Survivorship, Late Effects & Childhood Cancer

Karen Goddard

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CARE + RESEARCH
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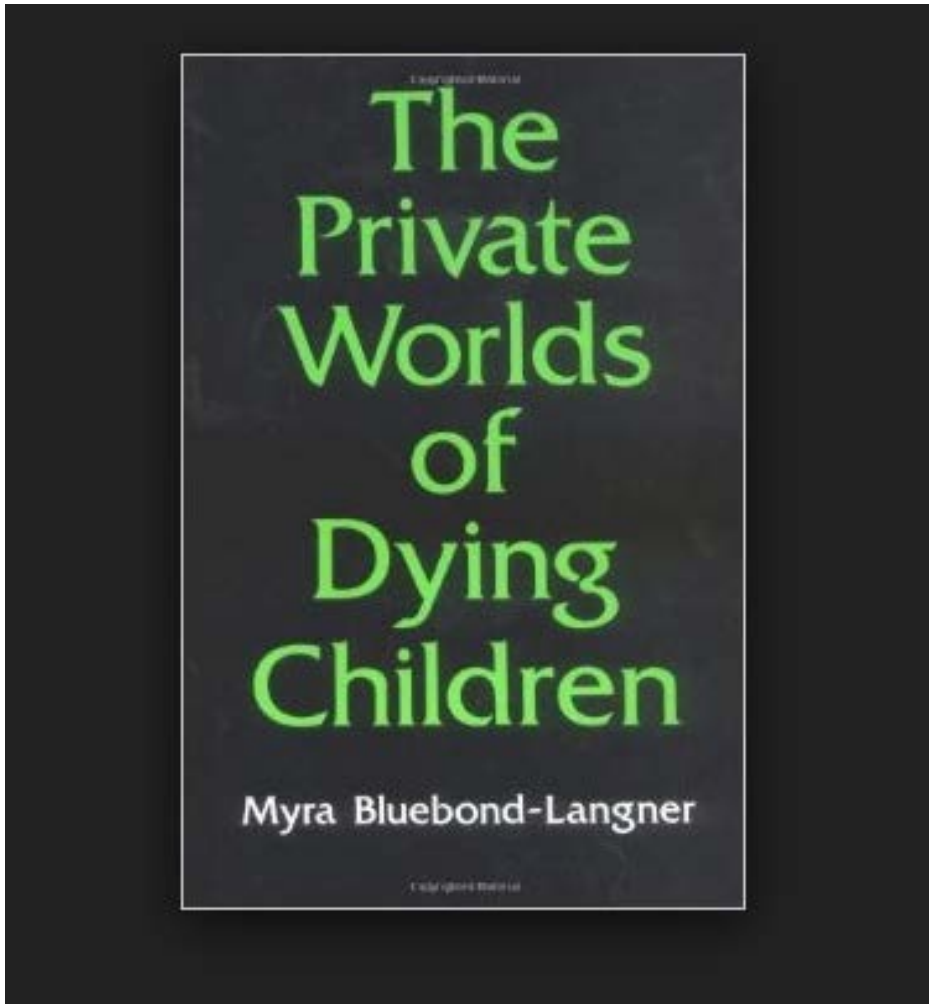
Conflicts of Interest

