

First published: 1 November 2013 Full publication history

DOI: 10.1002/pbc.24842 View/save citation

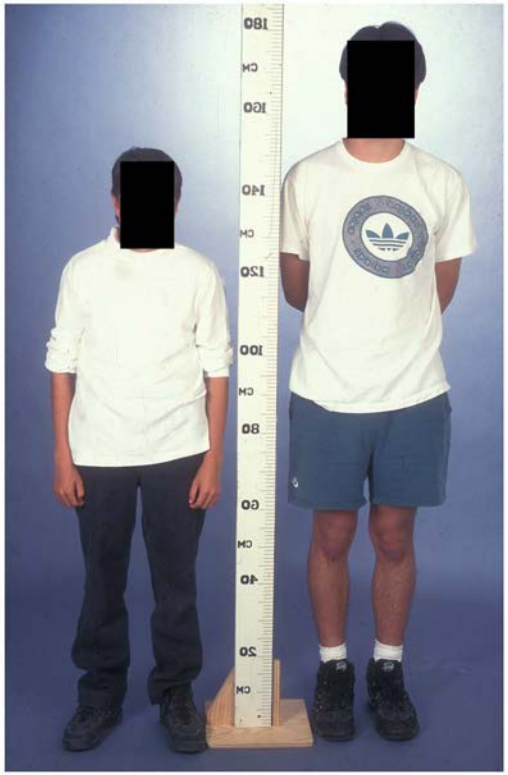
Facial Hypoplasia

- Lucy Grealy " *Autobiography of a face*"



Musculoskeletal

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



Endocrinopathy

- Common
  - >50% of ACSS

Eur J Endocrinol. 2013 Feb 20;168(3):465-72. doi: 10.1530/EJE-12-1043. Print 2013 Mar.

Endocrine health conditions in adult survivors of childhood cancer: the need for specialized adult-focused follow-up clinics.

Brignardello E[1], Felicetti F, Castiglione A, Chiabotto P, Corrias A, Fagioli F, Ciccone G, Boccuzzi G.

- CCSS study:
  - 14290 childhood cancer survivors (median 6 yrs post therapy)
  - Risk of endocrinopathy in survivors increased substantially over time
- Types of endocrinopathy
  - Pituitary dysfunction
    - GH, TSH, FSH & LH, ACTH
  - Thyroid damage
    - Primary Hypothyroidism, hyperthyroidism & thyroid nodules
  - Diabetes
  - Gonadal dysfunction

Endocrine Abnormalities in Aging Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

Sogol Mostoufi-Moab, Kristy Seidel, Wendy M. Leisenring, Gregory T. Armstrong, Kevin C. Oeffinger, Marilyn Stovall, Lillian R. Meacham, Daniel M. Green...

Metabolic Syndrome

- Associated with treatment for childhood cancer
- Cranial RT, TBI and abdominal RT 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

Oncology (Williston Park). 2015 Nov;29(11):849-55.

Obesity and Metabolic Disease After Childhood Cancer.

Barnea D, Raghunathan N, Friedman DN, Tonorezos ES.

Immune Dysfunction

- Intensive chemotherapy
  - Loss of vaccine related immunity
    - Pre-existing humoral immunity against measles, mumps, rubella, and VZV after completion of chemotherapy.
  - More common in children treated for ALL than in children with AML, solid tumors and Hodgkin disease.
  - Need post-chemotherapy revaccination in childhood cancer survivors.

Vaccine. 2014 Jun 5;32(27):3357-61. doi: 10.1016/j.vaccine.2014.04.042. Epub 2014 Apr 29.

Differential loss of humoral immunity against measles, mumps, rubella and varicella-zoster virus in children treated for cancer.

Bochennek K[1], Allwinn R[2], Langer R[1], Becker M[1], Keppler OT[2], Klingebiel T[1], Lehrnbecher T[3].

Asplenism

- No functioning spleen
  - Surgery
  - Radiation therapy to left flank or abdomen

Asplenism

BC Centre for Disease Control
An agency of the Provincial Health Services Authority

Anatomic or Functional Asplenia

Recommended vaccines for those with anatomic or functional asplenia [A, B]	
All routine inactivated vaccines	Immunize according to routine schedule.
Hib vaccine	All individuals 5 years of age and older require 1 dose regardless of immunization history. [C]
Meningococcal quadrivalent conjugate vaccine	Meningococcal quadrivalent conjugate vaccine for those 2 months of age and older. (This vaccine to be given in place of meningococcal C conjugate vaccine in the routine childhood immunization schedule). Reinforcement dose(s) are recommended. [D]
Pneumococcal vaccine	Conjugate and/or polysaccharide vaccine depending on age. Requires once only revaccination with polysaccharide vaccine.
Influenza vaccine	Immunize yearly (all those 6 months of age and older). Inactivated influenza vaccine should be used.
MMR vaccine [E]	Refer to Immunization with Inactivated and Live Vaccines. Use Referral Form for MMR Vaccination. [F]
Varicella vaccine [E]	Refer to Immunization with Inactivated and Live Vaccines. Use Referral Form for Varicella Vaccination. [F] Separate doses by 12 weeks.
Rotavirus vaccine	Refer to Immunization with Inactivated and Live Vaccines. Use Referral Form for Rotavirus Vaccination.

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Cardiovascular Disease in Adult Survivors of Childhood Cancer

Annual Review of Medicine
Vol.66:1-523 (Volume publication date January 2015)
DOI: 10.1146/annurev-med-070213-054849

Steven E. Lipshultz,[1,2] Vivian I. Franco,[1] Tracie L. Miller,[3] Steven D. Colan,[4,5] and Stephen E. Sallan[5,6,7]

- Etiology: Adriamycin and RT
  - Adriamycin:
    - Dose related cardiomyopathy
  - Mediastinal RT for Hodgkin lymphoma (HL): 5% of patients have symptomatic heart disease 10 years later
    - Cardiomyopathy
    - Coronary artery disease
    - Pericarditis
    - Valvular disease
    - Conduction system problems
      - AV and bundle branch block
  - Neck RT: Vascular problems
    - Carotid artery disease
- Hypertension

GU/Renal disease

- Kidneys especially vulnerable
  - Chemotherapy
    - Cisplatin
      - Magnesium-wasting tubulopathy
    - Ifosfamide
      - Proximal tubular dysfunction and less frequently decreased GFR
    - Methotrexate
      - Acute renal dysfunction
  - Radiation therapy:
    - Doses greater than 20 Gy result in significant nephropathy
  - Surgery
    - Reduction in renal tissue
- Hypertension

Renal Late Effects in Patients Treated for Cancer in Childhood: A Report from the Children's Oncology Group

Deborah P. Jones, M.D., Professor of Pediatrics, Sheri L. Spunt, M.D., Associate Member, Daniel Green, M.D., Member, and James E. Springate, M.D.

Pulmonary disease

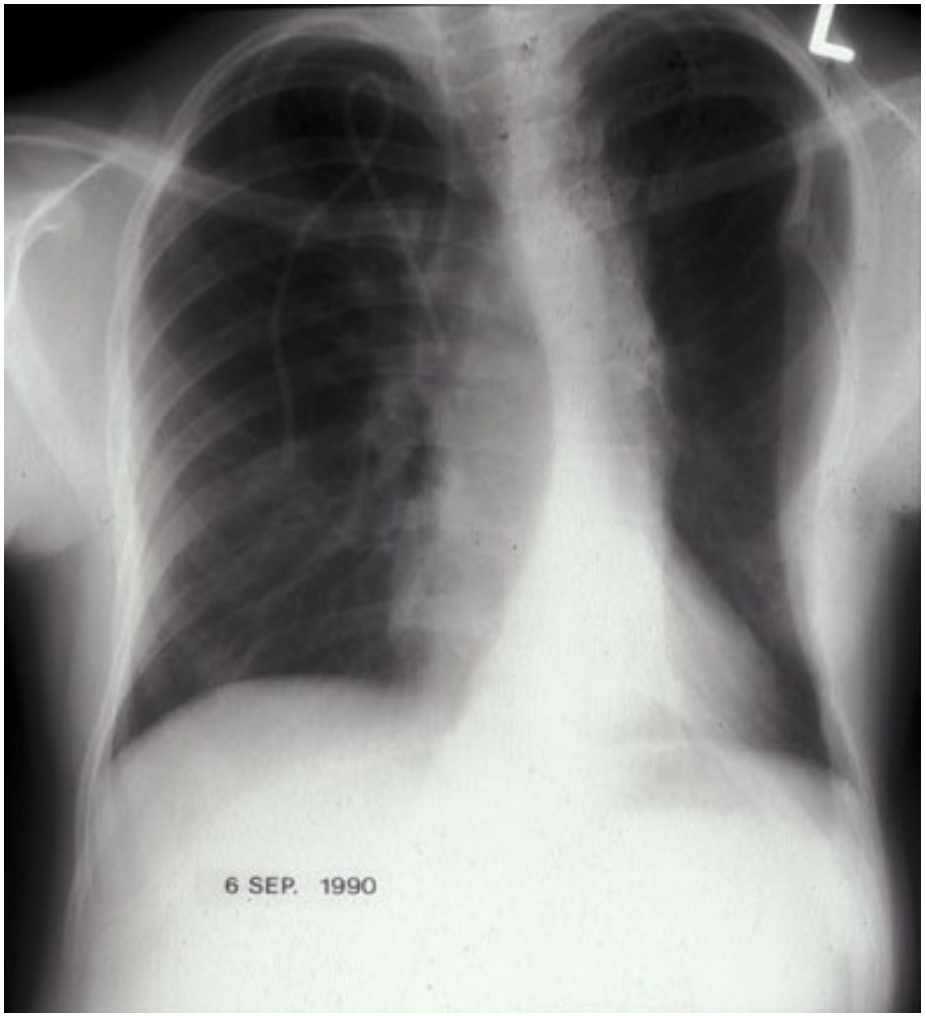
- Lungs very sensitive to both radiation therapy and chemotherapy
- Bleomycin:
  - Intra-alveolar exudates with subsequent organization
  - Hyaline membrane formation
  - Interstitial fibrosis
  - Atypical proliferation of alveolar cells
- Radiation therapy :
  - Lung inflammation (pneumonitis)
  - Chest wall deformity – restrictive defect

