

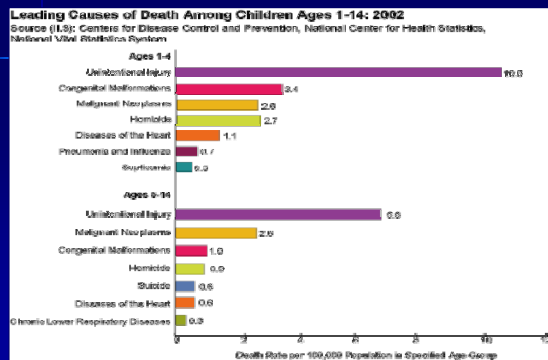
## Childhood and Adolescent Cancer Survivorship

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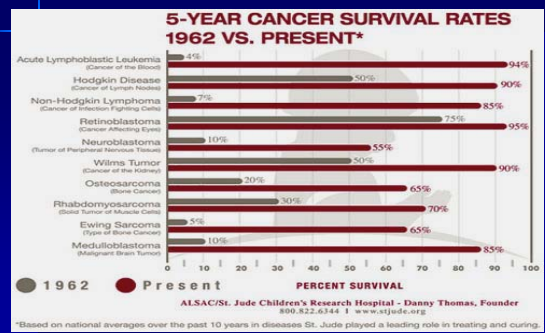
## Objectives

- 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



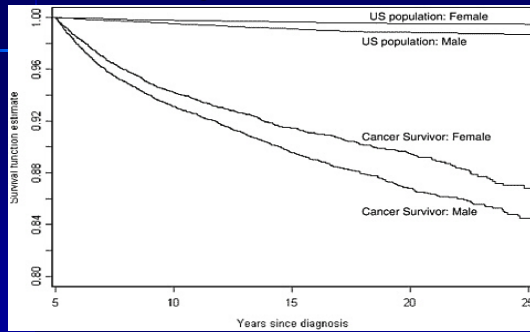
## About Survivors

- 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)

## About Survivors

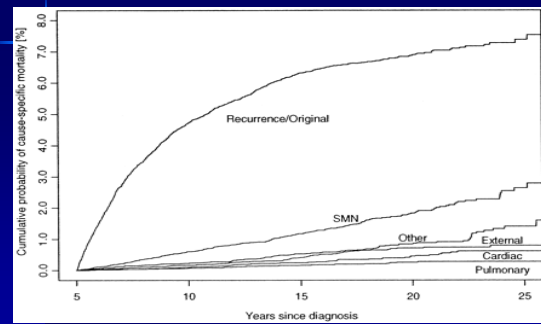
- Approximately 10% of patients do not recall receiving radiotherapy.
  - Overall 70% of these patients knew their sites of radiation.
- Survivors have many questions regarding their previous therapies and it's effects on their health and the health of their offspring.

## Mortality



(J Clin Oncol 2001;19:3163-3172)

## Cause of death



(J Clin Oncol 2001;19:3163-3172)

## 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 dactinomycin are associated with an increased risk of acute leukemia.
  - Doxorubicin associated with increased risk of second malignant solid tumors.

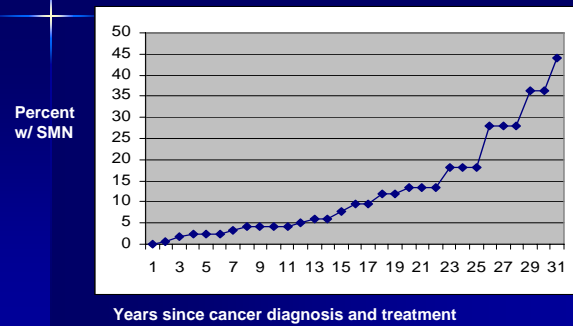
## Causes of SMNs

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

## 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.

## Incidence Curve for occurrence of SMN by interval since diagnosis



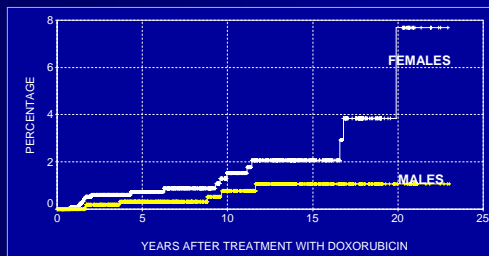
## Cardiac Causes of Mortality

- **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.