- None

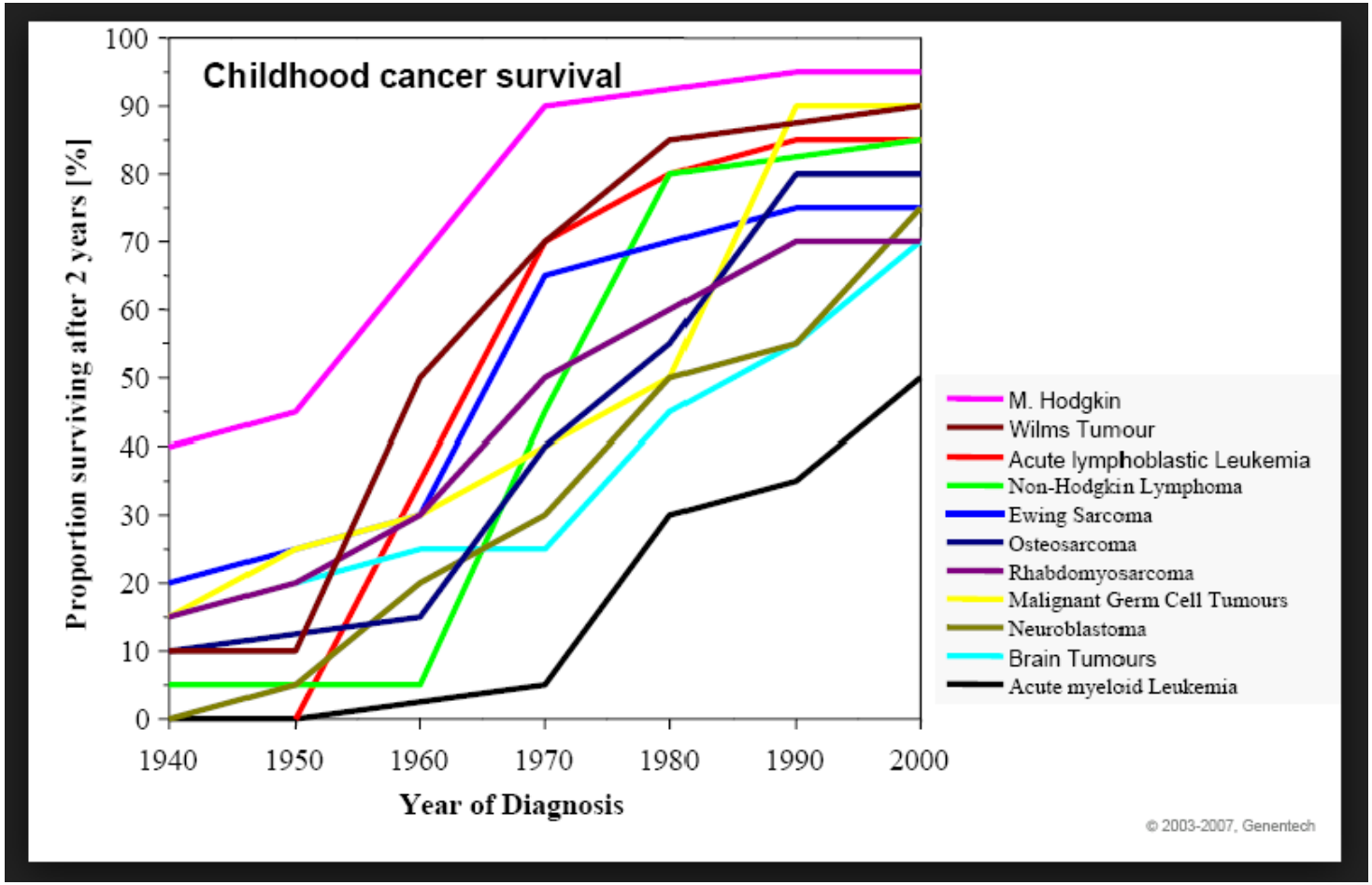
Objectives

- Consider
  - Childhood cancer treatments and cure rates
  - Survivorship
  - Late effects
    - Definition
    - Causes
    - Nature
      - Physical
        - Organ function
        - Second cancers
      - Psychological
  - Prevention
  - Health care implications
  - How can we best support survivorship?

Published in 1978



Survival Rates



Improvement related to

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

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
- 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

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.

Ellen Stovall

Ellen L. Stovall is a 42-year survivor of three bouts with cancer and has been advocating for more than 30 years to improve cancer care in America. Ms. Stovall is the Senior Health Policy Advisor at the National Coalition for Cancer Survivorship and was a founding member of the Institute of Medicine's National Cancer Policy Board and its successor, the National Cancer Policy Forum. The Forum allows government, industry, academic and survivor advocacy representatives to meet and privately discuss public policy issues that arise in the prevention, control, diagnosis and treatment of cancer.

Survivorship

Life, Interrupted: Am I a Cancer Survivor?

By SULEIKA JAOUAD

Seamus McKiernan.

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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

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Late Effects

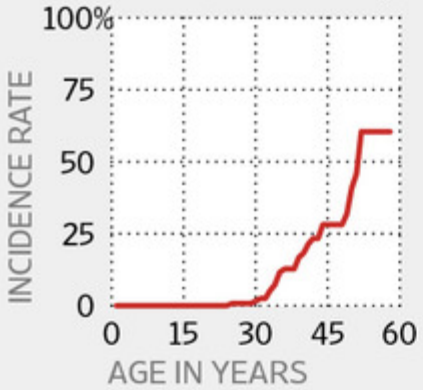
- At age 45 years:
  - 95.5% cumulative prevalence of any chronic health condition
  - 80.5% (95% CI, 73.0%-86.6%) for a serious/disabling or life-threatening chronic condition

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.

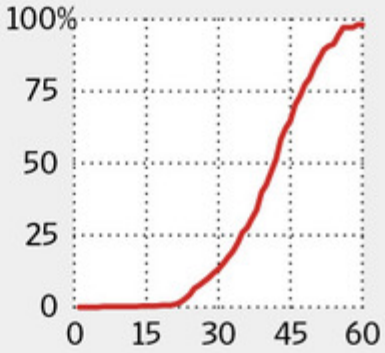
Adult condition: Breast cancer

Childhood treatment: Radiation to the breast (females only)



