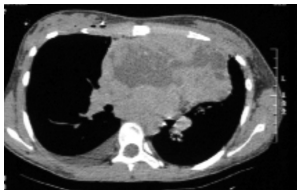
SURVIVORSHIP, LIFE AFTER TREATMENT FOR PEDIATRIC MALIGNANCIES

PEDIATRIC HEMATOLOGY/ONCOLOGY/BMT

TRISH MURPHY, RN, MSN
SURVIVORSHIP PROGRAM NURSE COORDINATOR

UCSF BENIOFF CHILDREN'S HOSPITAL, OAKLAND/SAN FRANCISCO



LONG-TERM FOLLOW UP AFTER CHILDHOOD CANCER

Why is this important?

What are the consequences?

Where are we going?

SURVIVORSHIP

In 2004, the CDC and the Lance Armstrong Foundation (now known as LiveSTRONG Foundation) released "A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies".

- Preventing secondary cancers and recurrence of cancer
- Promoting appropriate health management to ensure the maximum years of healthy life for cancer survivors
- Minimizing preventable pain, disability and psychosocial distress for survivors

www.cdc.gov

WHY IS THIS IMPORTANT?

12% OF CHILDREN DIAGNOSED WITH CANCER DO NOT SURVIVE.

CURESEARCH, 2017

WHY IS THIS IMPORTANT?

Although cancer in children is rare, it is a significant problem.

The cancer and the therapy can cause damage to normal tissues.

As more children survive cancer, there is a growing number of long-term survivors.

PEDIATRIC CANCER STATISTICS

More than 40,000 children undergo treatment for cancer each year.

99% of children who survive cancer will experience late effects such as infertility, heart failure, pulmonary conditions and secondary cancers.

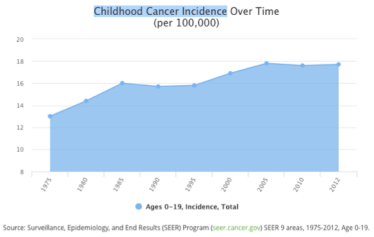
There are approximately 419,000 adult survivors of children's cancer in the United States.

That equates to 1 in 530 adults ages 20-39

(Curesearch, 2017)

CHILDHOOD CANCER INCIDENCE OVER TIME

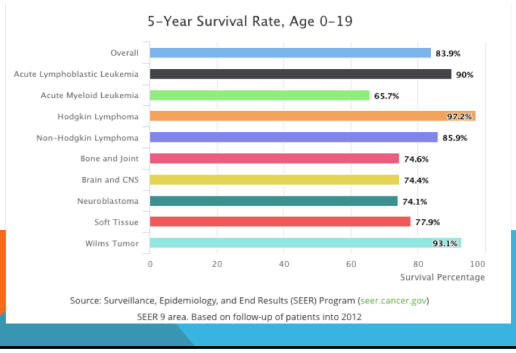
Even as the cure rate continues to improve, the incidence of childhood cancer has been steadily increasing over the last few decades, from about 13 children per 100,000 in 1975 to over 17 children per 100,000 since 2005.



Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov) SEER 9 areas, 1975-2012, Age 0-19.

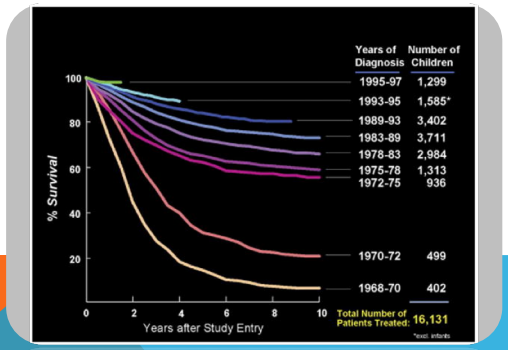
5 YEAR SURVIVAL RATES

IN THE LAST 40 YEARS, SURVIVAL RATES FOR PEDIATRIC CANCER HAS INCREASED FROM 10% TO ALMOST 90 PERCENT TODAY, ALTHOUGH MANY RARE CANCERS, THE SURVIVAL RATE IS MUCH LESS



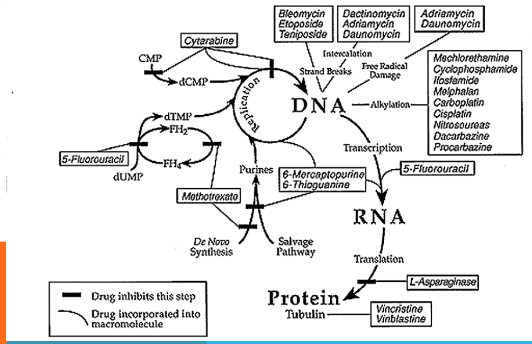
Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov)
SEER 9 area. Based on follow-up of patients into 2012

