Objectives

- Understand the knowledge gaps in long term survivors of childhood cancer.
- Recognize the physical complications facing long term survivors of childhood cancer.
- Recognize the psychosocial issues that survivors endure.
- Understand the ways in which we may improve the health of long term survivors.

Childhood Mortality

Survival Rates

About Survivors

- Survivors do not have complete knowledge regarding their past diagnosis and treatment.
- Approximately 30% of survivors can not accurately report their diagnosis.
- Approximately 10% of patients do not recall receiving chemotherapy.
  - Only 30-50% recall receiving anthracyclines.

(JAMA 2002;287:1832-1839)

- Approximately 10% of patients do not recall receiving radiotherapy.
  - Overall 70% of these patients knew their sites of radiation.
- Survivors have many questions regarding their previous therapies and it's effects on their health and the health of their offspring.
Causes of Secondary Malignancy Neoplasms (SMNs)

- **Chemotherapy**
  - Alkylating agents i.e. nitrogen mustard, cyclophosphamide, and melphalan are associated with myelodysplastic syndromes and AML.
  - Topoisomerase II inhibitors include etoposide, anthracycline, and daunomycin are associated with an increased risk of acute leukemia.
  - Doxorubicin associated with increased risk of second malignant solid tumors.

- **Radiation Therapy**
- **Genetics**
  - BRCA genes
  - Li-Fraumeni Syndrome- mutation of the p53 tumor suppressor gene
  - Retinoblastoma gene germline mutations
  - Chromosomal breakage syndromes

Secondary Malignant Skin Cancer

- Non-melanoma skin cancer is the most frequently diagnosed secondary malignant neoplasm.
  - Locations include head and neck (43%), back (24%), chest (22%), abdomen and pelvis (5%), extremity (3%) and unknown (4%).
  - Ninety percent of non-melanoma skin cancers occur in prior areas of radiation.
Cardiac Causes of Mortality

- Cardiomyopathy
  - The anthracyclines (i.e., doxorubicin, daunomycin and idarubicin) are well-known causes of cardiomyopathy.
  - Cardiomyopathy can occur many years after completion of therapy, and the onset may be spontaneous or coincide with exertion or pregnancy, especially during the third trimester.

- Left ventricular contractility is abnormal during the first three years after diagnosis, normalizes during the period 3-9 years after diagnosis, then deteriorates with increased follow-up.

- Pattern of echocardiographic abnormalities consistent with early dilated cardiomyopathy, followed by late restrictive cardiomyopathy.

(J Clin Oncol 2005;23:2629-2636)

Congestive Heart Failure After Treatment For Wilms Tumor

(J Clin Oncol 2001;19:1926-1934)

Causes Of Excess Cardiac Mortality Risk Factors

- Obesity - Body mass index (BMI)
- Nicotine addiction
- Exercise
- Genetics (cholesterol, triglycerides, glucose)

Pulmonary Causes of Mortality

- Radiation- pulmonary fibrosis and pneumonitis
- Chemotherapy
  - Bleomycin
  - Busulfan
  - BCNU
  - CCNU
- Smoking

Endocrine Causes of Morbidity

- Growth Retardation/ Growth Hormone Deficiency- standing height below the 5th percentile
- Hypo/Hyper- thyroidism- related to radiation
- Adrenal Insufficiency
- Obesity
Obesity - Male ALL Survivors

<table>
<thead>
<tr>
<th>Overweight BMI= 25-29.9</th>
<th>Obese BMI &gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N OR CI</td>
<td>N OR CI</td>
</tr>
<tr>
<td>Siblings</td>
<td>1193 1 1</td>
</tr>
<tr>
<td>Chemo only</td>
<td>204 1.02 71-1.43 1.31 77-2.04</td>
</tr>
<tr>
<td>Chemo +CRT &gt;10-19g</td>
<td>269 1.16 85-1.6 1.25 8.1-1.92</td>
</tr>
<tr>
<td>Chemo + CRT &gt;20gy</td>
<td>124 1 0-1.92</td>
</tr>
</tbody>
</table>

Obesity - Female ALL Survivors

<table>
<thead>
<tr>
<th>Overweight BMI= 25-29.9</th>
<th>Obese BMI &gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>N OR CI</td>
<td>N OR CI</td>
</tr>
<tr>
<td>Siblings</td>
<td>1323 1 1</td>
</tr>
<tr>
<td>Chemo only</td>
<td>217 1.07 7-1.59 1.09 63-1.71</td>
</tr>
<tr>
<td>Chemo +CRT &gt;10-19g</td>
<td>234 1.36 62-1.97 1.27 77-1.95</td>
</tr>
<tr>
<td>Chemo + CRT &gt;20gy</td>
<td>124 1 0-1.92</td>
</tr>
</tbody>
</table>

Fertility - Males

- Radiation, surgery, or chemotherapy causes germ cell depletion and abnormalities of gonadal endocrine function.
- Direct radiation leads to decrease in testicular volume and sperm production.
- Leydig cells are more resistant to RT than Sertoli cells.
- Dose dependent effects.
- Inversely related to age - adolescents and young adults testes are more radioresistant.
- Chemotherapy: alkylating agents i.e. cyclophosphamide, ifosfamide.

Fertility - Females

- Radiation effects are age and dose dependent.
- Prepubertal females are less affected than adolescents and adults.
- Patients that undergo BMT with TBI are likely to have primary amenorrhea and absent secondary sexual characteristics.
- Premature ovarian failure and premature menopause are primarily related to chemotherapy with alkylating agents.

Pregnancy Outcomes - Males

- Of 4106 sexually active males, 1227 reported 2323 pregnancies: 69% live births, 1% stillbirths, 13% miscarriages, 13% abortions, 5% unknown.
- Male fertility was lower than male sibling survivors RR = 0.77.

Pregnancy Outcomes - Females

- Of 1940 sexually active females, 4029: 63% live births, 1% stillbirths, 15% miscarriages, 17% abortions, 3% unknown.
- A higher risk of miscarriage was seen but was not statistically significant, among those whose ovaries were irradiated.


(Am J Obstet Gynecol 2002;187:1070-80)
Pregnancy Outcome - Females

Pregnancy Outcomes - Radiation and Gestational Age

Pregnancy Outcomes - Offspring

Neurocognitive Function

Psychosocial Issues

Psychosocial Issues
### Prevention
- Health maintenance - age appropriate general health screening including cancer screening, eye exams, dental exams.
- Exposure related screening - cardiac, second malignant neoplasms, pulmonary disease, neuropsychological screening, psychosocial screening
- Patient education - risk reduction (alcohol, tobacco, exercise, sun exposure), anticipatory guidance (e.g. fertility and pregnancy)

### Summary
- Increasing population of adult survivors of childhood cancer with varying chemotherapy, radiotherapy, and/or surgery exposures.
- Five year survivors have excess mortality primarily due to recurrence and secondary malignancies.

### Summary
- Risk of many late effects depends upon treatment exposures.
- Medical follow-up problematic
  - Survivor knowledge base limited
  - Expense of follow-up - insurance reimbursement, lost wages, healthcare access
  - Physician expertise


### Long Term Follow Up Project at RPCI
- Database started in the 1980’s comprising of patients that were treated at RPCI whom were <20 yrs of age at diagnosis and were more than 5 years off therapy.
- Follow-up is updated annually via clinic visits, mail, or RPCI medical records.
- The largest number of survivors includes patients diagnosed with Hodgkin disease, Acute lymphoblastic leukemia, and non-Hodgkin lymphoma.