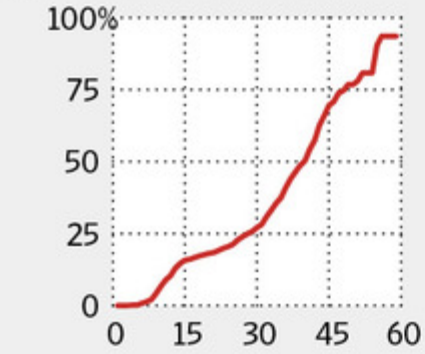
Heart-valve disorder

Radiation to the heart



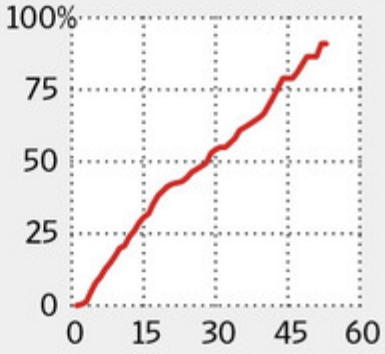
Pituitary dysfunction

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

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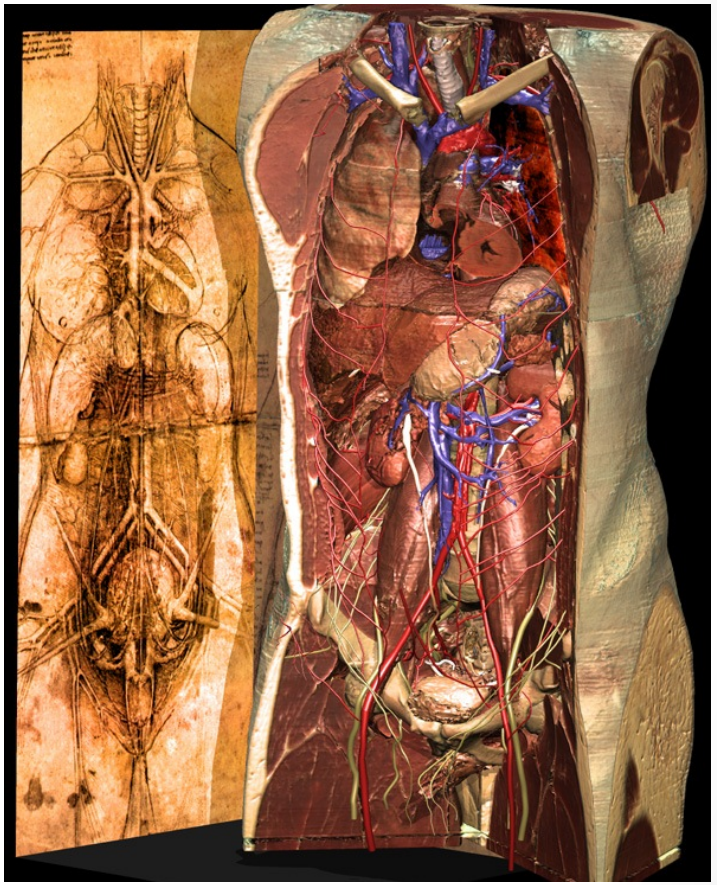
Organs at Risk

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



Causes

- Tumor related
- 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

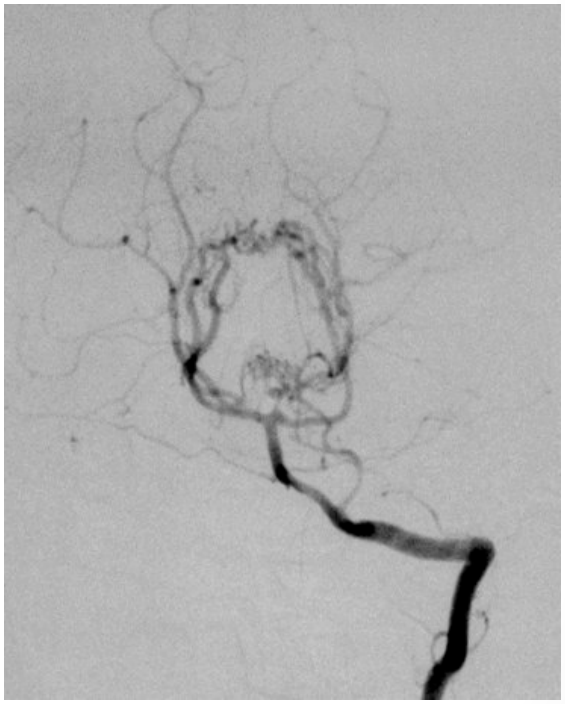
- Chemotherapy prime modality for systemic control
- Depends on agent and sensitivity of target organs
  - Adriamycin – cardiomyopathy
  - Cisplatin – nephrotoxicity and hearing loss
  - Alkylating agents – infertility and second cancers
  - Vincristine and peripheral neuropathy

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:
    - Ataxia-telangectasia
    - Radio-genomics

