Childhood, Adolescent, and Young Adult Cancer Survivorship

John van Doorninck, MD
May 30, 2018
Objectives

- Discuss improvement in cure rates of childhood cancer
- Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival
- Describe strategies used to improve health problems associated with cancer survivorship
- Describe how these interventions have improved the health of childhood/AYA cancer survivors
- Discuss two specific issues of childhood/AYA cancer survival
  - Fertility
  - Psychosocial

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Childhood Cancer: Improved Outcomes

- 1960s: <50% overall survival
- 1975: 60% overall survival
- 2010: 80-90% overall survival

Armstrong, GT, et al. NEJM. 2016
Childhood Cancer: Epidemiology

>83% of children and adolescents who are diagnosed with cancer will become long term survivors

By 2020, an estimated 500,000 survivors of childhood cancer in the United States

Armstrong, GT, et al.  NEJM.  2016
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Challenges facing Childhood/Young Adult Cancer Survivor

Children’s Cancer Survivor Study (CCSS)
- Initial cohort: Patients diagnosed with childhood cancer between 1970-1986 and alive at least 5 years from diagnosis
- Described morbidity and mortality associated with childhood cancer treatment
  - Late effects experienced by patients treated in later eras could be compared to this cohort
Mortality after treatment for childhood cancer: The Childhood Cancer Survivor Study (CCSS):

🌟 Study population: 20,227 five-year survivors of childhood cancer diagnosed between 1970-1986

🌟 Key finding: 11-fold excess in mortality than expected versus population controls

All-cause mortality--sex-specific survival.
(Compared with age-adjusted expected survival in U.S.)

Armstrong GT, et al. JCO. 2009

18% mortality at 30yrs from diagnosis
Armstrong GT, et al. JCO. 2009
Cumulative cause-specific mortality

Armstrong GT, et al. JCO. 2009

Second Malignancies
Armstrong GT, et al. JCO. 2009

Second Malignancies

Cardiac Toxicity
Cumulative cause-specific mortality

Second Malignancies
Cardiac Toxicity
Pulmonary toxicity

Armstrong GT, et al. JCO. 2009
Morbidity after treatment for childhood cancer: The Chronic Health Conditions in Adult Survivors of Childhood Cancer Study

• Study population: 10,397 survivors of childhood cancer diagnosed between 1970-1986

• Key findings:
  • 62.3% had at least one chronic condition (RR 3.3)
  • 27.5% had a severe or life-threatening chronic illness (RR 8.2)

Oeffinger, K. NEJM 2006;355:1572-82
### Table 2. Cancer Survivors and Siblings with a Chronic Health Condition, According to the Severity Score.*

<table>
<thead>
<tr>
<th>Health Condition</th>
<th>Survivors (N=10,397) no. (%)</th>
<th>Siblings (N=3034) no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No condition</td>
<td>3887 (37.4)</td>
<td>1917 (63.2)</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>1931 (18.6)</td>
<td>610 (20.1)</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>1635 (15.7)</td>
<td>349 (11.5)</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>2128 (20.5)</td>
<td>128 (4.2)</td>
</tr>
<tr>
<td>Grade 4 (life-threatening or disabling)</td>
<td>653 (6.3)</td>
<td>30 (1.0)</td>
</tr>
<tr>
<td>Grade 5 (fatal)</td>
<td>163 (1.6)</td>
<td>NA†</td>
</tr>
<tr>
<td>Any condition‡:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1–4</td>
<td>6482 (62.3)</td>
<td>1117 (36.8)</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>2858 (27.5)</td>
<td>158 (5.2)</td>
</tr>
<tr>
<td>Multiple health conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>3905 (37.6)</td>
<td>397 (13.1)</td>
</tr>
<tr>
<td>≥3</td>
<td>2470 (23.8)</td>
<td>163 (5.4)</td>
</tr>
</tbody>
</table>

* The severity of health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3). Health conditions of survivors did not include conditions the patients had before their cancer diagnosis or acute conditions they had within 5 years after the diagnosis. NA denotes not applicable.

† All siblings were alive at the time of enrollment. Survivors may have died in the interval between 5 years after their cancer diagnosis and the time of the study. The composite percentage for survivors with grade 3 or 4 conditions includes conditions that were reported before the time of death in the 163 survivors who died.