## Cardiac Causes of Mortality

- 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 5<sup>th</sup> percentile
- Hypo/Hyper- thyroidism- related to radiation
- Adrenal Insufficiency
- Obesity

## Obesity – Male ALL Survivors

	Overweight BMI= 25-29.9			Obese BMI >30	
	N	OR	CI	OR	CI
Siblings	1193	1		1	
Chemo only	204	1.02	.71-1.43	1.31	.77-2.04
Chemo +CRT10-19g	269	1.16	.85-1.6	1.25	.8-1.92
Chemo + CRT >20gy					
0-4 yrs	193	.97	.64-1.41	2.15	1.31-3.38
5-9 yrs	123	.96	.58-1.46	1.93	1.07-3.28
10-14 yrs	76	1.28	.71-2.43	2.02	1-4.13
15-21 yrs	30	.93	.4-2.19	.71	0-1.92

(J Clin Oncol 2003;21:1359-1365)

## Obesity – Female ALL Survivors

	Overweight BMI= 25-29.9			Obese BMI >30	
	N	OR	CI	OR	CI
Siblings	1323	1		1	
Chemo only	217	1.07	.7-1.59	1.09	.63-1.71
Chemo +CRT10-19g	234	1.36	.93-1.97	1.27	.77-1.95
Chemo + CRT >20gy					
0-4 yrs	178	3.19	2.07-4.82	3.81	2.34-5.99
5-9 yrs	137	1.28	.76-2.09	2.3	1.39-3.59
10-14 yrs	81	1.65	.84-2.82	2.16	1.11-3.61
15-21 yrs	23	1.22	.27-3.43	.88	0-2.63

(J Clin Oncol 2003;21:1359-1365)

## 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.

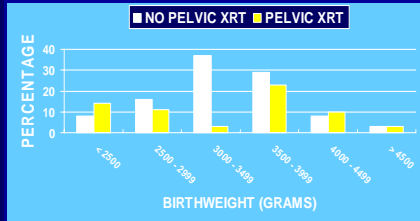
(J Clin Oncol 2003;21:716-21)

## 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.

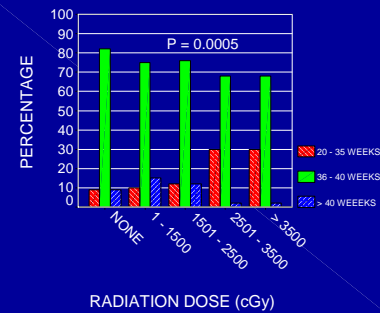
(Am J Obstet Gynecol 2002;187:1070-80)

## Pregnancy Outcome - Females



(Am J Obstet Gynecol 2002;187:1070-1080)

## Pregnancy Outcomes- Radiation and Gestational Age



RADIATION DOSE (cGy)

## Pregnancy Outcomes- Offspring

	Offspring of Survivors (N = 2198)	Offspring of Siblings (N = 4544)
Chromosomal Syndrome	0.2% (4)	0.1% (6)
Single Gene Disorder	0.6% (14)	0.2% (10)
Major Congenital Malformation	2.7% (59)	2.8% (127)

(Am J Hum Genet 1998;62:45-52)

## Neurocognitive Function

- Loss of IQ
- Problems with receptive and expressive language
- Academic difficulties in math, reading, and language
- Risk Factors
  - Cranial radiation therapy (dose-dependent)
  - Young age at the time of treatment
  - Systemic or Intrathecal chemotherapy (Methotrexate)

## Psychosocial Issues

- Increased risk for smoking, drinking, and other risky behaviors
- Increased risk for not completing school
- Poor body image and self-esteem
- Social Withdrawal
- Increased risk of mental health disorders
  - Depression and anxiety
  - Post-traumatic stress
  - Fatigue

## Psychosocial Issues

- Risk Factors
  - Female gender
  - Adolescents and Young Adults
  - Prior Trauma
  - Previous mental health history
  - Poor support system
  - Family History of Mental Health disorders
  - CNS cancer or Bone Marrow Transplantation

## 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

<http://www.survivorshipguidelines.org/pdf/LTFUGuidelines.pdf>

## 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.