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

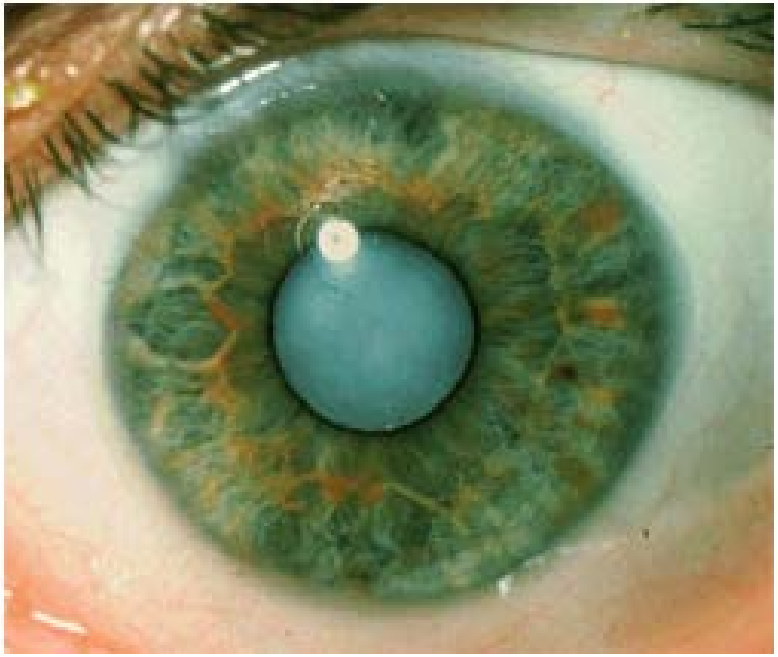


CNS: Brain Tumors

- Long term 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

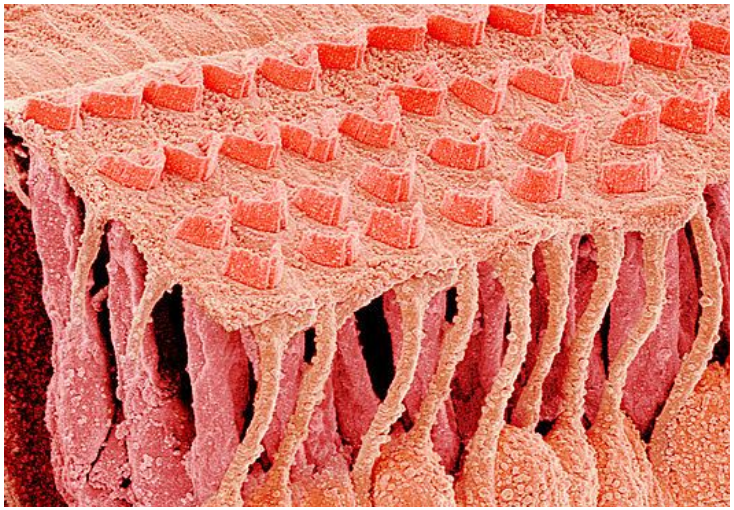
Eye

- Visual loss
  - High dose RT:
    - Anterior chamber damage
    - Acute glaucoma
    - Painful red eye
    - Treated by enucleation
  - Low dose RT:
    - Cataracts



Hearing loss

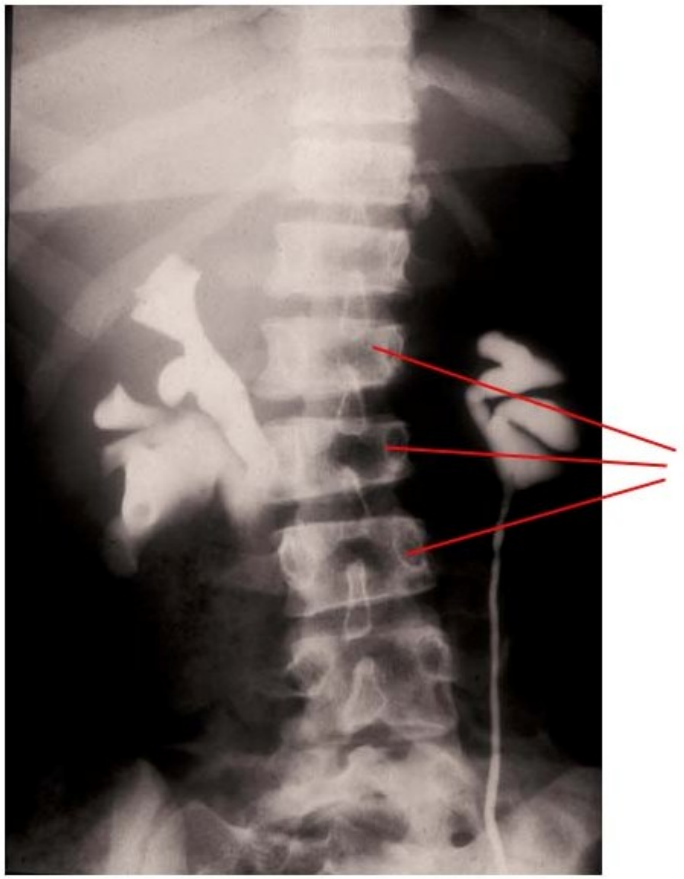
- Radiation Therapy:
  - Conductive: wax build up
  - Sensorineural: direct damage to cochlea
- Chemotherapy:
  - Sensorineural
  - Cisplatin causes high frequency hearing loss
    - Sensory hair cells in the cochlea



Musculoskeletal

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

Musculoskeletal

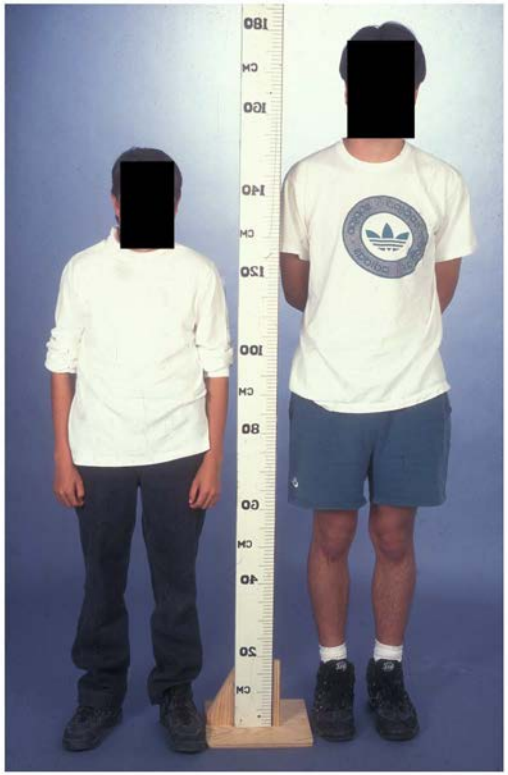


Facial Hypoplasia

- Lucy Grealy " *Autobiography of a face*"