Cancer. 2016 Dec 1;122(23):3687-3696. doi: 10.1002/cncr.30200. Epub 2016 Aug 9.

Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study.

Dietz AC[1], Chen Y[2], Yasui Y[3], Ness KK[3], Hagood JS[4], Chow EJ[5], Stovall M[6], Neglia JP[7], Oeffinger KC[8], Mertens AC[9], Robison LL[3], Armstrong GT[3], Mulrooney DA[3].

Chest wall deformity:



GI disease

- Intestines very sensitive to radiation therapy:
  - Malabsorption
  - Strictures
  - Adhesions and obstruction
  - Fistula
- Previous surgery increases risk

Survivors of Childhood Cancer Have Increased Risk for Gastrointestinal Complications Later in Life

Robert Goldsby,[1] Yan Chen,[2] Shannon Raber,[1] Linda Li,[1] Karen Diefenbach,[3] Margarett Shnorhavorian,[4] Nina Kadan-Lottick,[3] Fay Kastrinos,[5] Yutaka Yasui,[2] Marilyn Stovall,[6] Kevin Oeffinger,[7] Charles Sklar,[7] Gregory T. Armstrong,[8] Leslie L. Robison,[8] and Lisa Diller[9]

Reproductive System

- Gonads very sensitive to both RT and chemotherapy
  - Alkylating agents
  - RT to ovaries:
    - The dose of RT needed to destroy 50% of the oocytes = LD50
    - Oocytes are very sensitive with an LD_{50} of < 200 cGy
- Damage to developing uterus

Reproductive System

- Male infertility
- Major factors decreasing the likelihood of a cancer survivor achieving a pregnancy (Childhood Cancer Survivor Study (CCSS) 2009)
  - Radiation therapy to testes of > 7.5 Gy
  - Cumulative alkylating agent dose score of ≥2
  - Treatment with procarbazine
  - Treatment with high doses of cyclophosphamide

Ann Pediatr Endocrinol Metab. 2013 Dec; 18(4): 168–172.
Published online 2013 Dec 31. doi: 10.6065/apem.2013.18.4.168

Reduced male fertility in childhood cancer survivors

Sun Hee Lee, MD[1] and Choong Ho Shin, MD, PhD[2]

Author information ▶ Article notes ▶ Copyright and License information ▶

Second Cancers

- 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

SMN Causes

- Factors associated with a risk of second neoplasm
  - Patient related
  - Disease related
  - Treatment related

SMN Causes

- Patient related:
  - Age
    - Increased risk if young at diagnosis
    - Time since Rx
  - Lifestyle and environment
    - Smoking
  - Underlying genetic condition
    - Clearly defined:
      - Bilateral retinoblastoma
      - NF1
      - Li-Fraumeni
        - Germ line mutation in tumor suppressor genes
    - More complex genetic factors
      - Radiogenomics

SMN Causes

- Disease related:
  - Hodgkin lymphoma
  - Ewing sarcoma
- Therapy related:
  - Chemotherapy alone
    - Alkylating agents
    - VP-16
  - **Radiation therapy (RT)**
  - Combined RT and chemotherapy

SMN Causes

- Proposed mechanisms for RT induced SMN:
  - DNA damage and gene mutations:
    - Rearrangements within the genome place proto-oncogenes within regions with high rates of translation
    - Double strand DNA breaks and imperfect repair
    - Tumour suppressor gene deactivation
  - Radiation-induced genomic instability
  - Telomere shortening observed in response to intensive chemotherapy and/or ionizing radiation exposure.
    - Less telomere content associated with treatment-related SMN in childhood cancer survivors.

Telomere Content and Risk of Second Malignant Neoplasm in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

Maria M. Gramatges, Qi Liu, Yutaka Yasui, M. Fatih Okcu, Joseph P. Neglia, Louise C. Strong, Gregory T. Armstrong, Leslie L. Robison, and Smita Bhatia

DOI: 10.1158/1078-0432.CCR-13-2076 Published 15 February 2014

SMN 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. Pediatrc Clin North Am 2002)
- Childhood cancer survivor study:
- 14,364 survivors of childhood cancer diagnosed between 1970 and 1986
- Cumulative incidence of new SNs and SMNs occurring after age 40 years was 34.6%.

Risk of Subsequent Neoplasms During the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort

Lucie M. Turcotte ✉, John A. Whitton, Debra L. Friedman, Sue Hammond, Gregory T. Armstrong, Wendy Leisenring, Leslie L. Robison, Joseph P. Neglia

BC CANCER

SMN Incidence

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

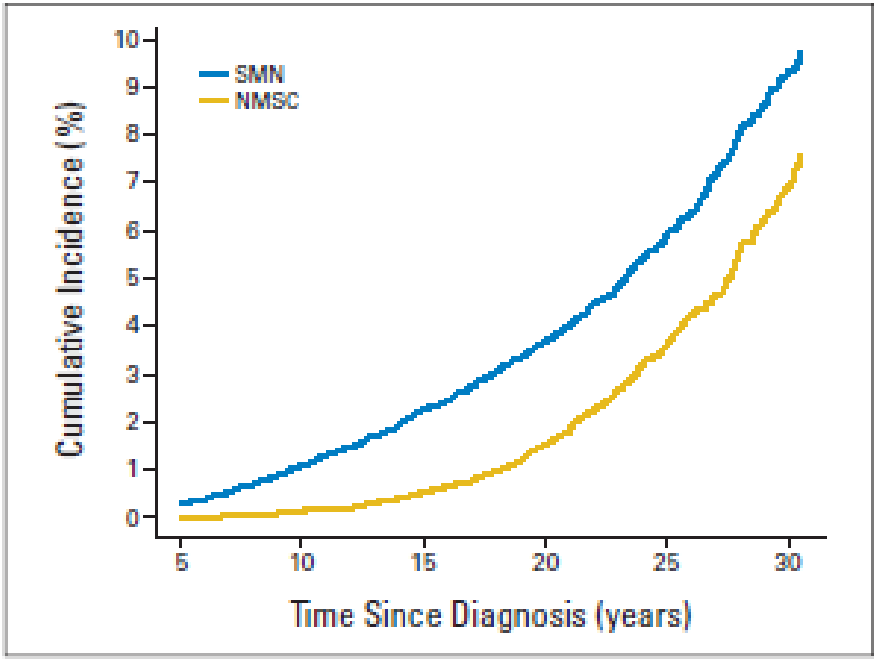
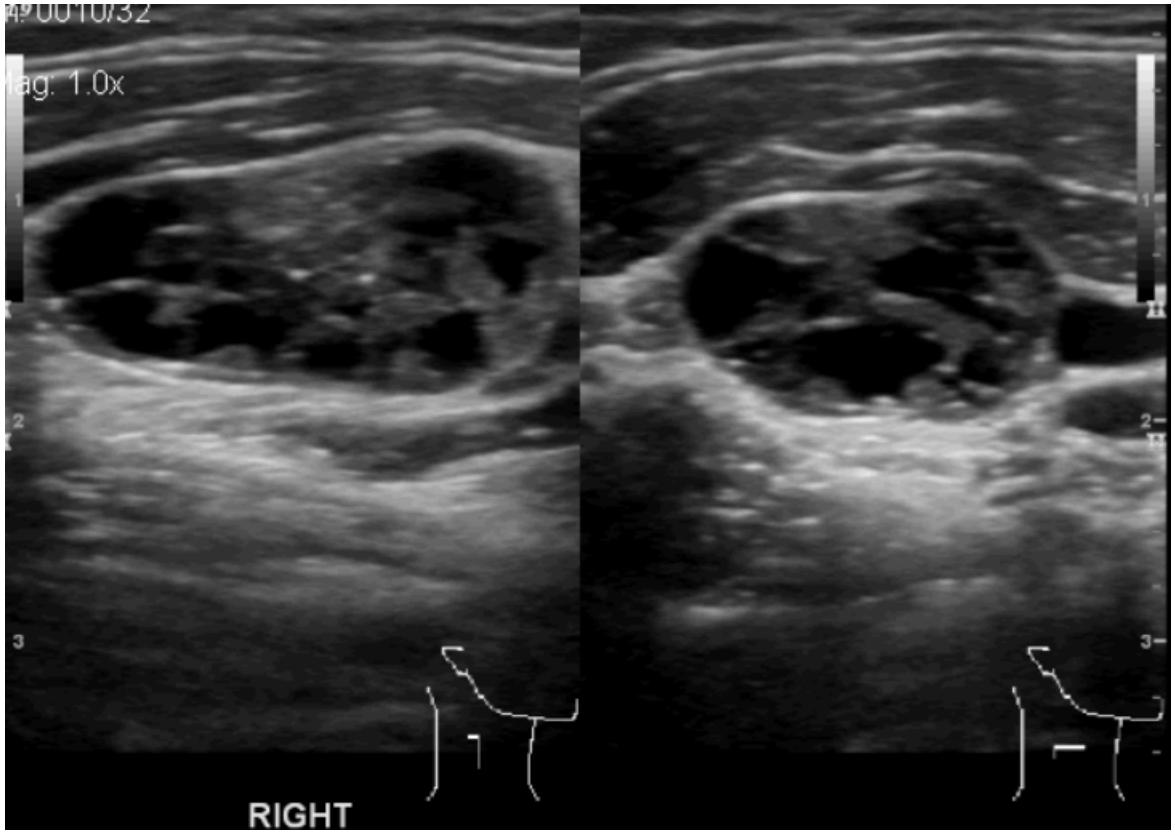


