A Diagnosis of Childhood Cancer Lasts a Lifetime
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Objectives
- To review the advances made in childhood cancer therapy over the last 60 years.
- To understand the many disease and therapy-specific complications of childhood cancer treatment.
- To recognize that childhood cancer survivorship may be accompanied by chronic medical and psychosocial issues which require specialized knowledge for optimal care.
- To discuss future directions of childhood cancer therapy and late effects research.

Disclosures
- Relationships with commercial interests:
  - Consulting fees for interviews for drug development and marketing
  - Patient Access Solutions
  - Canada Market Research

Collaborative Research for Childhood Cancer
- An example for clinical research across all medical disciplines
- Over 80% of children and adolescents diagnosed with cancer will be cured
  - Better use of established agents
  - To a lesser extent use of novel agents
  - Supportive care measures have improved significantly

But our work is not done
- No significant progress over the last 30 years for
  - Many central nervous system tumours
  - Sarcomas
  - Germ cell tumours
  - Wilms tumours
- These tumours account for over 25% of childhood cancer diagnoses
- Adolescents and young adults have not seen major improvements in survival despite progress for children and older adults
Aftermath of childhood cancer treatment

Cytotoxic chemotherapy

Targeted therapy

How big is the problem?

- ~40,000 survivors of childhood cancer in Canada
- We want these survivors to live for decades
  - With good quality of life
  - Without living dependent on a caregiver
  - Able to achieve educational and vocational goals
  - Able to have meaningful social and romantic relationships

We are good at curing childhood cancer—but the price of cure is still too high.

Childhood CNS tumours
- Most common solid tumours in children
- Medulloblastoma is the most common malignant CNS tumour

Medulloblastoma Survivors (Childhood Cancer Survivor Study)
- Late onset hearing loss - HR 36
- Stroke - HR 33.9
- Seizures - HR 12.8
- Poor balance - HR 10.4
- University degree - RR 0.49
- Marry - RR 0.35
- Live independently - RR 0.58

So we go from...

But we are not in the habit of giving up easily.

We’ve got work to do. Let’s get started.

- First we have to know the extent of the challenge we are facing
- We must also acknowledge that we fully learn about the late effects of our treatments decades later
  - Many treatments have changed significantly over that time
  - We are always playing “catch-up”
  - But there is still much to learn from our experiences
What are unique aspects of childhood cancer treatment and survivorship?

- Childhood cancer diagnosis and treatment often interferes with development in the following domains:
  - Social
  - Educational
  - Recreational
- Children and growing and developing
- Exposure of chemotherapy and radiation to tissues which are still maturing carries different risks:
  - Brain - neurocognition
  - Heart - myocytes

It takes a village

Childhood Cancer Survivor Study

- Retrospective cohort study
  - 10,397 survivors (mean age 26 years)
  - 1,034 siblings (mean age 29 years)
- 62% of survivors had at least one chronic health condition
- 27.5% had a severe or life-threatening condition
- Cumulative incidence of a chronic health condition was 73.4% at 30 years post cancer diagnosis, 42.4% for a severe, life-threatening or disabling condition

Oeffinger et al. NEJM 2006

Cardiovascular disease

- Most common organ system affected
- Sevenfold increase in risk of cardiac death compared to general population
  - Anthracycline exposure
  - Mediastinal radiation
  - Young age at treatment
  - Females higher risk

Cardiovascular disease

Important points about cardiovascular disease for childhood cancer survivors

- Long latency between exposure and clinical cardiovascular disease
  - Sometimes years or decades
  - Screening at risk populations important
  - 5 year survival after heart failure develops is less than 50%
- Cardiomyopathy is of particular concern
  - Coronary artery disease
  - Valvular abnormalities
  - Conduction abnormalities
  - Pericardial disease

Endocrine Dysfunction

- Childhood Cancer Survivor Study
  - Hypothyroidism - RR 6.6
  - Thyroid nodules - RR 6.3
  - Thyroid cancer - HR 9.2
  - Growth hormone deficiency - HR 5.3
Infertility

- After survival, one of the most important concerns for adolescent and young adult cancer survivors
- Fertility preservation options are expanding
- Such (non-experimental) options should be offered routinely

Risk factors for infertility
- Gonadal radiation or radiation to uterus/ovaries/pituitary
- Alkylating agents, typically greater than 5-8 g/m²
- Tumour/surgical disruption of reproductive structures
- Premature ovarian failure
- Fertility may be preserved, but window for childbearing may be reduced