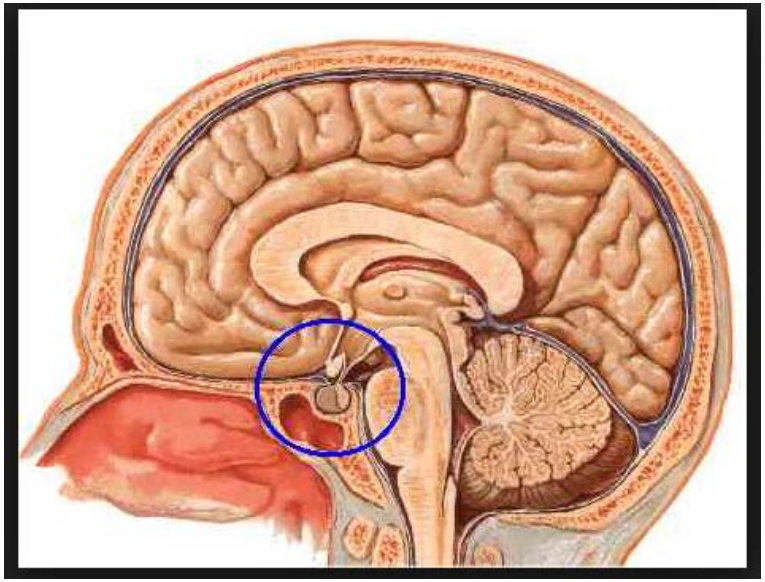
Musculoskeletal

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



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

Cardiovascular disease

- 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

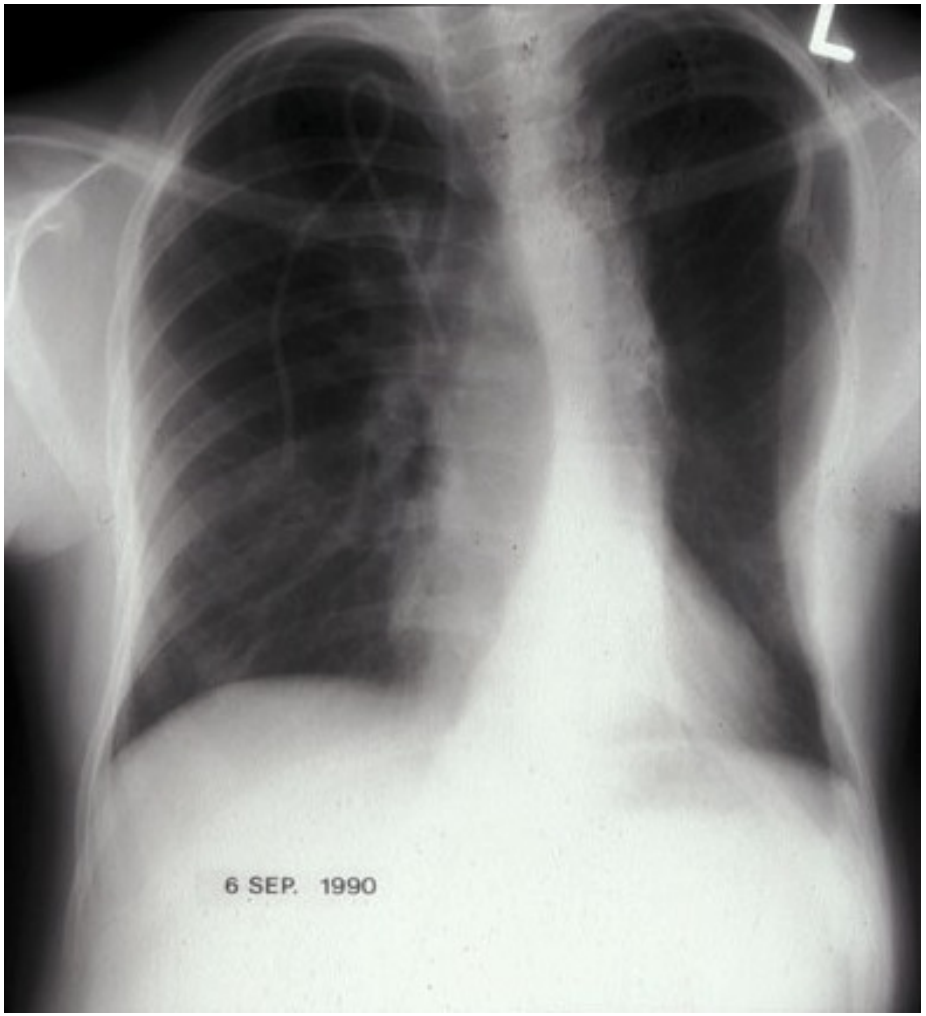
GU/Renal disease

- 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

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

Chest wall deformity:

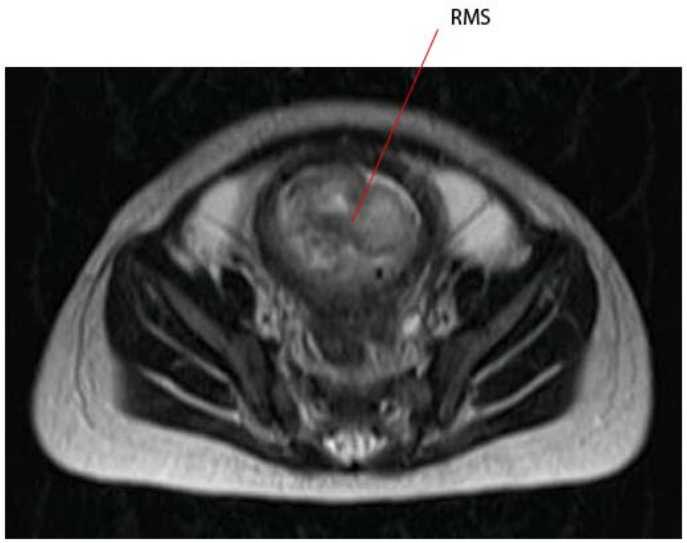


GI disease

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

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



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

Causes

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

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

Causes

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

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

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**
- 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%