Fig 1. Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At the 30-year follow-up, the cumulative incidence of SMNs and NMSC continues to increase with time since 5 years after diagnosis of primary childhood cancer.

Types of Secondary Tumors

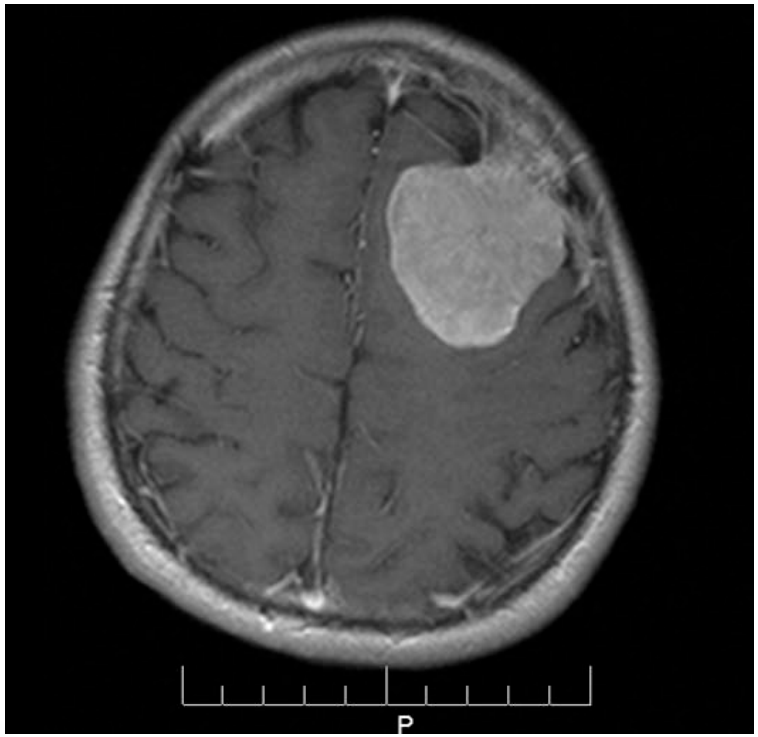
- Most common:
  - Radiation therapy induced meningioma
  - Thyroid carcinoma
  - Skin cancers
    - Basal cell
    - Melanoma
  - Breast carcinoma
  - Colorectal carcinoma
  - Sarcomas (bone)
  - Myelodysplastic syndrome (MDS) and AML

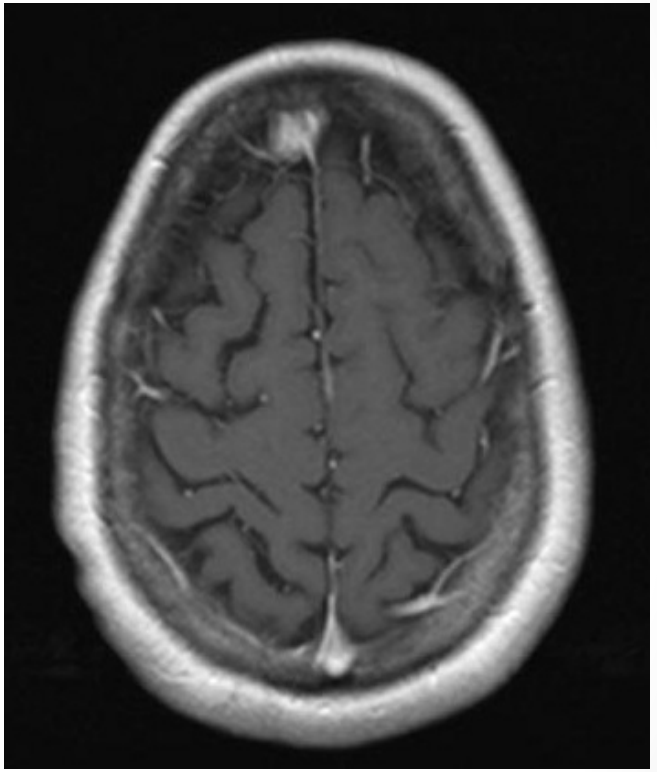
Thyroid cancer



Radiation induced Meningioma

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



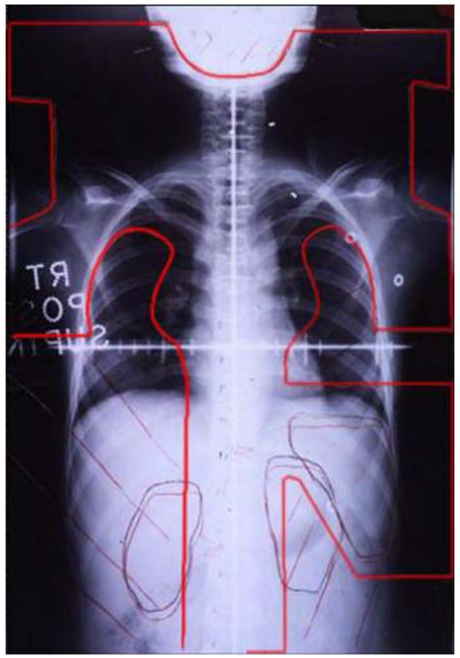


Skin Cancer

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

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



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ORIGINAL ARTICLE

Breast Cancer and Other Second Neoplasms after Childhood Hodgkin's Disease

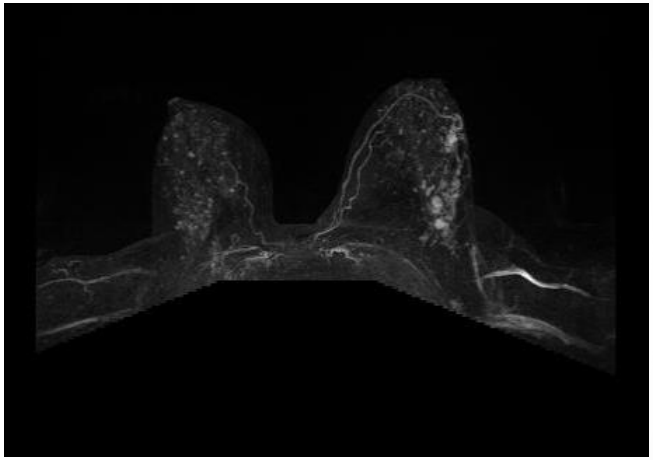
Smita Bhatia, M.D., M.P.H., Leslie L. Robison, Ph.D., Odile Oberlin, M.D., Mark Greenberg, M.B., Ch.B., Greta Bunin, Ph.D., Franca Fossati-Bellani, M.D., and Anna T. Meadows, M.D.

