Late Effects of Childhood Cancer

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Childhood Cancer in Oregon

- about 155 new cases Oregon/yr
- 80% of children will be cured
- = about 116 new survivors Oregon each year
<table>
<thead>
<tr>
<th>Health Assessment</th>
<th>Survivors (%)</th>
<th>Siblings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair or Poor Health</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>
Cumulative incidence of medical conditions reported ≥ 5 years after diagnosis.

Diller L et al. JCO 2009;27:2339-2355
2 Out of 3 Will Have a Late Effect
Incidence of severe or life threatening chronic illness

Diller et al 2009  N= 9535 survivors and 2916 siblings

Cumulative incidence was 33% at 25 yrs out.
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Event Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>End Treatment</td>
<td>Well Known</td>
</tr>
<tr>
<td>10 Years</td>
<td>Generally Known</td>
</tr>
<tr>
<td>20 Years</td>
<td>Data coming in</td>
</tr>
<tr>
<td>30 Years</td>
<td>Limited</td>
</tr>
<tr>
<td>40 Years</td>
<td>?</td>
</tr>
</tbody>
</table>
Where data comes from

- Childhood Cancer Survivors Study US
  - 20,505 survivors
- British Childhood Cancer Survivors Study
  - 18,046 survivors
- Netherlands Survivors Study
  - 13,362 survivors
Causes of late effects

- Primary disease
- Surgery
- Radiation therapy
- Chemotherapy
- Life-threatening illness

- Treatment summary must
LATE EFFECTS CAN AFFECT EVERYTHING

Neurocognitive effects/Learning disabilities (most common)

Heart Problems

Liver Disease

Infertility

Skin Damage

Abnormal Growth/Maturation

Amputation/Disfigurement

Depression, Post-Traumatic Stress Disorder

Hearing Loss

Dental Problems

Lung Problems

Kidney Damage

Functional/Activity Limitations

Bone Damage & Avascular Necrosis

Obesity

Secondary Cancers

Vision Problems

Secondary Cancers

Dental Problems

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Obesity

Secondary Cancers

Vision Problems
Cumulative incidence of chronic health conditions (grade 1 to 5 and grade 3 to 5).

Diller L et al. JCO 2009;27:2339-2355
Cumulative incidence of chronic health conditions by exposure (grade 3 to 5 only).

Diller L et al. JCO 2009;27:2339-2355
Neurocognitive deficits

- **Core symptoms:**
  - Attention/concentration
  - memory
  - processing speed

- **Secondary symptoms:**
  - IQ loss
  - academic difficulties
  - vocational and social problems
Neurocognitive Deficits: Risk Factors

- Brain Tumor/brain surgery sequelae
- Cranial radiation therapy dose related
- Leukoencephalopathy/CNS relapse
- Seizures during treatment
- Young age at treatment
- Intrathecal and IV methotrexate
- Corticosteroids
- Female
Neurocognitive deficits: interventions

Cognitive remediation:
- Massed practice or drills
- Performance improvement strategies
- Behavioral coaching

Pharmacotherapy:
- Methylphenidate for attention deficit
Neurocognitive deficits: interventions

School interventions:
- Testing format ➔ extended time limits,
- Written handouts
- Use of computers instead of handwriting
- Decreased volume of homework
- Structured school re-entry program
Age- and sex-adjusted percentages of Childhood Cancer Survivor Study participants who reported in 2003 having been employed at some time during the previous 12 months.

Gurney J G et al. JCO 2009;27:2390-2395
“Even the wind feels better on the other side
Touching my skin, I get high
Sensation, Elation All the time
From now on”

“Even the rain feels better on the other side
Soaking my skin, I get high
Contemplation-creation-all of the time
From now on”
“It was like coming back from a war, I mean 8 of my friends died, nobody at school could understand what that feels like.”
Psychosocial

- Depression
- Anxiety
- Post traumatic stress disorder
- Education
- Being accepted into military service
- Financial
  - Career
  - Obtaining health and life insurance
PTSD Diagnostic Criteria

- PTSD symptoms. Must be all three; >1 month; with functional impairment
  - Intrusive thoughts (re-experiencing, worries, memories)
  - Avoidance, numbing, emotionally disconnected
  - Anxiety/ hypersensitive arousal
Obesity

- 1765 subjects with ALL; > 18 yrs old
- Mean post treatment 17 years
- Treated with cranial XRT
- More Obesity in patients than siblings
- Greatest risk under 4 yrs; XRT dose $\geq 20\text{Gy}$

Oeffinger, Mertend, Sklar, Yausui, Yutaka, Fears, Stovall,vik, Terry, Inskip and Robison 2003
Percent of male and female survivors by primary diagnosis and body mass index category.