SURVIVAL OF CCG PATIENTS WITH ALL 1968-1997

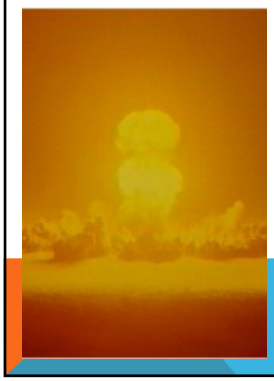


Surgery
Radiation
Chemotherapy

SITES OF ACTION OF COMMON ANTICANCER DRUGS

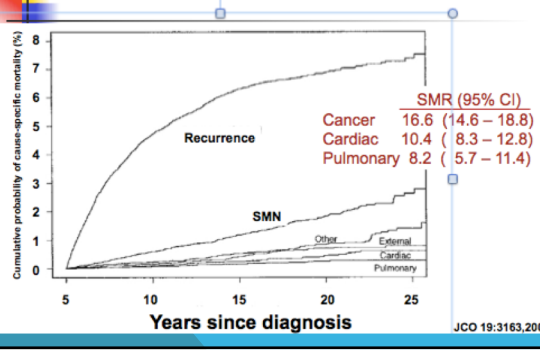


RADIATION EFFECTS



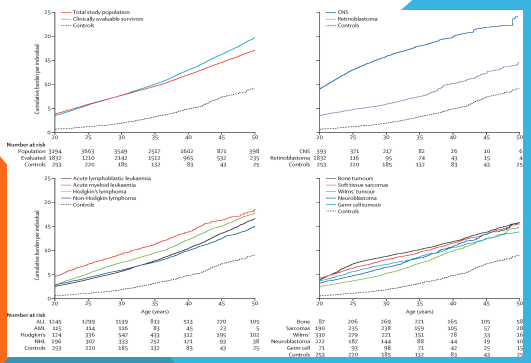
- **1890s –radiation discoveries (Becquerel and Curie)**
- **Early 1900s**
  - Radiation used to treat tumors and other skin diseases, lupus, arthritis
  - Drinking water, spas with radium were popular
- **1927**
  - Xrays were found to be mutagens (Muller)
  - Radium girls
- **Hiroshima/Nagasaki**
  - Linear relationship between mortality and radiation exposure

Cause-Specific Late Mortality



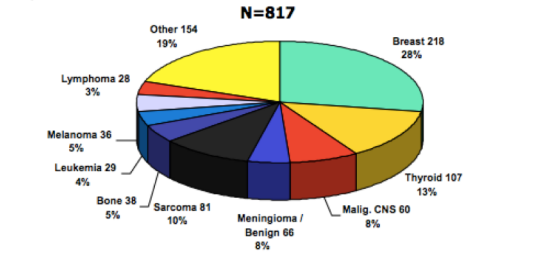
JCO 19:3163,2001

CUMULATIVE BURDEN OF CHRONIC HEALTH CONDITIONS
ST JUDE LIFETIME COHORT STUDY



THE LANCET 2017 390, 2569-2582

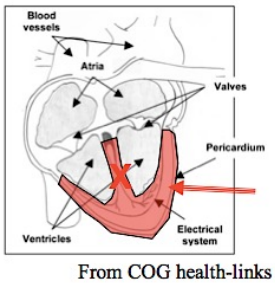
Reported Subsequent SMNs



Overall: SIR = 5.2 (Increasing with time)

With updated numbers since JNCI, 2001

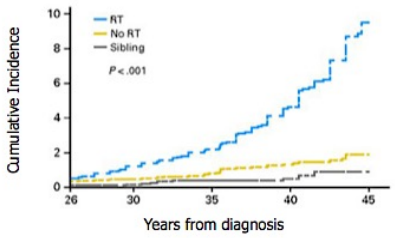
Heart Damage



From COG health-links

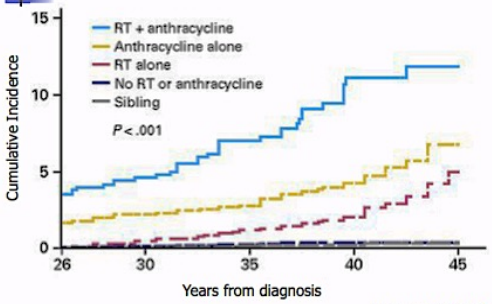
- Anthracyclines
- Radiation
- Other factors
  - Young age
- Types of damage
  - Cardiac cell damage with ventricular dysfunction (Cardiomyopathy)
  - Arryhthmias

