



Long Term Effects for Pediatric and Young Adult Survivors of Leukemia and Lymphoma

Lone Star Blood Cancer Conference

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February 23, 2013

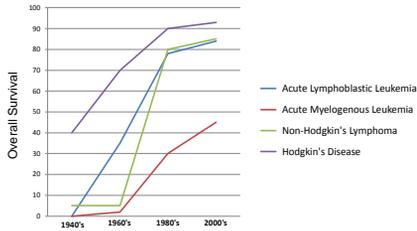
Outline:

- Introduction
- Medical Updates
 - Case Presentations
 - Fertility
- Screening for late effects
- Conclusion

Number of New Cases of Childhood Leukemia and Lymphoma

Malignancy	Per Year in the United States
Acute Lymphoblastic Leukemia	2400
Acute Myelogenous Leukemia	500
Non-Hodgkin's Lymphoma	800
Hodgkin's Disease	400
Total	4100

Improved Survival of All Childhood Leukemias and Lymphomas



Number of Survivors of Childhood Leukemia and Lymphoma

Malignancy	Number of Survivors in the United States
Acute Lymphoblastic Leukemia	50,000
Acute Myelogenous Leukemia	7,000
Non-Hodgkin's Lymphoma	19,000
Hodgkin's Disease	32,000
Total	108,000

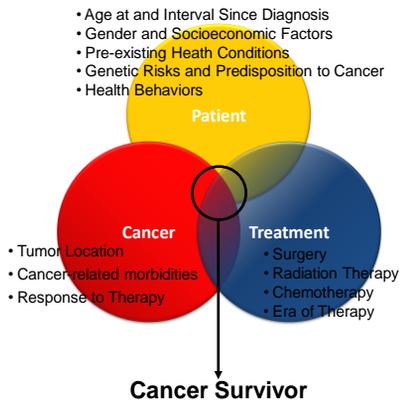
Childhood Leukemia and Lymphoma Survivorship:

- > 80% of children diagnosed with leukemia and lymphoma will be long-term survivors
- > 108,000 childhood leukemia and lymphoma survivors in the United States
- 1/1000 of young adults is a survivor of leukemia or lymphoma
- Increasingly recognized that these patients have unique long-term medical issues

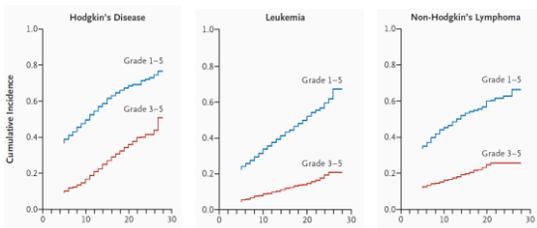
Late Effect: Any adverse medical or behavioral condition present after completion of cancer treatment and is attributable to the cancer or its treatment

Examples:

- Second cancers
- Congestive heart failure
- Infertility
- Hypothyroidism



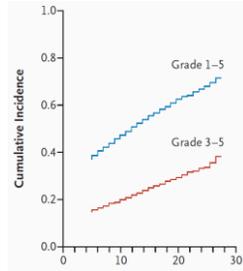
Prevalence of Chronic Health Conditions among Survivors of Childhood Leukemia and Lymphoma



Oeffinger, KC. *N Engl J Med* 2006;355:1572-1582

Types of late effects:

- Major joint replacement
- Congestive heart failure
- Secondary cancers
- Learning disabilities
- Stroke
- Kidney failure or need for dialysis
- Hearing loss and vision loss
- Infertility



Oeffinger KC *N Engl J Med* 2006;355:1572

Risks factors for chronic health conditions:

- Exposure to radiation:
- Chemotherapy
 - Anthracyclines (Doxorubicin, Daunorubicin)
 - Bleomycin
 - Alkylating agents (Cyclophosphamide)

Oeffinger KC *N Engl J Med* 2006;355:1572

Case Presentations:

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- Female survivors exposed to radiation therapy to the chest have a increased risk of breast cancer
- Radiation therapy treatment fields that increase risks of breast cancer:
 - Chest
 - Lung
 - Mantle
 - Spine
- Approximately 20% cumulative incidence of breast cancer among women treated for Hodgkin's disease with chest radiation therapy
- Risk is higher among women treated prior to age 21 years compared with older women
- Increased risk of breast cancer seen among women treated on more contemporary treatment regimens

A 30 year old woman who was treated for Hodgkin disease, including mantle field radiation therapy, at the age of 14 years, reports a new lump in her breast.

- Breast cancer onset: 8 years after radiation
- Median interval: 16 yrs after radiation
- Median age at diagnosis: early 30's
- 5 year prognosis strongly associated with stage of disease at diagnosis
- Limitations in treatment options due to previous exposures
 - Radiation
 - Anthracycline chemotherapy

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Breast Cancer Screening:

- Self-exams are important
- Screening options:
 - Mammogram
 - Ultrasound
 - MRI

When do you begin screening? Annual screening mammography starting at 25 years of age or 8 years after radiation therapy, whichever occurs last.