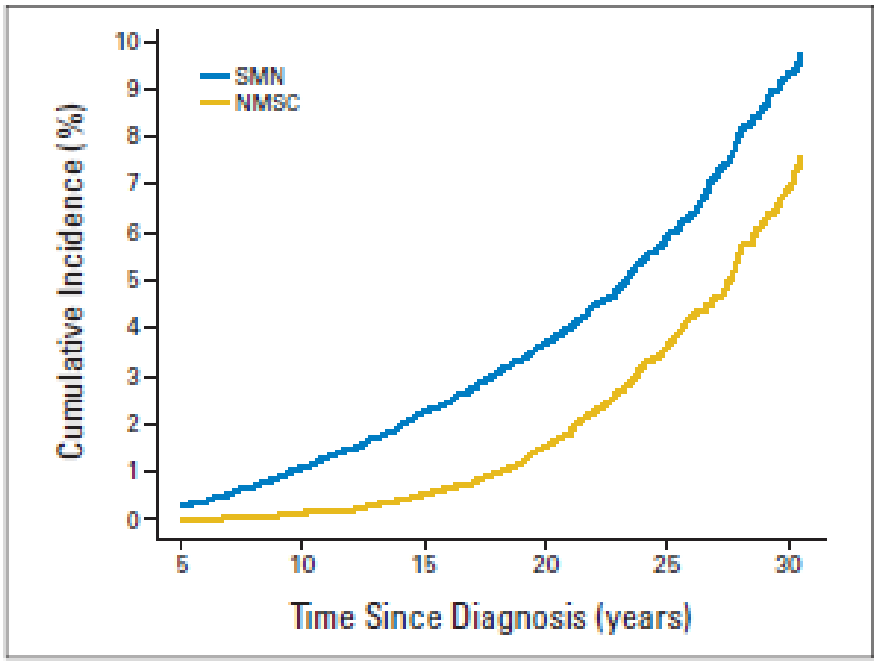


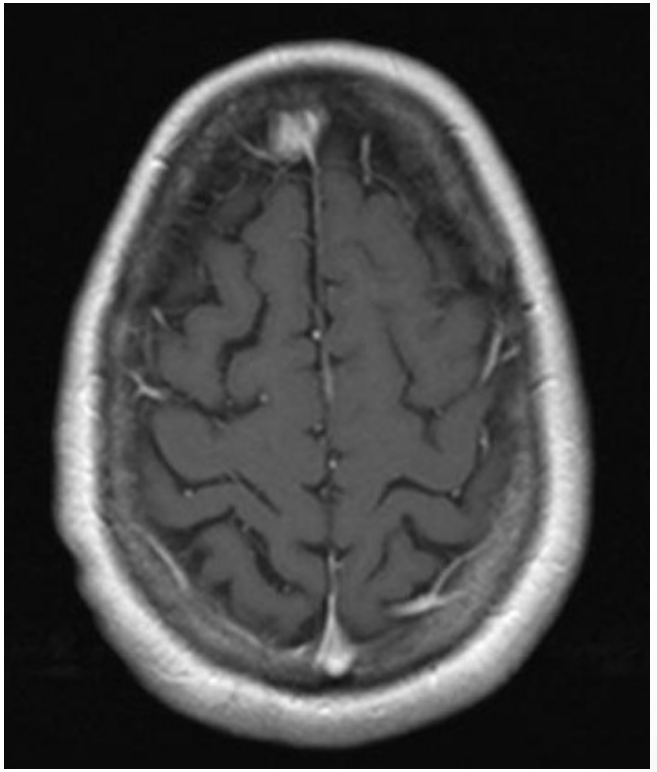
Fig 1. Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At the 30-year follow-up, the cumulative incidence of SMNs and NMSC continues to increase with time since 5 years after diagnosis of primary childhood cancer.