N Engl J Med 1996; 334:745-751 | March 21, 1996 | DOI: 10.1056/NEJM199603213341201

Share:

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



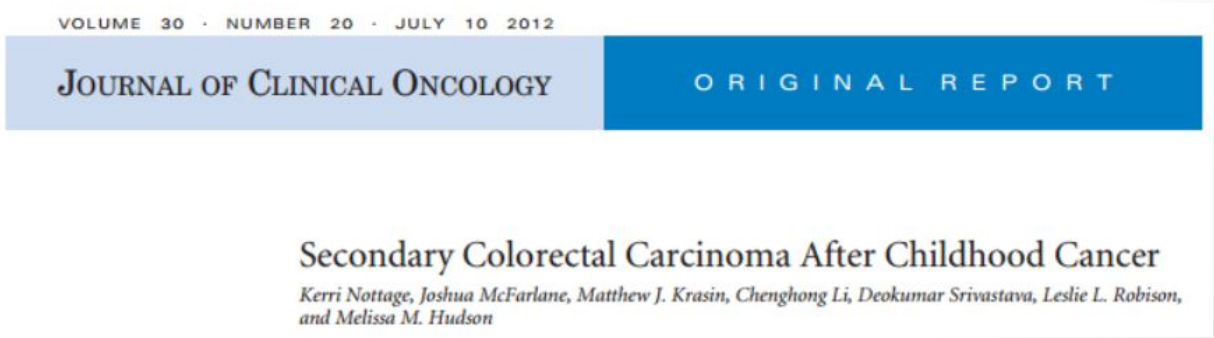
Int J Radiat Oncol Biol Phys. 2008 Sep 1;72(1):34-40. doi: 10.1016/j.ijrobp.2008.04.068.

Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease.

Basu SK[1], Schwartz C, Fisher SG, Hudson MM, Tarbell N, Muhs A, Marcus KJ, Mendenhall N, Mauch P, Kun LE, Constine LS.

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.



Sarcomas

The New York Times

Books

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David Rakoff, 47, Comic Essayist, Dies

By MARGALIT FOX
Published: August 10, 2012

David Rakoff, a prizewinning humorist whose mordant, neurotic essays examined everything from his surreal stint portraying Sigmund Freud in a Christmastime shop window display to his all-too-real battles with cancer, died on Thursday in Manhattan. He was 47.

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Louis Lanzano/Associated Press

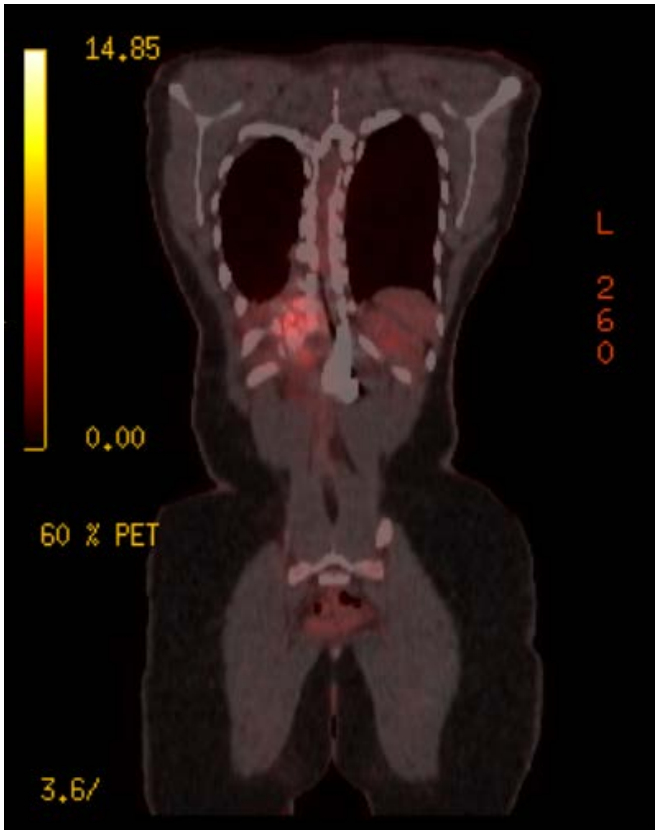
David Rakoff in Central Park in 2001. His most recent collection of comic essays, "Half Empty," was published in 2010.

His death was announced by his mother, Gina Shochat-Rakoff. Mr. Rakoff's cancer had first appeared when he was 22 and recently reappeared as a tumor in his left shoulder.

The return of his cancer, and the possibility that his arm and shoulder would have to be amputated, were the subjects of the concluding essay in Mr.

Related

ArtsBeat: David Rakoff, A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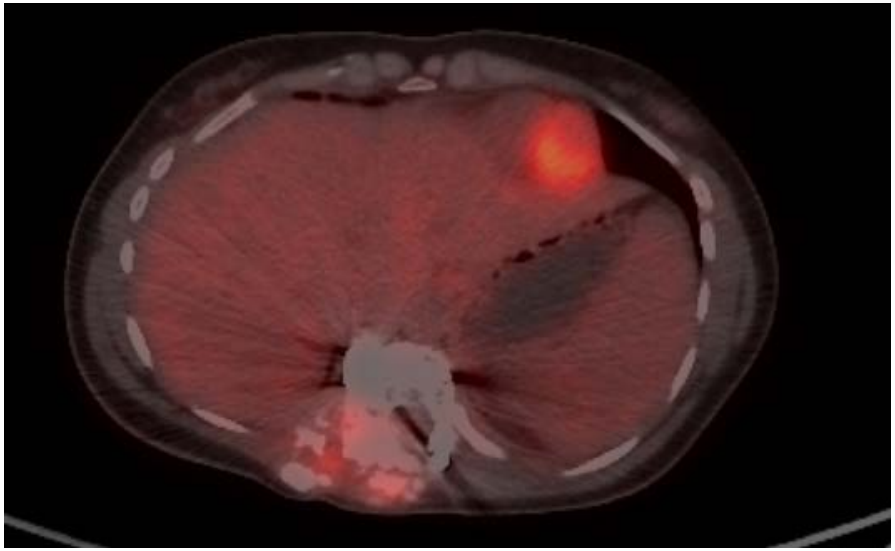
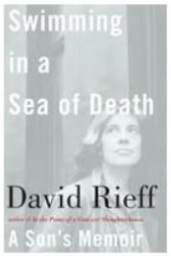


Myelodysplasia and AML

- Myelodysplastic syndrome (MDS) and AML associated with:
- Chemotherapy
  - Alkylating agents
  - Topoisomerase II inhibitors (VP 16 also called Etoposide)
- Radiation therapy

David Rieff
The Guardian, Saturday 31 May 2008



Buy Swimming in a Sea of Death at the Guardian bookshop

Swimming in a Sea of Death: A Son's Memoir

by David Rieff

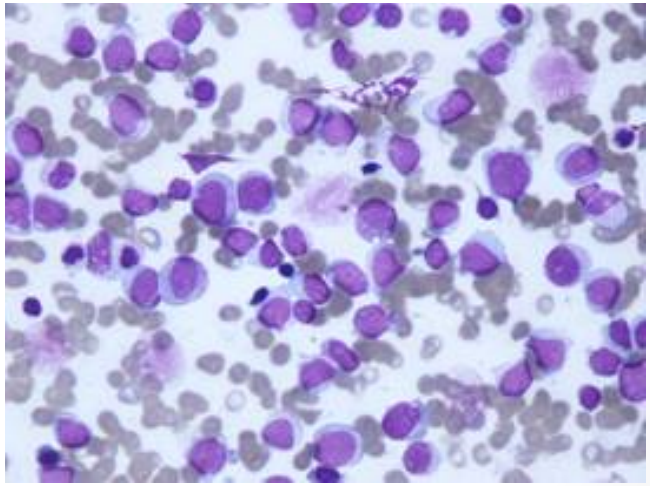
192pp, Granta, £12.99

When a partner or parent dies, it's not just loss people feel, but guilt. For David Rieff, whose mother, Susan Sontag, died of leukaemia at the age of 71 in 2004, the guilt is still gnawing four years on. He was there when his mother visited consultants and lay in a hospital bed; no son could have been more solicitous. But the palace of guilt has many pavilions, and as well as suffering from survivor's guilt and filial guilt he's haunted by a sense of failure: "I still cannot believe that there was nothing I could do to help."