‡ The number of patients in each subgroup may not reflect the sum of the grades of conditions, since grades 1 through 5 were calculated by taking the maximum grade per subject. A subject with grade 5 may have had other lower grades.
Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Survivors (N = 10,397)</th>
<th>Siblings (N = 3034)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major joint replacement*</td>
<td>1.61%</td>
<td>0.03%</td>
<td>54.0 (7.6–386.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.24%</td>
<td>0.10%</td>
<td>15.1 (4.8–47.9)</td>
</tr>
<tr>
<td>Second malignant neoplasm†</td>
<td>2.38%</td>
<td>0.33%</td>
<td>14.8 (7.2–30.4)</td>
</tr>
<tr>
<td>Cognitive dysfunction, severe</td>
<td>0.65%</td>
<td>0.10%</td>
<td>10.5 (2.6–43.0)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.11%</td>
<td>0.20%</td>
<td>10.4 (4.1–25.9)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1.56%</td>
<td>0.20%</td>
<td>9.3 (4.1–21.2)</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
<td>0.52%</td>
<td>0.07%</td>
<td>8.9 (2.2–36.6)</td>
</tr>
<tr>
<td>Hearing loss not corrected by aid</td>
<td>1.96%</td>
<td>0.36%</td>
<td>6.3 (3.3–11.8)</td>
</tr>
<tr>
<td>Legally blind or loss of an eye</td>
<td>2.92%</td>
<td>0.69%</td>
<td>5.8 (3.5–9.5)</td>
</tr>
<tr>
<td>Ovarian failure‡</td>
<td>2.79%</td>
<td>0.99%</td>
<td>3.5 (2.7–5.2)</td>
</tr>
</tbody>
</table>

* For survivors, major joint replacement was not included if it was part of cancer therapy.
† For both groups, this category excludes basal-cell and squamous-cell carcinoma (grade 2). For siblings, this category includes a first cancer.
‡ Values are for women only.
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- Fertility
- Psychosocial

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Strategies to Improve Long Term Side Effects:

❖ **Primary Prevention:**
  - Reduce exposure to and/or risk from agents cause late side effects

❖ **Secondary prevention:**
  - Reduce risk of complications of agents already received

Chow, E. ASPHO. 2018
Strategies to Improve Long Term Side Effects:

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Strategies to Improve Long Term Side Effects

 Warfare Prevention:

- Changes in chemotherapy
  - Less reliance on traditional agents
  - Targeted therapy
    - Imatinib (CML, Ph +ALL). Can eliminate BMT
    - Immunotherapy
- Co-administration of medicines to reduce toxicity from chemotherapy agents being received
  - Dexrazoxane (reduce cardiac toxicity)
  - Sodium thiosulfate (reduce ototoxicity)

Chow, E. ASPHO. 2018
Strategies to Improve Long Term Side Effects

ียว Primary Prevention:

 Decrease radiotherapy

 • ALL:
   – 1970’s: 80% received radiation
   – 1990’s: 19% received radiation

 • Wilms tumor
   – 1970’s: 78% received radiation
   – 1990’s: 43% received radiation

 • Hodgkin lymphoma:
   – 1970’s: 87% patients received radiation
   – 1990’s: 61% patients received radiation

 Changing form of radiation (from photons to protons)

Chow, E. ASPHO. 2018
Strategies to Improve Long Term Side Effects:

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- Reduce exposure to and/or risk from agents cause late side effects

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Chow, E. ASPHO. 2018
Strategies to Improve Long Term Side Effects

👩‍⚕️ Secondary prevention:

● Improving adherence of recommended screening
Strategies to Improve Long Term Side Effects

🌟 Secondary prevention:

🔍 Improving adherence of recommended screening
Passport for Care: Implementing the Survivorship Care Plan

By Marc E. Horowitz, MD, Michael Fordis, MD, Susan Krause, Julie McKellar, and David G. Poplack, MD

Texas Children’s Cancer Center; and Center for Collaborative and Interactive Technologies, Baylor College of Medicine, Houston, TX

www.rockymountainhospitalforchildren.com
Strategies to Improve Long Term Side Effects

Secondary prevention:

- Medications to reduce long term risk of agents received (clinical trials)
  - Reduce breast cancer (i.e. women receiving radiation therapy)
    - Tamoxifen prophylaxis x2 years
  - Reduce cardiac toxicity
    - Carvedilol x2 years
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Primary and Secondary Prevention Strategies have reduced late mortality

CCSS:

- Initial cohort: Patients diagnosed with childhood cancer between 1970-1986 and alive at least 5yrs from diagnosis
- New expanded cohort to include patients diagnosed between 1987-1999
  - 10,004 patients

Primary and Secondary Prevention Strategies have reduced late mortality

Good News!
Good News!