Diller L et al. JCO 2009;27:2339-2355
Scatterplot for unadjusted body mass index (BMI) by age at diagnosis of acute lymphoblastic leukemia for females treated with $\geq 20$ Gy cranial radiotherapy.

Diller L et al. JCO 2009;27:2339-2355
Age- and sex-specific percentiles for height and body mass index (BMI) among brain cancer survivors by age at diagnosis (upper panel) and treatment types (lower panel).

Diller L et al. JCO 2009;27:2339-2355
• **Overweight**
  - Age 2-20 years: BMI for age ≥ 85th - < 95th percentile
  - Age ≥ 21 years: BMI ≥ 25 - 29.9

• **Obesity**
  - Age 2-20 years: BMI for age ≥ 95th percentile
  - Age ≥ 21 years: BMI ≥ 30
Metabolic Syndrome

A clustering of cardiovascular risk factors that may further increase risk for cardiovascular disease.

- insulin resistance
- Dyslipidemia
- Elevated blood pressure
- +/- obesity
Cardio toxicity

- Highest risk Anthracyclines >300 mg/m² and/or radiation to heart
- Myopathy
- Arrhythmias
- Atherosclerotic disease
Systolic and diastolic function in doxorubicin-treated bone tumor survivors

Findings: Progressive Cardiac Dysfunction  n=223 with SF < 29%; one symptomatic

<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>14 yrs post</th>
<th>22 yrs post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>9%</td>
<td>27%</td>
</tr>
<tr>
<td>Diastolic</td>
<td>18%</td>
<td>45%</td>
</tr>
</tbody>
</table>

2006 Brouwer, Gietema, van den Berg, Bink-Boelkens, Eizenga, Haaksma, Kamps, Vonk deVries and Postma
Incidence of Cardiac Disease

- Brain Tumors 18%
- AML 4.7%
Highest Risk Treatment Factors

- **Cumulative anthracycline doses:**
  - Patients 18 years or older $\geq 550$ mg/m$^2$
  - Patients younger than 18 $\geq 300$ mg/m$^2$
  - Any dose in infant
  - Chest radiation $\geq 30$ Gy
## Relative Risk of Selected Severe Health Conditions among Cancer Survivors as Compared with Sibling

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major joint replacement*</td>
<td>54.0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>15.1</td>
</tr>
<tr>
<td>Second malignant neoplasm†</td>
<td>14.8</td>
</tr>
<tr>
<td>Cognitive dysfunction severe</td>
<td>10.5</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10.4</td>
</tr>
<tr>
<td>CONDITION</td>
<td>RELATIVE RISK</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>9.3</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
<td>8.9</td>
</tr>
<tr>
<td>Hearing loss not corrected</td>
<td>6.3</td>
</tr>
<tr>
<td>Legally blind or loss of eye</td>
<td>5.8</td>
</tr>
<tr>
<td>Ovarian failure</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Pulmonary Risk Factors

- **Highest Risk**
  - BCNU $\geq 600\ \text{mg/m}^2$
  - Busulfan $\geq 500\ \text{mg}$
  - Combined with: Chest radiation or TBI
  - Bleomycin dose $\geq 400\ \text{U/m}^2$

Survivorshipguidelines.org
Infertility High Risk Factors

- **Treatment Factors**
  - MOPP $\geq$ 3 cycles
  - Busulfan $\geq$ 600 mg/m$^2$
  - Cyclophosphamide cumulative dose $\geq$ 7.5 gm/m$^2$ or as conditioning for SCT
  - Any alkylators combined with:
    - Testicular radiation
    - Pelvic radiation
    - TBI
Risk of Infertility for Pediatric Cancers

- High risk > 80% risk of infertility
  - Radiation to gonads
  - Stem Cell Transplant conditioning
  - Hodgkin’s disease with cytoxan/procarbazine
  - Soft Tissue Sarcoma
  - Ewings Sarcoma
Lupron is

A. Experimental
B. Not very effective
C. Helpful in many patients
Minimum time required to delay therapy when considering egg freezing

A. One week
B. Two weeks
C. Three weeks
D. Four weeks
Out of pocket cost of oocyte freezing

A. $22,000
B. $12,000
C. $5,000
D. $2,000
The current number of babies born worldwide from oocyte freezing.

A. 50-100
B. 200-500
C. > 2000
D. >10,000
There are no human pregnancies yet with ovarian tissue freezing, but animal studies are going very well.