Myelodysplasia and AML

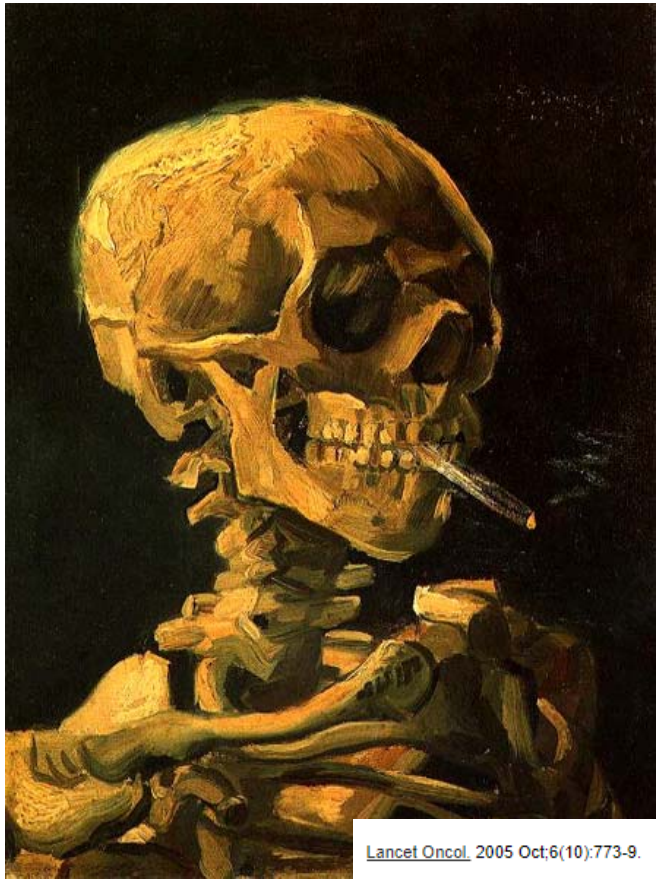
- Etoposide related AML:
  - Short latency period of about 30 months
  - Poor prognosis
  - Chromosomal translocations of the MLL gene at chromosome band 11q23

- Alkylating agent related AML:
  - 5-10 years post treatment
  - Risk plateaus after 10 years
  - Prognosis poor



Lung cancer

- Smoking after therapy for Hodgkin lymphoma



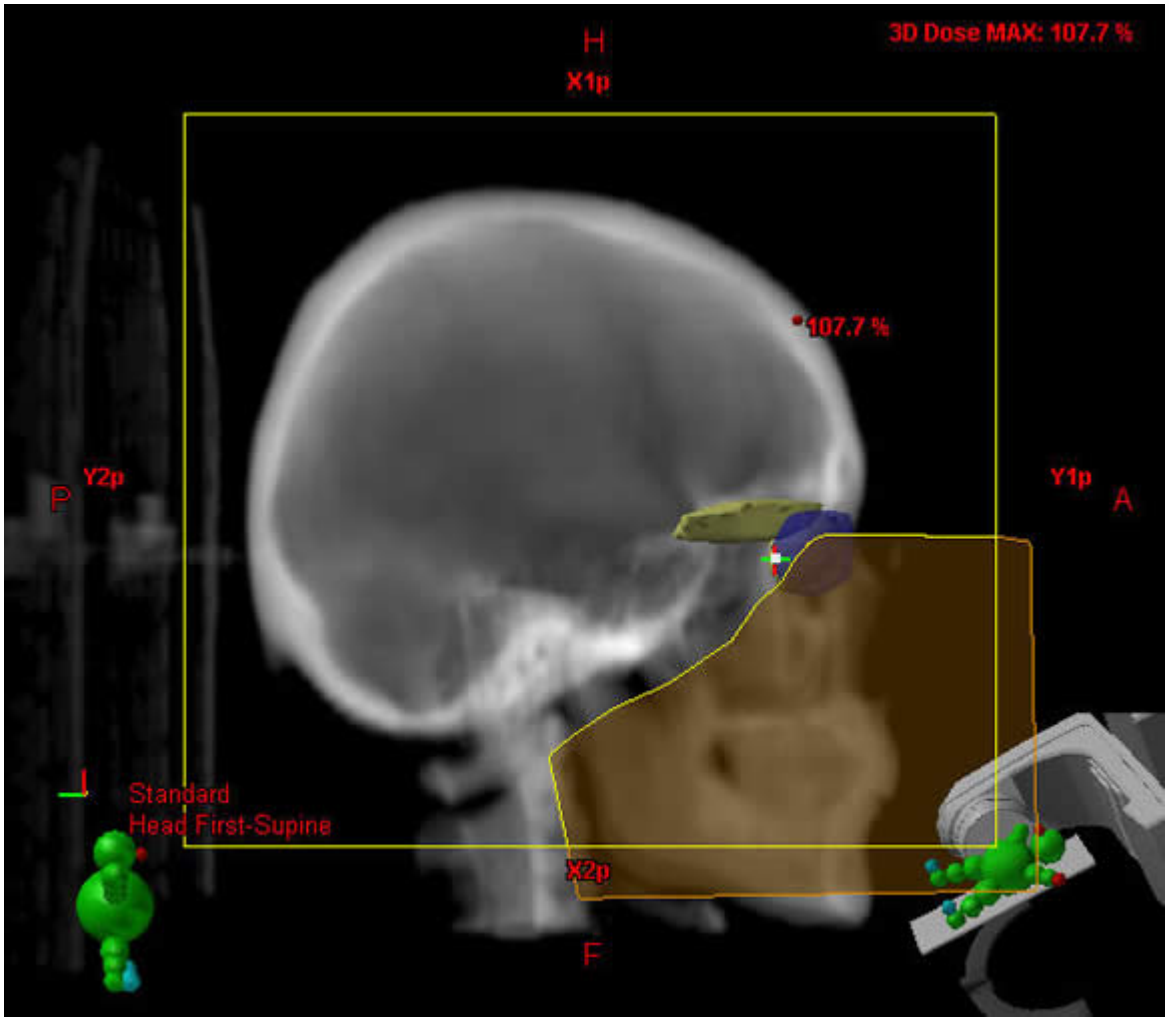
Lancet Oncol. 2005 Oct;6(10):773-9.

Lung cancer after treatment for Hodgkin's lymphoma: a systematic review.

Lorigan P[1], Radford J, Howell A, Thatcher N.