Any organ system can be affected

- Important to review the patient’s treatment exposure history to determine what organs are at risk and how to screen
- **Kidney**: platinum agents, calcineurin inhibitors, high dose methotrexate
- **Hearing**: platinum agents, radiation therapy
- **Liver**: most chemotherapy can be hepatotoxic, graft-versus-host disease
- **Skin**: radiation, many chemotherapy agents
- **Bone health (osteopenia/osteoporosis/avascular necrosis)**: corticosteroids, methotrexate

Neurocognition

- Children are learning and developing
- **Radiation** is a major risk for neurocognitive deficits
  - Especially children under 3 years of age
  - Contained with high dose methotrexate, cytarabine or corticosteroids
- Brain tumours and neurosurgery are also risk factors
- Time in hospital, missed school, family and social time are also important
- Family history of learning difficulties and socioeconomic status are important predictors

Lungs

Consider Pulmonary Function Testing Surveillance if Hx of:
- Bleomycin
- Nitrosourea compounds
- Carmustine
- Lomustine
- Busulfan
- Lung radiation
  - 1200 cGy or greater
- Thoracotomies

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Neurocognitive Difficulties Post-Therapy for Acute Lymphoblastic Leukemia

- CNS prophylaxis is necessary
- Radiation is more toxic with similar efficacy to intrathecal chemotherapy
- However, when compared to sibling controls, most studies show significant differences between survivors and siblings (which may or may not be clinically significant)
- Problems include difficulties with:
  - Processing speed
  - Executive function
  - Attention
  - Memory (visual, sequencing)
  - Mathematics, reading

Moleski. Arch Clin Neuropsychol 2000; survivorguidelines.org

Mental Health Disorders
- Depression
- Anxiety
- Post-traumatic stress
- Suicidal ideation

Psychosocial/QOL Effects
- Social withdrawal
- Educational problems
- Relationship problems
- Under-employment
- Dependent living

Risk Factors
- Female sex
- Younger age at Dx
- Neuro-cognitive problems
- Physical factors
- Low socioeconomic status
- Family history of mental health challenges

Second Malignant Neoplasms

- Topoisomerase inhibitors
  - Etoposide
  - Alkylating agents
    - Cyclophosphamide, ifosfamide, nitrosoureas, platinums
  - Radiation therapy
    - Depends on dose, field of radiation, sex, age of exposure

Topoisomerase inhibitors increase risk of acute myeloid leukemia (AML)

Risk of second malignancy due to CNS-directed therapy usually 2-3% risk

Radiation Therapy and Second Cancers

- Radiation therapy
  - Depends on dose, field of radiation, sex, age of exposure
  - Common cancers include
    - Skin, particularly non-melanomatous skin cancer
    - Thyroid
    - Brain tumors if cranial RT
    - Gliomas and high grade gliomas
    - Colorectal
  - Radiation therapy may also increase risk of second cancers

Who should care for these survivors?

- Most Canadian centers have multi-disciplinary survivor clinics
  - Not all can follow these survivors indefinitely
  - The number of survivors is outgrowing our current models of care
    - A good problem!
      - We need to include and engage primary care providers

- Registries needed
  - To access survivors to update them with new guidelines/screening recommendations
  - To allow for good research to improve outcomes


Future directions

- We need to be able to better predict who will develop toxicities
  - Allows for better screening
  - Allows for better therapies which do not cause late effects in individuals at risk

- We need better therapies which cure without acute or late effects
A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer.

**Pediatric Anthracycline Cardiotoxicity Risk Prediction Tool**

Risk of Cardiotoxicity (%)

- ~23% of population. Risk estimate based upon 139 patients. Includes carriers of protective SLC28A3 variant.
- ~60% of population. Risk estimate based upon 356 patients. Includes non-carriers, and carriers of 1 risk + 1 protective variant.
- ~13% of population. Risk estimate based upon 80 patients. Includes carriers of 1 risk variant, or 2 risk + 1 protective variant.
- ~2% of population. Risk estimate based upon 11 patients. Includes carriers of 2 RARG risk variants.
- ~2% of population. Risk estimate based upon 9 patients. Includes carriers of 1+ RARG and 1+ UGT risk variants.

**Terry Fox PROFILE**

Precision Oncology For Young people

Canadian-wide initiative led by The Hospital for Sick Children

Precision medicine platform to choose targeted therapies for “hard to treat” cancers.

Molecular characterizations of tumor and pathways of oncogenesis will allow for drugs to be selected based on an individual's tumor.

**We can do better**

We must do better

We will do better

In the last 20 years, only 3 cancer medications have been specifically approved for children.