- True
- False
The best time to think about fertility preservation in your patient.

A. When pathology comes back
B. When the chemo plan is finalized
C. During the first admission for chemotherapy
D. When you first take the consult call
The proportion of women who achieve menarche over time, adjusted for ethnicity, birth year, and abdominal radiotherapy.

Diller L et al. JCO 2009;27:2339-2355
Cumulative incidence curves of nonsurgical premature menopause in survivors compared with siblings.

Green D M et al. JCO 2009;27:2374-2381
Fertility Sparing Treatments
Established Options

- **Males**
  - Sperm Banking (before treatment begins)
  - Gonadal shielding

- **Females**
  - Embryo banking
  - Gonadal shielding
  - Oophoropexy

Up and coming experimental interventions
Gonadotropin deficiency

- FSH
- LH
- Estradiol

(Baseline at age 13, and as clinically indicated in patients with delayed puberty, irregular menses, primary or secondary amenorrhea, or clinical signs and symptoms of estrogen deficiency)
Thyroid

- 1791 subjects treated for Hodgkin's 79% treated with XRT
- Median 16 yrs post treatment; sibling controls
- 34% had either
  - Hypothyroid 28% 17x
  - Hyper thyroid (5%)
  - Thyroid nodule 9% 27 x
  - Thyroid cancer 20 patients

Sklar, Whitton, Mertens, Stovall, Green, Marina, Greffe, Wolden, Robinson  2000
Hypothyroidism

- **Treatment Factors**
  - Radiation dose $\geq 10$ Gy
  - Thyroid gland directly in radiation field
- TBI

Survivorshipguidelines.org
Probability of developing an underactive thyroid after diagnosis of Hodgkin's lymphoma.

Diller L et al. JCO 2009;27:2339-2355
Endocrine Growth Hormone Deficiency

- GH deficiency
  - 39 pts with ALL, + XRT
  - Time since XRT 21 yrs
  - 50% GH deficient
Height standard deviation scores (SDS) across exposure groups by pubertal status at acute lymphoblastic leukemia diagnosis.

Diller L et al. JCO 2009;27:2339-2355
Growth Hormone Deficiency

- **Treatment Factors**
  - Higher radiation doses
  - Surgery in suprasellar region
  - Pretransplant radiation
  - TBI ≥ 10 Gy in single fraction
  - TBI ≥ 12 Gy fractionated

- Endocrine consultation for: Height below 3rd percentile on growth chart; Drop ≥ 2 percentile rankings on growth chart; Growth velocity < 4-5 cm/year during childhood; Lack of pubertal growth spurt
Bones Osteopenia

- **High Risk Factors**
  - Older age at time of treatment
  - Glucocorticoid cumulative dose ≥ 9 gm/m² prednisone equivalent

Survivorshipguidelines.org
Cumulative incidence of osteonecrosis among all survivors stratified by age at diagnosis.

Diller L et al. JCO 2009;27:2339-2355
Cumulative incidents of osteonecrosis among survivors and a sibling comparison group starting 5 years after diagnosis.

Diller L et al. JCO 2009;27:2339-2355
HEENT

- Nose sinuses
- Throat strictures
- Dental abnormalities
  - Root deformities
  - Enamel dysplasia
  - Caries
  - Dental Care q 6 mos
Ears

- **High risk Treatment Factors**
  - Carboplatin conditioning for HCT
  - Radiation involving ear
  - Cumulative cisplatin dose ≥ 360 mg/m²

Survivorshipguidelines.org
Eyes- Cataracts and other ocular toxicity

• High risk Factors
  o TBI
  o Cranial, orbital, or eye
  o Radiation combined with Corticosteroids
  o Busulfan
  o Ocular Tumors

Survivorshipguidelines.org
Organ Dysfunction

- Kidney/Bladder
  - Chem and U/A annually for high risk

- Liver
Secondary Malignancies in Survivors of Childhood Cancer

All cancers       3.2% at 20 yrs
[n=13,581]