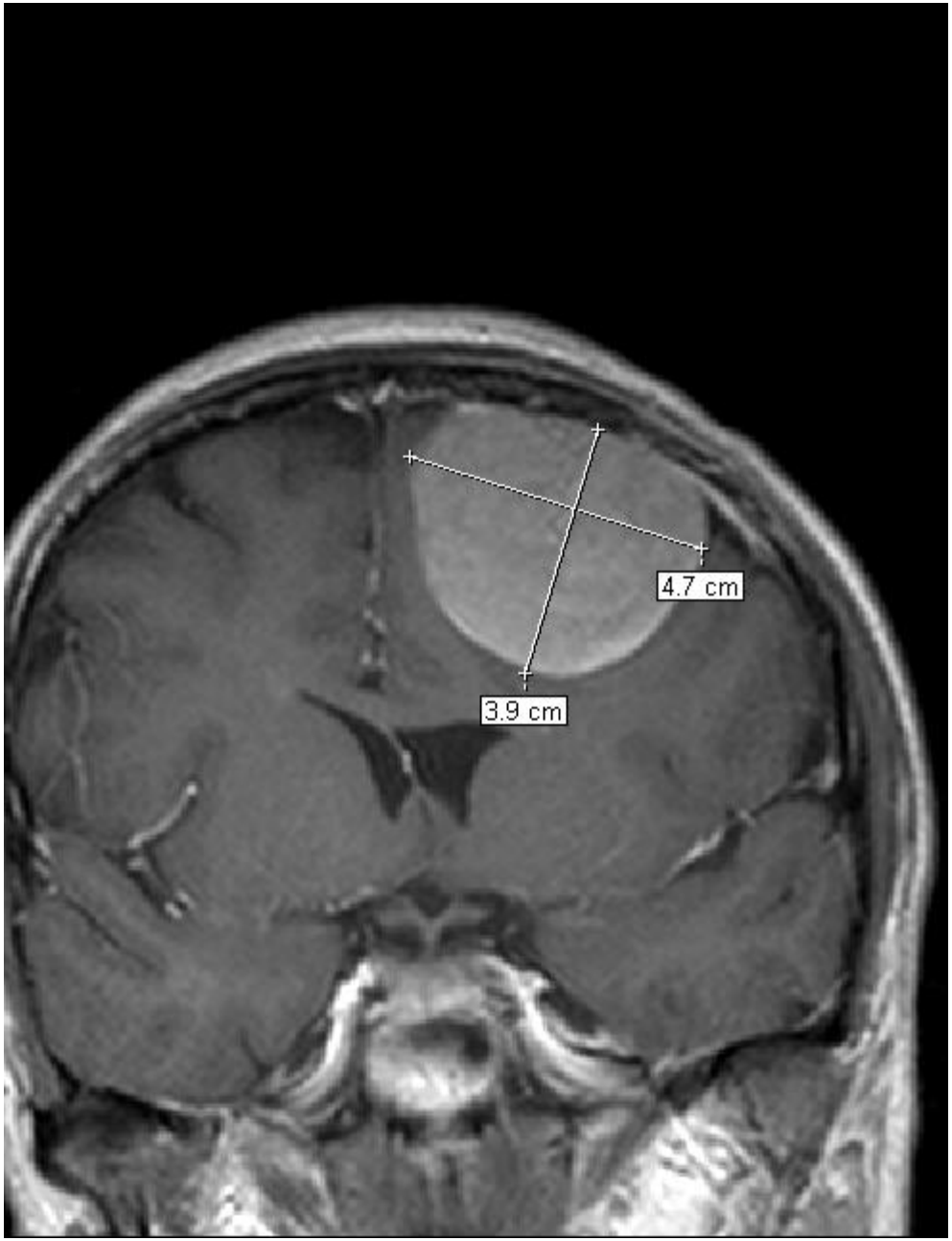
After Acute Leukemia Rx

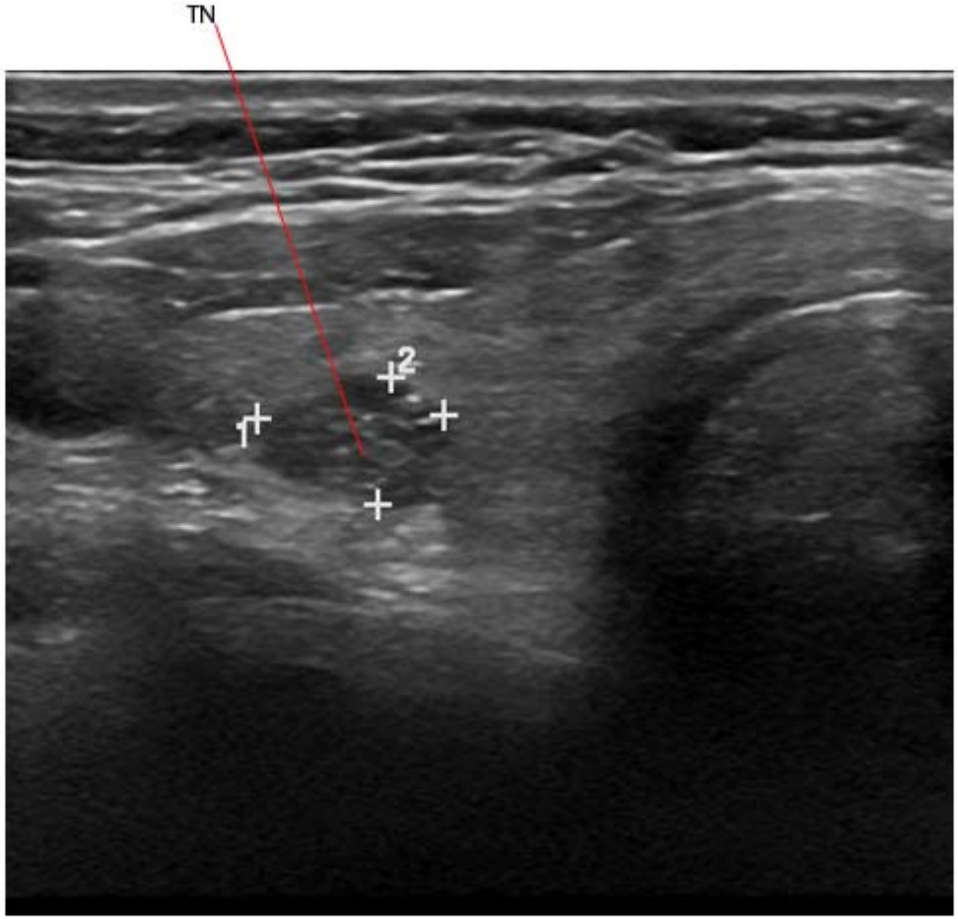
- 35 year old man treated at the age of 7 for high risk acute lymphoblastic leukemia
- Chemotherapy included:
  - Adriamycin
  - IV and IT Methotrexate
- Prophylactic, low dose cranial radiation therapy (18 Gy in 10#)


H
X1p
3D Dose MAX: 107.7 %
107.7 %
P
Y2p
Y1p
A
Standard
Head First-Supine
X2p
F

Health Risks after ALL Rx

- 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 goiter)
  - Meningioma
  - Malignant brain tumor (very small risk)
- Increased risk of stroke and vascular disease


4.7 cm
3.9 cm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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

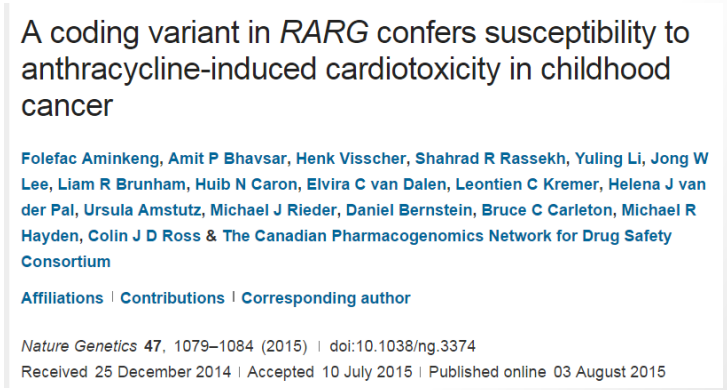
Impact on Life

- 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”

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



A coding variant in *RARG* confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer

Folefac Aminkeng, Amit P Bhavsar, Henk Visscher, Shahrad R Rassekh, Yuling Li, Jong W Lee, Liam R Brunham, Huib N Caron, Elvira C van Dalen, Leontien C Kremer, Helena J van der Pal, Ursula Amstutz, Michael J Rieder, Daniel Bernstein, Bruce C Carleton, Michael R Hayden, Colin J D Ross & The Canadian Pharmacogenomics Network for Drug Safety Consortium

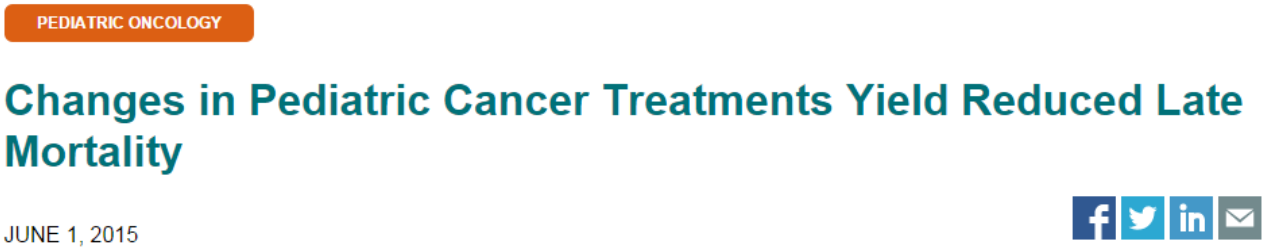
Affiliations | Contributions | Corresponding author

Nature Genetics **47**, 1079–1084 (2015) | doi:10.1038/ng.3374

Received 25 December 2014 | Accepted 10 July 2015 | Published online 03 August 2015

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



Lifestyle

Cancer Survivors Who Stay Active Live Longer

By GRETCHEN REYNOLDS MAY 16, 2012 12:01 AM 81 Comments

Prevention

- Lifestyle:
  - Diet
  - Exercise
  - Smoking
  - Sun/UV exposure


TODAY'S
SPECIALS
NO ICE CREAM


No ice cream

Prevention

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

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

Guidelines

Pediatric Blood & Cancer

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Clinical Practice Guidelines

A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: A report from the international late effects of Childhood Cancer Guideline Harmonization Group†

Leontien C.M. Kremer MD, PhD ✉, Renée L. Mulder MSc, Kevin C. Oeffinger MD, Smita Bhatia MD, MPH, Wendy Landier RN, PhD, Gill Levitt MD, Louis S. Constine MD, W. Hamish Wallace MD, Huib N. Caron MD, PhD, Saro H. Armenian MD, MPH, Roderick Skinner MB, PhD, Melissa M. Hudson MD