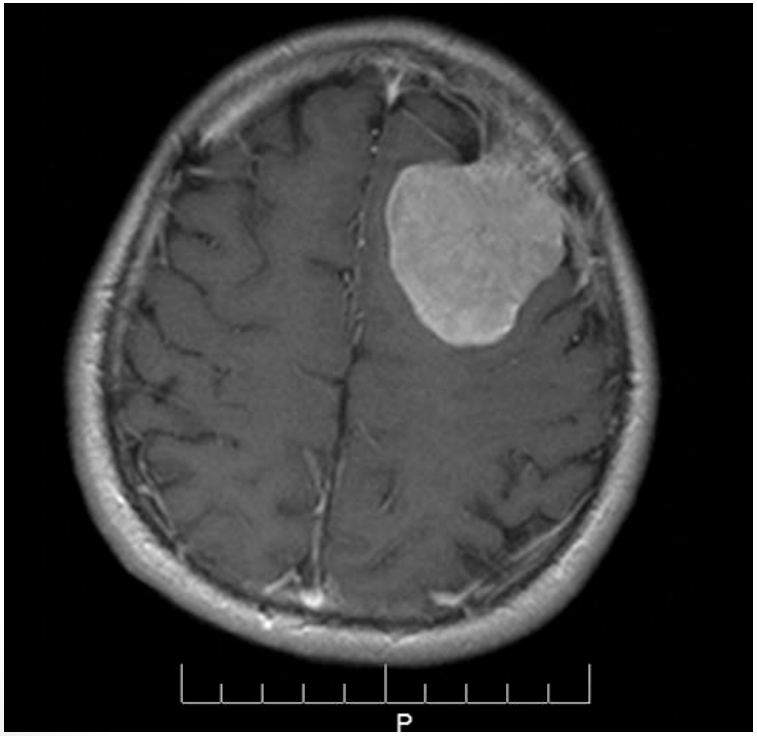
Types of Secondary Tumors

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

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

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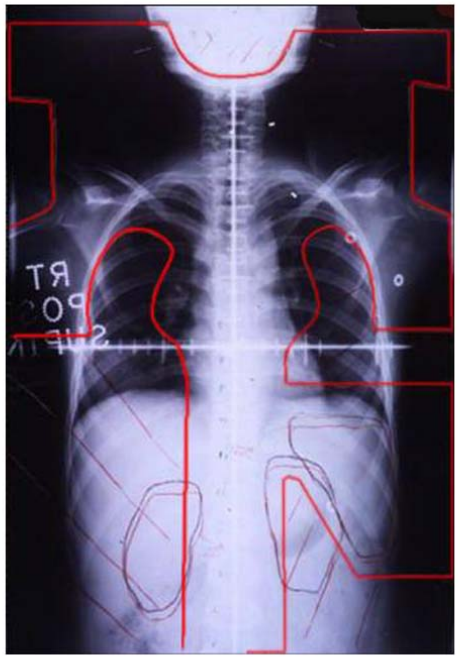
Breast Cancer

- 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

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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

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.

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Secondary Colorectal Carcinoma After Childhood Cancer

Kerri Nottage, Joshua McFarlane, Matthew J. Krasin, Chenghong Li, Deokumar Srivastava, Leslie L. Robison, and Melissa M. Hudson

Sarcomas

The New York Times

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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.

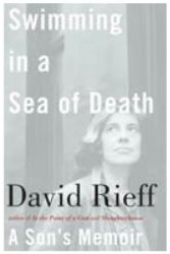
Related

ArtsBeat: David Rakoff, A

Myelodysplasia and AML

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

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

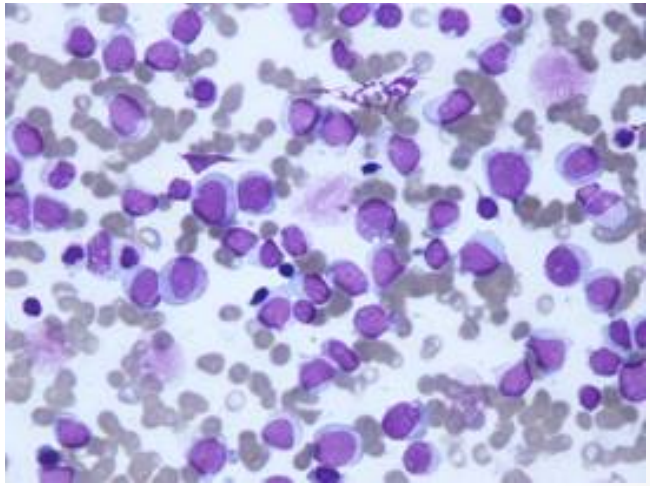
192pp, Granta, £12.99

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

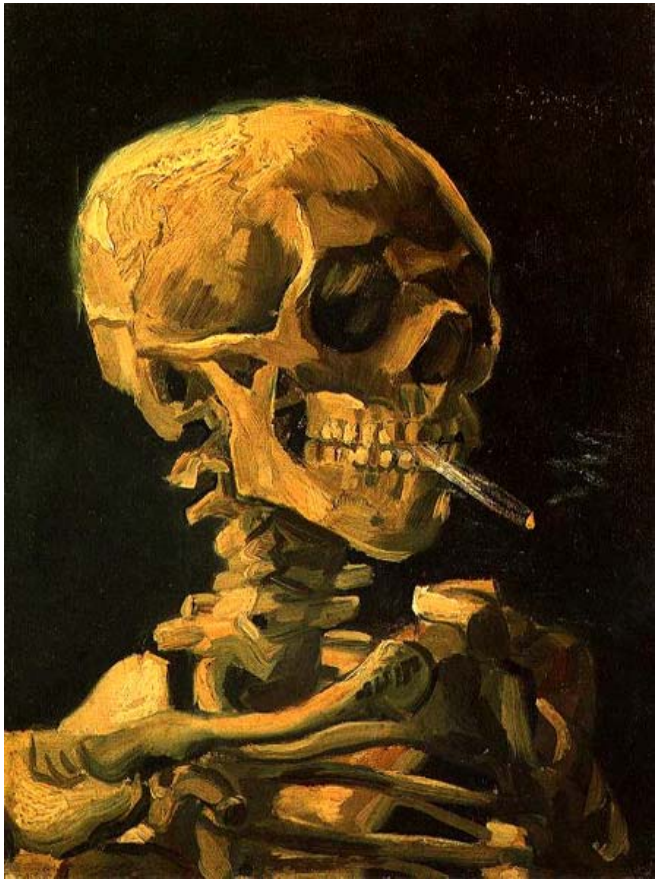
- Etoposide related AML:
  - Short latency period of about 30 months
  - Poor prognosis
  - Chromosomal translocations of the MLL gene at chromosome band 11q23