ALL with RT   2.0% at 20 yrs   Mostly CNS
CNS tumors   2.1% at 20 yrs   Mostly CNS
Hodgkin’s     7.6% at 20 yrs

- 25,965 subjects
- 436 new primary cancers in 400 individuals
- 6x higher risk

Inskip and Curtis 2007
Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors.
Secondary Malignancies in Survivors of Hodgkin’s Lymphoma

Multiple series:  \( n = \sim 2800 \)

- 7-9% at 15 yrs  breast cancer
- 35% at 40 yrs  breast cancer
- 4% at 15 yrs  leukemia/lymphoma
Higher Risk Primary Diagnoses

- Hodgkin's disease (7.6%)
- Soft tissue sarcoma (4%)
- Bone sarcoma (3.3%)
- Leukemia (2.1%)
- Brain tumor (2.1%)
- Neuroblastoma, non Hodgkin's lymphoma, renal tumor (<2% each)
Genetic Syndromes

- Hereditary Retinoblastoma
- Neurofibromatosis
- Li Fraumeni
- Ataxia Telangiectasia
Breast Cancer

- **Treatment Factors**
  - Family history of breast cancer
  - Higher radiation dose to breast
  - Longer time since radiation ≥ 5 years)
Second Malignancy Screening

- **AML/Myelodysplasia**
  - CBC/differential - yearly, up to 10 years post

- **Skin Cancer**
  - Skin checks annually

Survivorshipguidelines.org
<table>
<thead>
<tr>
<th>Types of cancer by age</th>
<th>Young Adults 20-29</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18% lymphomas</td>
<td>23% leukemia</td>
</tr>
<tr>
<td></td>
<td>17% germ cell</td>
<td>18% CNS/brain</td>
</tr>
<tr>
<td></td>
<td>12% melanoma</td>
<td>15% lymphomas</td>
</tr>
<tr>
<td></td>
<td>10% sarcomas</td>
<td>13% sarcomas</td>
</tr>
<tr>
<td></td>
<td>10% thyroid</td>
<td>11% embryonal</td>
</tr>
<tr>
<td></td>
<td>5% leukemia</td>
<td>8% germ cell</td>
</tr>
<tr>
<td></td>
<td>6% CNS/brain</td>
<td>1% other</td>
</tr>
<tr>
<td></td>
<td>5% Breast Carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17% Other</td>
<td></td>
</tr>
</tbody>
</table>
Blood Product Exposure

- Prior to 1972 screen for hepatitis B
- Prior to 1993 screen for Hepatitis C
- 1977- 1985 screen for HIV

Survivorshipguidelines.org
Late Mortality

- 20,227 subjects
- > 5 years from diagnosis
- 10% died
  - 67% of those from original malignancy
    - (Leukemia, CNS, Hodgkin's, Bone Tumors)
  - 21% late effects of treatment

Mertens, Yasui, Neglia, Potter, Nesbit, Ruccione, Smithson, Robison, 2001
Late Mortality Risk Factors

- XRT to chest
- Alkylating agents (Cytox, Procarb, Thiotep)
- Anthracyclines (Dauno, Doxo, Ida, Mito)
- Etoposide
- Bleomycin
(A and B) All-cause mortality, survival by original cancer diagnosis in the Childhood Cancer Survivor Study.

Armstrong G T et al. JCO 2009;27:2328-2338
(A) All-cause mortality (survival function estimate): entire cohort.
Bonus Question

- Which drugs list no known late effects?
Prevention of late effects

- Early diagnosis of primary disease
- Improved surgical techniques
- Improved radiation techniques
- Decrease in radiation therapy
- Evaluation of chemo protective agents
Prevention of late effects

- Decrease chemotherapy (only exactly what you need)
- Assess/support psychosocial needs and neurocognitive deficits
- Research gene polymorphisms
  - SNP’s (Single Nucleotide polymorphism)
    - Genetic variations (mutations) shared in the general population
Long term follow-up

- Survey for long term toxicity of treatment
- Monitor growth and development
- Educate patient on long term health care needs
- Monitor for recurrence of primary cancer
- Survey for secondary malignancies
Living Healthy

Medical Follow-up (early detection)
Dental Care
Diet (calcium)
Exercise
Sunscreen
Lifestyle
Sexuality
Connectedness
Mental Health
Childhood Cancer Survivor Resources

- Livestrong.org
- Candlelighters.org
- Beyondthecure.org
- Curesearch.org
- Survivorshipguidelines.org