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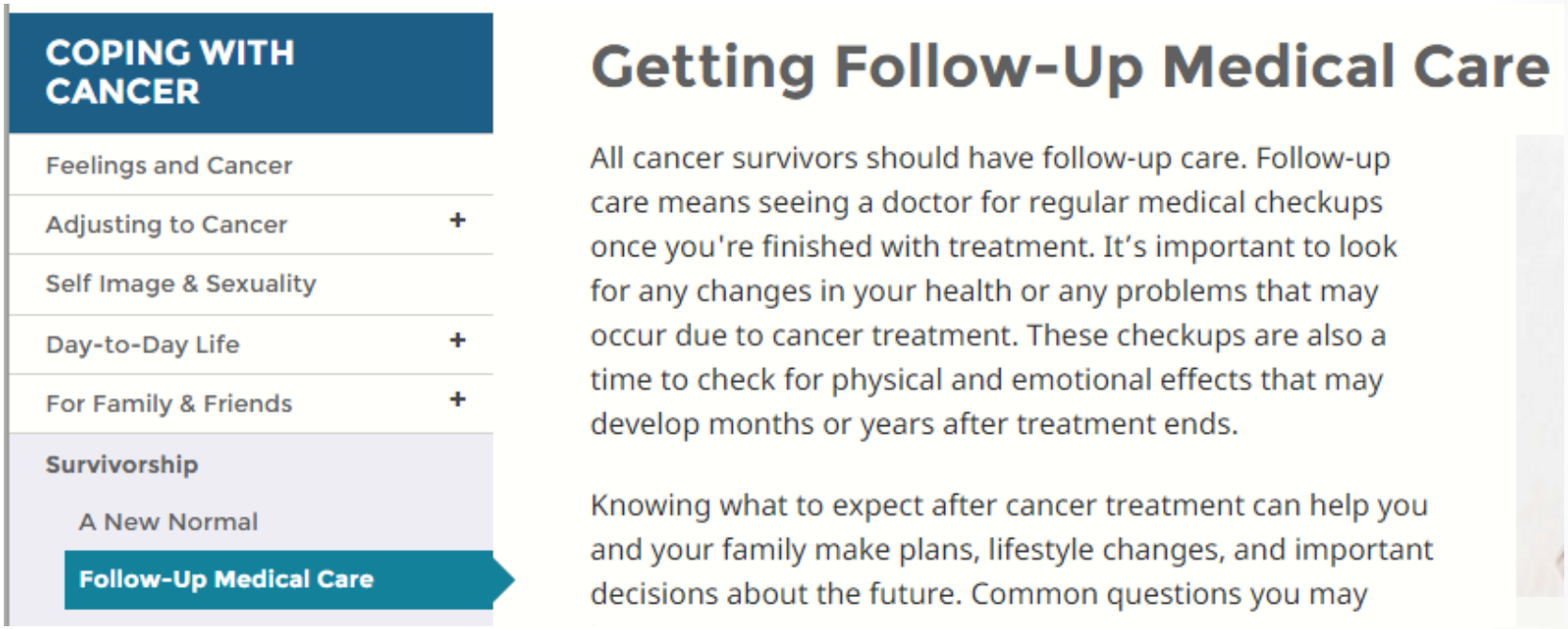
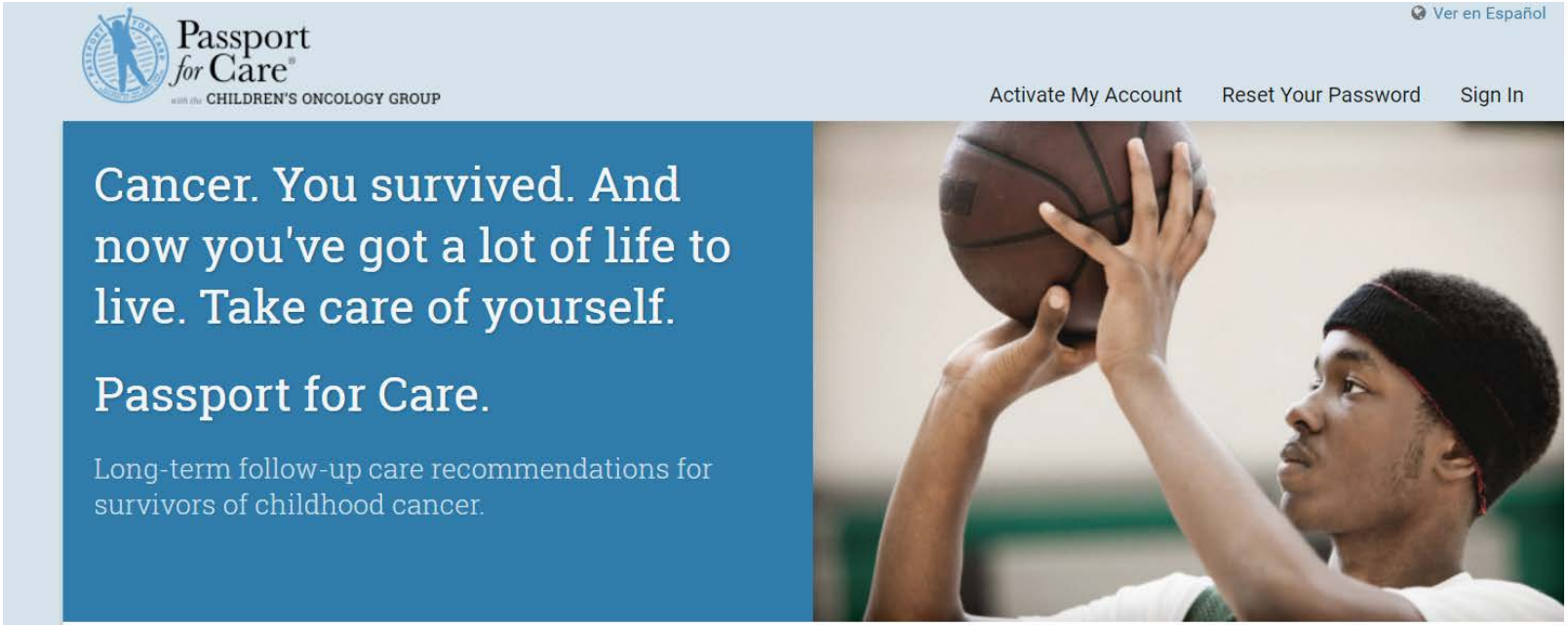
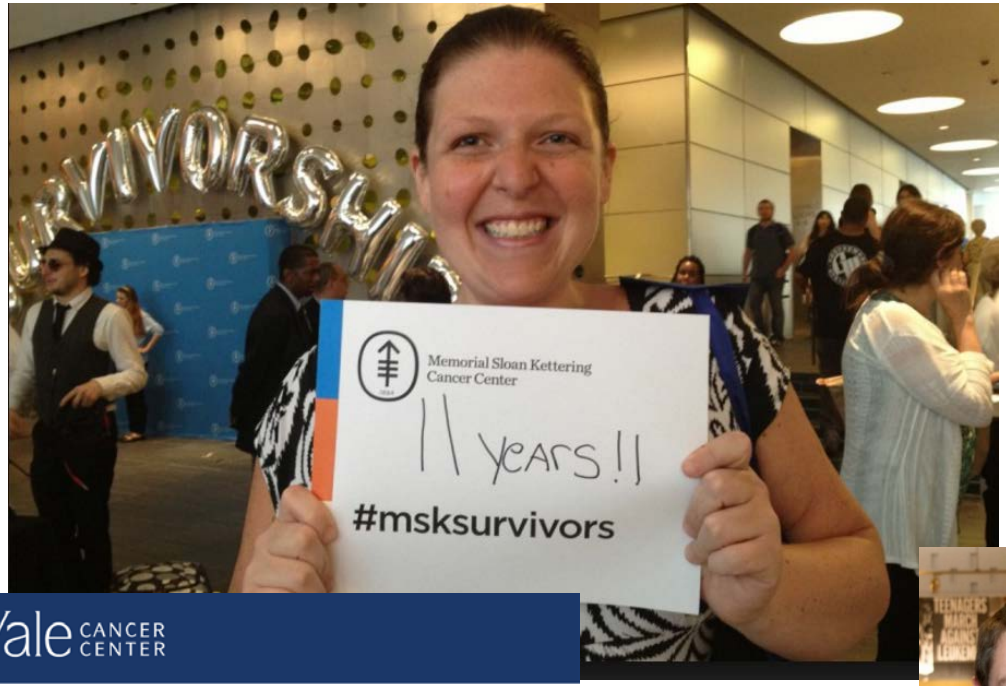
Follow-up Care Plan

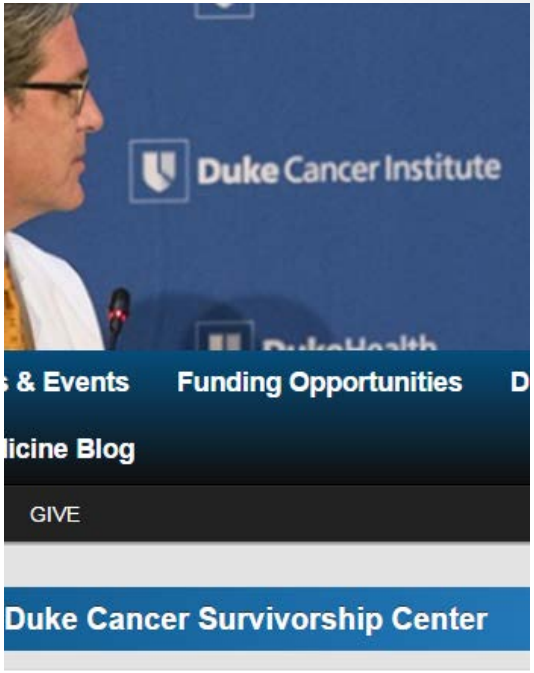


Passport for Care



Survivorship Clinics





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Survivorship Clinic

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Appointments at Mayo Clinic

Mayo Clinic offers appointments in Arizona, Florida and Min
Mayo Clinic Health System locations.