– COG Late Effects Screening Committee

A 30 year old woman who was treated for Hodgkin disease, including mantle field radiation therapy, at the age of 14 years, reports a new lump in her breast.

- Early screening is critical for early diagnosis of breast cancers
- Prognosis for women with secondary breast cancers:
 - Appears to be similar to women without a prior history of cancer
 - Demonstrates improved prognoses when the breast cancer is detected an earlier stage.
- Adherence with recommendations:
 - Half of women in the United States aged 25 – 39 years who had been treated with radiation to the chest have never had a mammogram or MRI
 - Half of women aged 40 – 50 years were having regular screening mammograms or breast MRI

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- Anthracycline chemotherapy (doxorubicin, daunorubicin and mitoxantrone) is used to treat nearly 40 – 50% of childhood cancers
 - Leukemia
 - Lymphoma
 - Bone tumors
 - Neuroblastoma
- Late-onset anthracycline-related cardiomyopathy may not become clinically apparent until more than two decades after exposure
- Cancer survivors are at increased risks of experiencing premature coronary artery disease, myocardial infarction, arrhythmias, pericardial disease and heart valve abnormalities

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Anthracycline-related cardiomyopathy correlates with the cumulative dose of anthracycline chemotherapy

Anthracycline dose:	Prevalence of cardiomyopathy:
< 300 mg/m ²	0 – 15 %
> 300 mg/m ²	15 – 25%

Other risk factors for late-onset cardiomyopathy:

- Duration of follow-up
- Females
- Younger age at treatment
- Radiation exposure to the heart

A 24 year old pregnant woman who was treated for high-risk acute lymphoblastic leukemia at the age of 8 years, complains of fatigue and progressively worsening shortness of breath

- Several reports: sudden onset of symptomatic congestive heart failure among pregnant women in the later stages of gestation and the peripartum period
- A report by Hinkle *et al.* described 30% of 40 pregnant women who had been treated with anthracyclines developed new-onset symptomatic heart disease, such as congestive heart failure and ventricular tachycardia
- Pregnancy should be considered a situation where pregnant women are at risk of exacerbation of symptomatic heart disease and should closely monitored for heart disease

A 28 year old man who is a survivor of acute lymphoblastic leukemia diagnosed at the age of 4 years, treated with cranial radiation therapy following a CNS relapse of the leukemia, has obesity, dyslipidemia and hypertension

- Risk factors for obesity:
 - Prior diagnosis of acute leukemia
 - Treatment with cranial radiation therapy to the hypothalamus
 - Females
 - Cancer diagnosed between the ages of 5 – 9 years
 - Decreased physical activity
 - Radiation therapy directed to the hypothalamus and pituitary gland
 - Treatment with anti-depressants
 - Physical activity was associated with reduced risks of obesity

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Screening and Interventions:

- Long-Term Follow-Up Guidelines recommendations:
 - Screened every 2 years with a fasting blood glucose and lipid profile
 - High-risk populations: patients who are exposed to radiation therapy to the brain
- Cancer survivors at risk of obesity:
 - Close monitoring of weight
 - Encouragement of healthy diets
 - Encourage increased physical activity
 - Lipid-lowering drug therapy when indicated

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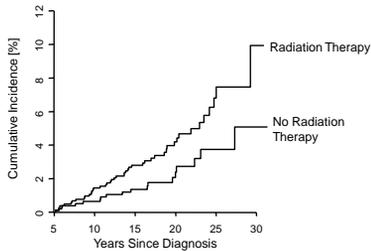
- Cognitive impairment after exposure to cranial radiation:
 - Disorders of attention
 - Short-term memory
 - Slow Processing speed
 - Impaired working memory
- High risk populations:
 - Younger children (especially children less than 6 years old)
 - Females
 - History of hydrocephalus
- Outcomes and Interventions:
 - Tutoring, special education services, accommodations at school
 - As they enter adulthood, they are less likely to become employed, drive a car and live independently

A 25 year old man, survivor of T-cell acute lymphoblastic leukemia at the age of 5 years, with cognitive impairment and obesity, has new-onset left sided weakness.

- Causes of new-onset neurological symptoms
 - Stroke
 - Secondary cancer
- Increased risk of strokes following radiation exposure:
 - Brain tumor
 - Leukemia
 - Hodgkin's disease
- Strokes are usually due to large cerebral artery occlusive disease and often occur among young adult survivors

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5+ Year Brain Tumor Survivors: Frequency of Stroke Over Time



A 25 year old man, survivor of T-cell acute lymphoblastic leukemia at the age of 5 years, with cognitive impairment and obesity, has new-onset left sided weakness.