Risk of coronary artery disease



Armstrong G T et al. JCO 2013;31:3673-3680

Risk of heart failure by therapy



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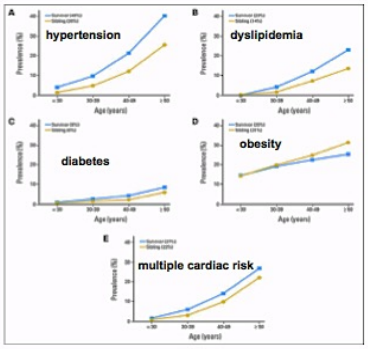
Prevalence of cardiovascular risk factors by age



Armstrong G T et al. JCO 2013;31:3673-3680

EFFECT ON THE LUNGS

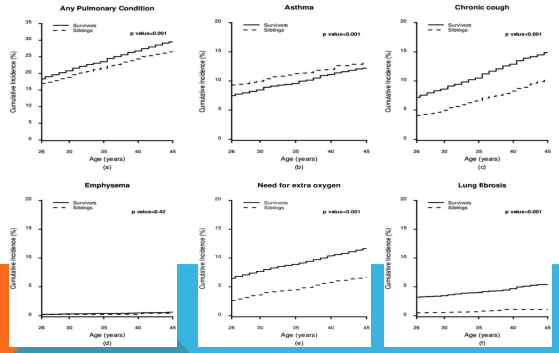
Therapy specific

- Radiation to the chest
- Chemotherapy
  - Bleomycin
  - Cyclophosphamide
  - Busulfan
  - CCNU and BCNU

Lung Surgery

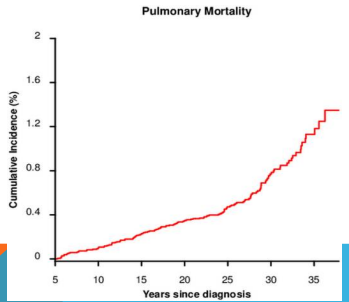
(COG Healthlinks)

CUMULATIVE INCIDENCE OF PULMONARY CONDITIONS



Cancer 2016; 122: 3687-96

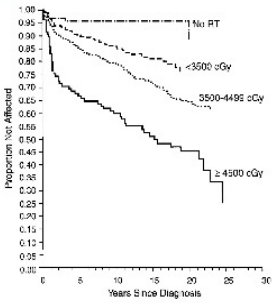
THE CUMULATIVE INCIDENCE OF DEATH DUE TO PULMONARY CONDITIONS



Cancer 2016; 122: 3687-96

Risk of Thyroid Disorders

XRT Dose Dependent

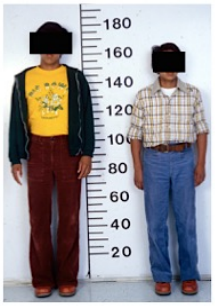


Hodgkins survivors

- 34% had at least 1 thyroid abnormality
- 27 fold increased risk of thyroid nodule

J Clin Endocrinol Metab 85: 3227–3232, 2000

Growth

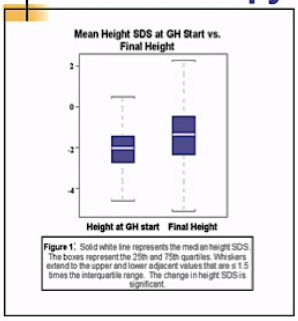


Identical twins

6 years after bone marrow transplant

Photo from A Ablin

Does GH therapy help?



- In order to maximize final height:
  - Begin GH at earliest possible bone age.
  - Treat with conventional, higher doses of GH
    - (>.3mg/kg/week).
  - When possible, minimize dose of spinal RT.

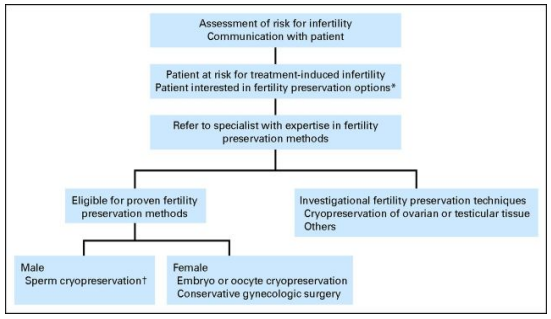
J Clin Endocrinol Metab 89: 4422–4427, 2004

EFFECTS ON FERTILITY

- Depends on therapy, dose, timing and gender
- Gonadotoxic chemotherapy
  Alkylating agents
  - Cyclophosphamide
  - Ifosfamide

  But also Busulfan, Melphalan, Thiotepa, CCNU, BCNU, Cisplatin, Cytarabine, Vinblastine, Etoposide,
- Radiation to ovaries or brain
- For women, fertility may be compromised despite the start of resumption of regular menses
- Azoospermia in men

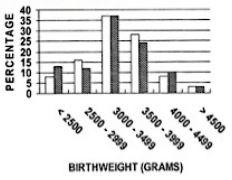
J Clin Onc, 24, 2006.