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



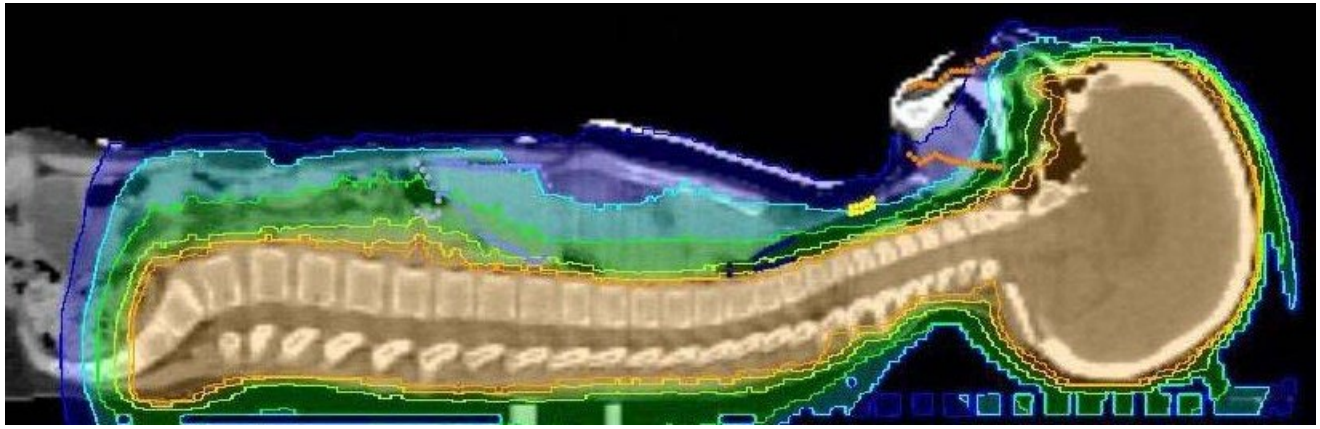
Lung cancer

- Smoking after therapy for Hodgkin lymphoma



Craniospinal RT:

- Multiple late effects:



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

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
  - Tailored therapy
    - Genomic studies to identify people more likely to develop side 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

PEDIATRIC ONCOLOGY

Changes in Pediatric Cancer Treatments Yield Reduced Late Mortality

JUNE 1, 2015

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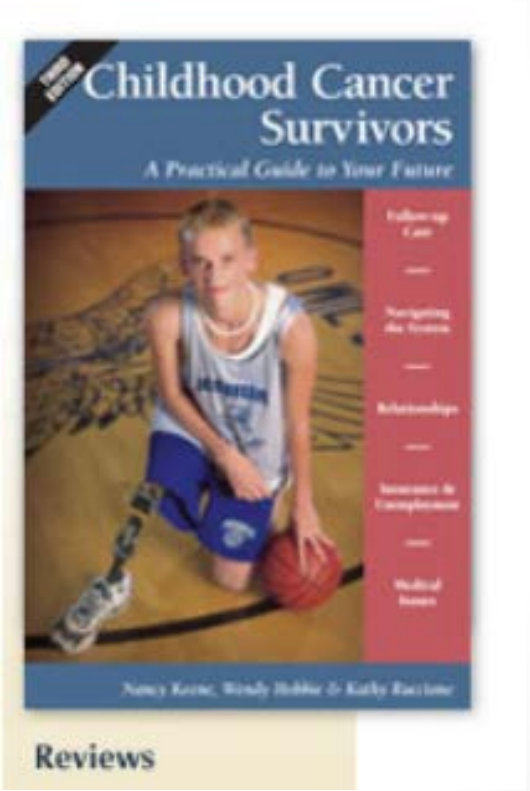
Prevention

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

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

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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

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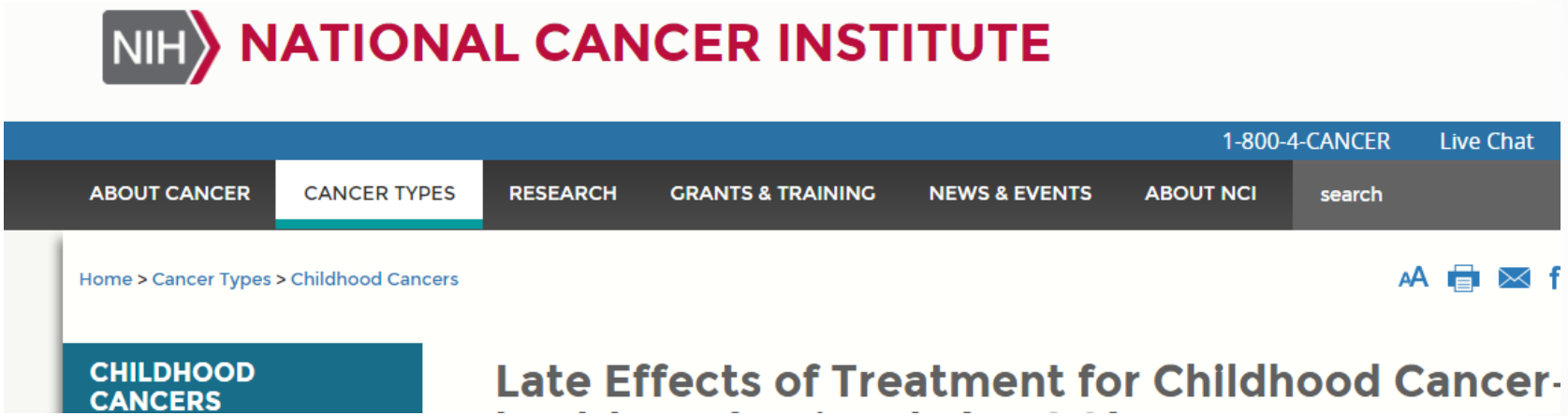
Resources

- National Cancer Institute:



Resources

[Pediatric Oncology Education Materials]

Late Effects

General Overview

- Introduction
- Resources
- References

- CNS
- Orbit
- Peripheral NS
- Hearing
- Cardiac
- Respiratory
- Musculoskeletal
- Bone Marrow
- Skin

Late Effects

General Overview

print [printer friendly] | email

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[1].

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.[2]

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)[3]
- Improved supportive care

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