- Causes of new-onset neurological symptoms in a cancer survivor
 - Stroke
 - Secondary cancer
- Risk factors for secondary cancers:
 - Prior treatment with radiation therapy
 - Genetic predispositions
 - Neurofibromatosis type-1
 - Li Fraumeni syndrome
- Types of secondary cancers:

Type of secondary cancer	Interval after treatment	Prognosis
High-grade glioma	< 15 years	Poor
Meningioma	> 15 years	Good

Fertility after Cancer Treatment

- Many cancer survivors are able to have children
- Infertility and gonadal dysfunction are common among certain subpopulations of survivors:
 - Children and young adults who are exposed to mid- and high-doses of alkylating agents
 - Cyclophosphamide
 - Ifosfamide
 - Busulfan
 - Procarbazine
 - Melphalan
 - Cisplatin
 - Radiation therapy to the pelvis or testes
- Recovery of fertility has occasionally been reported after years of infertility.
- Also, other chemotherapeutic drugs, such as anti-metabolites (methotrexate, 6-mercaptopurine, cytarabine, etc.) have little/no lasting effects on fertility and gonadal function

Fertility after Cancer Treatment

- Women treated with radiation therapy to the pelvis:
 - Premature menopause
 - Increased risks of complications and miscarriages during pregnancy
 - Preterm labor
 - Infants have lower birth weights
- Rates of congenital malformations and genetic disorders among offspring of cancer survivors
 - Appears to be low (including for offspring born to males and females exposed to radiation to reproductive organs and alkylating agents)
 - Exception: Increased risk of cancer among children born to survivors with inherited predispositions to cancer

Fertility after Cancer Treatment

- Routine health maintenance of cancer survivors during adolescence should include evaluations of pubertal status and sexual function
 - Screening: LH, FSH and testosterone (male patients) beginning at age 14 years and as clinically indicated
 - Consider semen analysis
- Information for healthcare professionals and patients regarding infertility:
 - American Society for Reproductive Medicine: www.asrm.org
 - Fertile Hope: www.fertilehope.org

Fertility after Cancer Treatment

- Indications for referred to an endocrinologist or urologist:
 - Delayed puberty
 - Persistently abnormal hormone levels
 - Hormonal replacement for hypogonadal patients
- Bone density evaluation should be considered for patients with hypogonadism
- Women at risk of premature menopause should be counseled regarding a potentially shortened fertile life span in making educational and career choices

Other Complications and Interventions for Adolescent and Young Adult Survivors of Cancer

Lung Complications:

- Types of Lung Complications
 - Abnormal chest wall movement
 - Lung fibrosis
 - Chonic pneumonia
- Causes:
 - Radiation exposure to the lung
 - Chemotherapy: Bleomycin, Busulfan, CCNU
 - Smoking
 - Treatment with bone marrow transplant
 - Younger age at diagnosis

Smoking Among Childhood Cancer Survivors

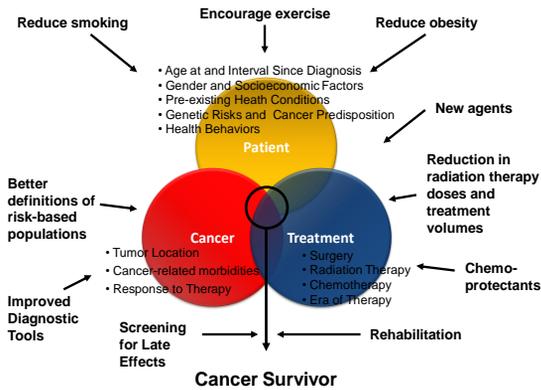
- Rates of Smoking:

	Childhood Cancer Survivors	General Population
Ever Smoked	28 %	33 %
Recently Smoked	10 %	9 %

- Smoking is associated with:
 - Peer smoking
 - Smokers in the household
 - Bing alcohol consumption
 - Suicidal behavior
 - No exposure to radiation therapy to the chest
- Smoking cessation:
 - Target the family and peers
 - Reminders of health benefits of not smoking

Decreased Bone Mineral Density

- Consequences
 - Increased risk of osteoporosis and fractures
- Risk Factors
 - Diagnoses: leukemia
 - Decreased activity, immobilization
 - Malnutrition
 - Chemotherapy: Steroids, Methotrexate, Cyclophosphamide
 - Radiation exposure
 - Reproductive organs, Brain, Total bone irradiation (TBI)
- Interventions
 - Increase calcium and Vitamin D intake
 - Estrogen / Testosterone replacement
 - Exercise and physical activity
 - Discourage smoking, alcohol and caffeine consumption



Cancer Follow-up Evaluations:

- Monitor for recurrence of cancer
- Surveillance for second cancers and late effects:
 - Early diagnosis and intervention
- Prevention:
 - Discourage smoking
 - Encourage physical activity
 - Discuss healthy diet
 - Encourage calcium intake
- Education about cancer and treatment

Recommendations for Screening:

Late Effects Screening Guidelines from the Children's Oncology Group:

www.survivorshipguidelines.org

Recommendations:

- Recognize a relationship between treatment exposure and late effect
- Screening/surveillance in high-risk populations

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent,
and Young Adult Cancers

Version 3.0 – October 2008

CureSearch

Children's Oncology Group

www-survivorshipguidelines.org

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