J Clin Oncol, 2013 Jul1;31(19): 2500-10

Minimal Impact on Pregnancy Outcomes

Birth weight with (hatched) and without (solid) pelvic XRT



- Offspring of women who received pelvic irradiation are at risk for low birth weight.

  Am J Obstet Gynecol 187:1070, 2002
- No adverse preganacy outcomes for partners of male survivors

  J Clin Oncol 21:716 ,2003

NO SIGNIFICANT INCREASED RISK OF CONGENITAL MALFORMATIONS

Congenital anomaly prevalence in cancer survivor offspring was 2.7% despite treatment modality

Not greater than that observed in the general population (3%)

J Clin Oncol. 2012 Jan 20; 30(3): 239-245

DISEASE OR TREATMENT-RELATED FACTORS THAT MAY INFLUENCE NEUROCOGNITIVE OUTCOMES

- Cranial radiation dose and field
- CNS tumor size/location
- Chemotherapeutic regimen
- CNS involvement (ie., leukemia)
- Endocrinopathies
- Hearing or vision loss
- Fatigue
- Stroke
- Hydrocephalus
- Neuropathy
- Physical appearance/limitations
- Posterior fossa syndrome
- Cranial nerve deficits

Current Opinion in Pediatrics, 2011, 23:27-33

WHAT ABOUT THE SIBLINGS?

DRINKING BEHAVIORS IN ADULT SIBLINGS OF CHILDHOOD CANCER SURVIVORS

Adult siblings of childhood cancer exhibit higher rates of high-risk behavior and heavy alcohol consumption compared to both peers and survivors

Addiction, 103:1139-1148, 2008

WELL...

Variable	CCSS-survivors n = 10 398 %	CCSS-siblings n = 3034 %	National-peers n = 4774 Wtd‡ %	Adjusted OR† survivor versus peer OR$_{adj}$ (95% CI)	Adjusted OR† survivor versus sibling OR$_{adj}$ (95% CI)
Current drinker‡‡				*P* < 0.01	*P* < 0.001
No	26.7	17.2	29.0		
Yes	73.3	82.8	71.0	1.1 (1.0–1.2)	0.6 (0.5–0.6)
Risky drinking, NIAAA-week/daily and weekly limit‡‡				*P* < 0.01	*P* < 0.001
No	83.8	79.7	82.0		
Yes	16.2	20.3	18.0	0.9 (0.8–1.0)	0.7 (0.6–0.8)
Heavy drinking, 5+/6+‡‡				*P* < 0.01	*P* < 0.001
No	91.7	89.6	90.0		
Yes	8.3	10.4	10.0	0.8 (0.7–0.9)	0.7 (0.6–0.8)

Addiction, 103:1139-1148, 2008

Other local effects:

Scoliosis after XRT


Photos from A.Ablin

DENTAL ISSUES

IDENTICAL TWINS

NO CANCER THERAPY


WHY IT MATTERS…

Patient EH

Now 28yo female who was dx with Wilm's Tumor in right kidney in Oct. 1994 at 5yo in Southern California

Treatment: right nephrectomy; 1050 cGy to entire abdomen; Vincristine, Dactinomycin, Doxorubicin – tolerated tx regimen well

Acute side effects: unresolved n/v; scoliosis

Moved to Bay Area and self-referred to UCSF Survivor clinic after an incidentally finding website on internet search

Late effects as of 2017: pancreatitis, diabetes, ovarian failure, anxiety, osteopenia with stress fractures, peripheral neuropathy – severe itching, burning with sores (dermatologist finally started Gabapentin after untreated for several months), Cushing syndrome, unresolved mod-severe n/v (blood and coffee ground), liver lesion presumed to be a benign mass by PMD

GOAL OF CARE PLAN

To anticipate and address the long-term physical, psychosocial, and practical needs of a cancer survivor's prior cancer treatment

SURVIVORSHIP CARE PLANS

In 2016, the Commission on Cancer (CoC) announced in new Survivorship Care Plan requirements

- **They must be patient and treatment specific**
- **To anticipate and address the long-term physical, psychosocial, and practical needs of a cancer survivor's prior cancer treatment**
- **The goal of the care plan is to bridge from the oncology setting to a primary care setting…. And educate and empower the cancer survivor!**