Survivorship Clinic

The Seattle Cancer Care Alliance Survivorship Clinic offers treatment, support, and edu
treatment is complete.

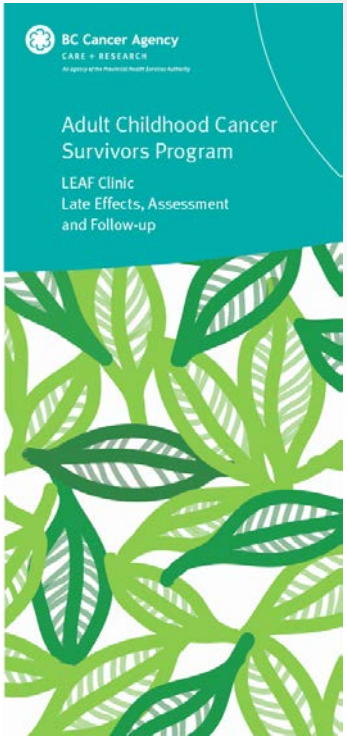
To schedule a clinic appointment please call (206)288-1024 and ask for the "Survivorship Clinic".

Departments and Centers

Cancer survivorship clinics

BC CANCER

LEAF Clinic

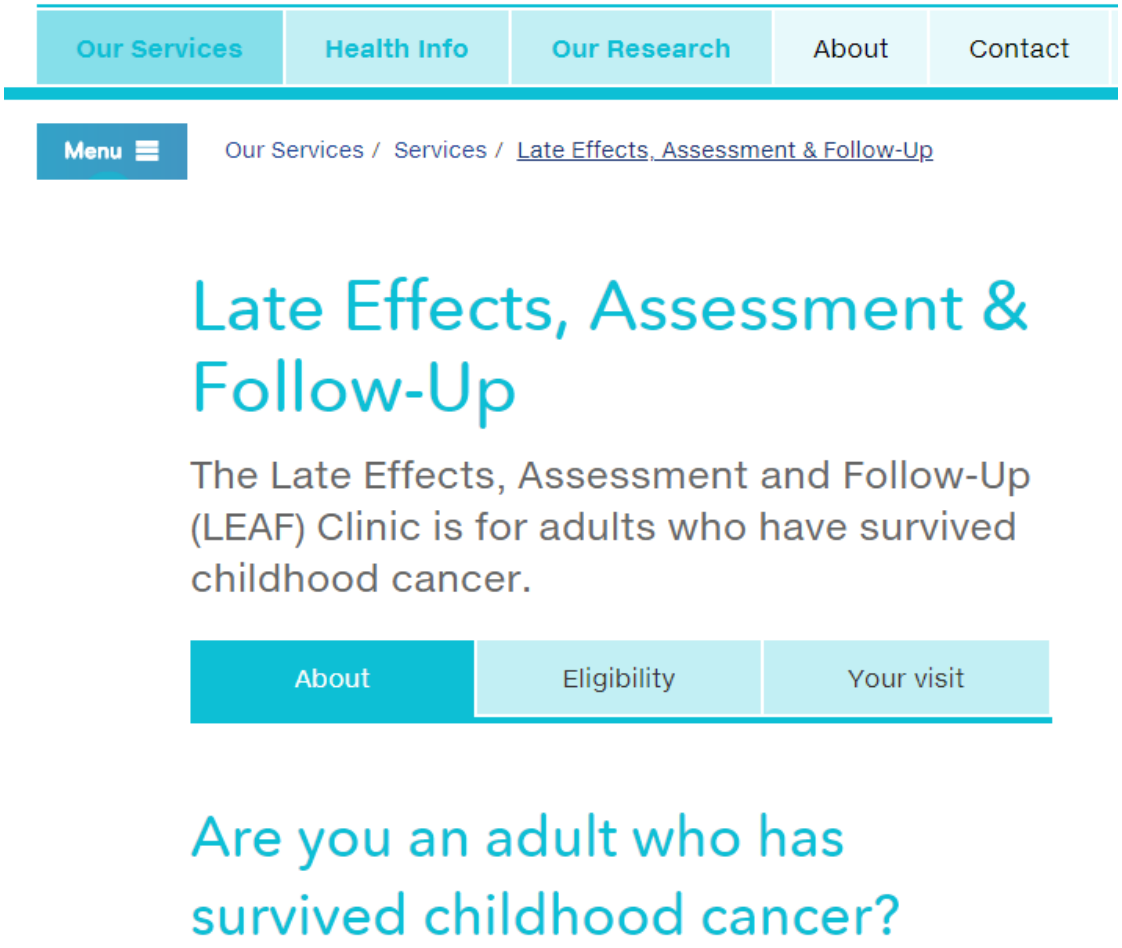


- Provincial survivorship program essential
  - Medical care
    - Detect and monitor for late effects
      - Screening
      - Coordinate specialist and primary care
  - Psychosocial support
    - Family counseling
    - Develop
      - Links with rehab programs
      - Support groups
      - Wellness 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 and severity of late effects and improve survivor's quality of life

LEAF Team

- LEAF Administrative Lead: Avril Ullett
- Medical Lead: Karen Goddard
- Nurse practitioner: Kimberley-Anne Reid
- Family counseling:
  - Bronwyn Barrett
  - Sharon Paulse

LEAF Clinic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Our Services / Services / Late Effects, Assessment & Follow-Up
Late Effects, Assessment & Follow-Up
The Late Effects, Assessment and Follow-Up (LEAF) Clinic is for adults who have survived childhood cancer.
About
Eligibility
Your visit
Are you an adult who has survived childhood cancer?

UBC CPD E-learning

Late Effects of Childhood Cancers

0.75 Mainpro+ / MOC Section 1 credits

Target Audience: Family physicians, specialists and other health care professionals in British Columbia involved in the health care of adult patients who are survivors of childhood cancer

Guests can not access this course, please try to log in. If you do not have an account, create a new account (it's free!).

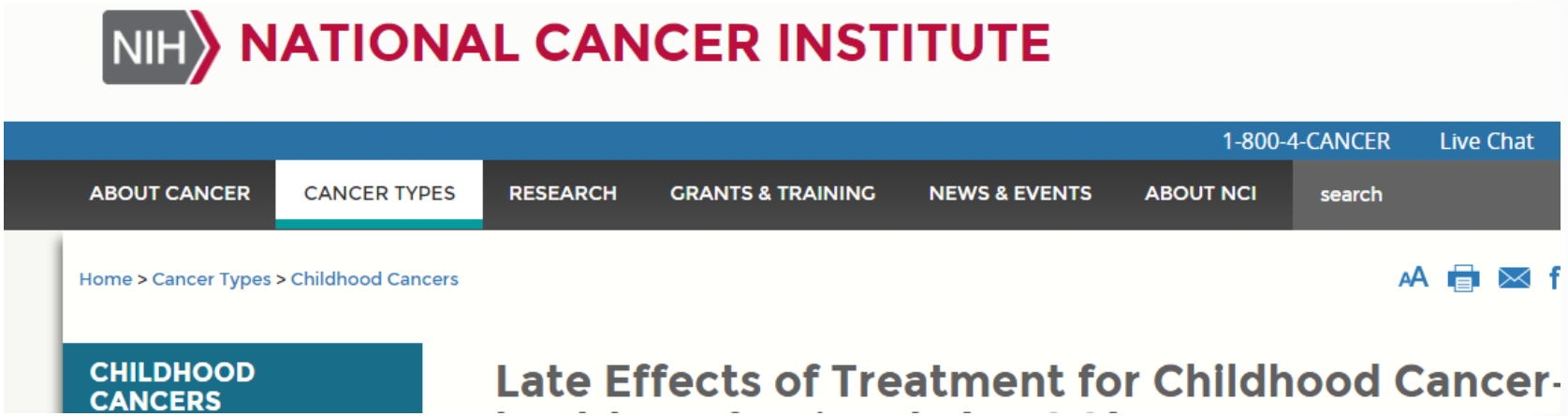
Continue

Other Resources

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

Other Resources

- National Cancer Institute:




What didn't kill me
made me Stronger

Thank you!

- Karen Goddard
  - kgoddard@bccancer.bc.ca