SURVIVORSHIP CARE PLAN

Concise and clear document that includes:

- Pt. name, diagnosis, date of diagnosis, protocol, start and end of treatment
- List of chemotherapy drugs and radiation along with doses
- Surgeries
- Specific guidelines for ongoing lifetime care along with surveillance testing (ECHO, PFTs…)
- Health promotion – smoking cessation, nutrition/dietary modifications, exercise, immunizations
- Psychosocial assessment and referrals to include emotional health, school aid, employment assistance

www.survivorshipguidelines.org

PORTABLE, ALWAYS ON HAND…

UCSF Children's Hospital — SWIM ACROSS AMERICA

Survivor Healthcare Passport

Patient: Example 1 — **Recommended Follow-Up** — DOB: 01/01/1991
Physician: UCSF Doc, MD — Phone: (415) 476-3831 — Updated: 02/05/2008

ALL SURVIVORS: History and Physical Exam Yearly, Dental Exam Every 6 Months

Specific Therapy-Related Risks

System	Exam	Time Frame
Cardiovascular	Detailed cardiovascular history/exam; ECHO	Yearly; Every 2 Years
	Fasting glucose/lipid profiles	Every 3-5 Years
	Exam for diminished brachial/radial pulse, pallor/coolness/unequal BP	Yearly
	Hx of memory impairment, exam for diminished carotid pulses/bruits	Yearly
	Hx of vasospasm of hands/feet/nose/face; Exam	Yearly; As Indicated
GI/Hepatic	Hx of dysphagia/heartburn	Yearly
Pulmonary	Pulmonary exam, Hx of cough/SOB/DOE/wheezing	Yearly
Reproductive	Pubertal/Sexual Function Hx; Semen Analysis	Yearly; At Pt Request
Second Cancer	CBC diff/plt; Fatigue/Bleeding/Bruising Hx	Yearly until 2007
	Palpation of bones in affected area, hx of bone pain	Yearly
	Hx of fatigue/endocrine problems,ht/wt/skin/hair/thyroid exam	Yearly
	Hx of bone pain/skin lesions/changing moles (esp in XRT area)	Yearly
Urinary	Voiding History, Urinalysis, Blood Pressure	Yearly

Please refer to: www.survivorshipguidelines.org for detailed Long-Term Follow-Up Guidelines from COG

UCSF SURVIVOR PASSPORT
A CREDIT CARD-SIZED SUMMARY

UCSF Survivors of Childhood Cancer Program — **Treatment History** — CureSearch Children's Oncology Group

Diagnosis: Ewing Sarcoma — Site: L Chest/Neck/Mediastinum
Protocol: CCG-7942, Regimen B — Start Tx: 08/26/1996 — End Tx: 04/23/1997

Chemotherapies	Age at 1st Dose	Cum Dose	Total Dose
Cyclophosphamide (Cytoxan) IV	5 Years 7 Months	12000 mg/m²	8610 mg
Doxorubicin (Adriamycin) IV	5 Years 7 Months	225 mg/m²	158 mg
Etoposide (VP-16) IV	5 Years 7 Months	3000 mg/m²	2175 mg
Ifosfamide IV	5 Years 7 Months	64000 mg/m²	42310 mg
Vincristine IV	5 Years 7 Months	12.75 mg/m²	9.3mg
Significant Surgery	**Site**		**Date**
Incisional Biopsy	L Chest		09/17/1996
Central Line Placement	R Subclavian		09/17/1996
Resection/Reconstruction	L Chest		12/12/1996
Central Line Removal	R Subclavian		05/13/1997

Radiation	Site	Start	End	Dose
External Beam	L Chest/Neck/Mediastinum	1/9/97	2/25/97	5000 cGy

FUTURE DIRECTIONS…

Treatments developed and refined over the past several decades have resulted in high cure rates and a large population of leukemia survivors. Studying the long-term health complications of these adult survivors will help to develop less toxic treatments while preserving earlier gains in efficacy.

NCI.gov

Advances in biomedical technology, immunotherapy and next-generation genome sequencing of leukemic cells and normal host cells, and high-throughput screening systems for new drugs should bring the promise of personalized treatment with targeted agents to fruition, resulting in more effective and less toxic treatments for patients with ALL.

Recent genome-wide association studies have begun to identify a number of inherited polymorphisms which are associated with the risk of childhood ALL in different ethnic and racial groups, paving the way for development of potential preventive measures, at least for certain subtypes of leukemia.

NCI.gov

ACKNOWLEDGEMENTS

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