🎉 Improved Outcomes

- 1960s: <50% overall survival
- 1975: 60% overall survival
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Good News!

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Decreased Treatment Related Mortality

![Graph showing improved survival rates over time](image)
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Challenges facing Childhood/Young Adult Cancer Survivor

🎉 Three quarters of young cancer survivors hope to have children in the future

🎉 Risk of infertility depends on the specific cancer diagnosis and treatments provided:
  - Certain chemotherapy agents
  - Radiation
    - Gonads
    - Cranial irradiation (pituitary)
### Best Risk Assessment of Subfertility after Current Treatment for Childhood/AYA Cancer

**Low risk (<20%)**
- Acute lymphoblastic leukaemia
- Wilms' tumour
- Soft-tissue sarcoma: stage I
- Germ-cell tumours (with gonadal preservation and no radiotherapy)
- Retinoblastoma
- Brain tumour: surgery only, cranial irradiation <24 Gy

**Medium risk**
- Acute myeloblastic leukaemia (difficult to quantify)
- Hepatoblastoma
- Osteosarcoma
- Ewing's sarcoma: non-metastatic
- Soft-tissue sarcoma: stage II or III
- Neuroblastoma
- Non-Hodgkin lymphoma
- Hodgkin's disease: alternating treatment
- Brain tumour: craniospinal radiotherapy, cranial irradiation >24 Gy

**High risk (>80%)**
- Whole-body irradiation
- Localised radiotherapy: pelvic or testicular
- Chemotherapy conditioning for bone-marrow transplantation
- Hodgkin's disease: treatment with alkylating drugs
- Soft-tissue sarcoma: stage IV (metastatic)
- Ewing's sarcoma: metastatic

Wallace et al. 2005

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Females

Brief review of physiology:

- Females have a finite number of eggs ("oocytes"), most of which naturally die off
  - Fetus: about 5 million
  - Birth: 600,000-800,000
  - Puberty: about 180,000

- Only about 400 oocytes mature and are ovulated in the typical female lifespan

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Oocyte Depletion

![Graph showing oocyte depletion over age](link)
Fertility: Females

Effects of treatment are therefore dependent upon the age at which therapy is given.

Early menopause an issue:
- 42% of female patients treated with chemotherapy and radiation before age 20 had reached menopause by age 31 years.

\(^1\)Byrne et al. 1992.
Fertility Preservation Options: Females

- Embryo cryopreservation
- Oocyte cryopreservation
- Surgically displace ovaries outside of the radiation field
- Hormonal suppression of ovulation
- Ovarian tissue cryopreservation
Fertility Preservation Options: Females

🌟 Embryo cryopreservation

- Ovarian stimulation, egg retrieval, fertilization, storage (freezing), and transfer of embryo into the uterus
- Requires a male partner or sperm donor at time of procedure
- Requirement for hormonal stimulation and time may preclude use due to need to embark on therapy
Fertility Preservation Options: Females

🌟 Oocyte cryopreservation

- Ovarian stimulation, egg retrieval, storage, then fertilization and transfer of embryo into the uterus
- Requirement for hormonal stimulation and time may preclude use due to need to embark on therapy
Fertility Preservation Options: Females

MITIGATING EFFECTS OF RADIATION:
- Surgically displace ovaries outside of the radiation field
- Shielding ovaries from radiation

PRESERVING OOCYTES: Hormonal suppression of ovulation
Fertility Preservation Options: Females

🌟 Ovarian tissue cryopreservation
- Surgery to remove part or all of an ovary
- Tissue frozen
- After treatment, surgically re-implanted with hopes of regaining ovarian function
- Still experimental: 130 live births as of June 2017
- Advantage: immediacy of procedure, little delay in treatment
- Limited availability: About 100 centers worldwide
  - Children’s Hospital Orange County; Texas Children’s, Houston; Children’s Memorial Hospital in Chicago; University of Pittsburgh

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Fertility Effects: Males

様々 Risks:
- Irradiation
- Chemotherapy
- Disease itself may effect sperm count (Hodgkin lymphoma)
Challenges of a Young Adult Cancer Survivor: Fertility

🌸 Fertility preservation options: Males:

🔵 Sperm banking
  • Viability for decades
  • Adolescents less successful
Challenges of a Childhood/AYA Cancer Survivor: Psychosocial
Erik Erickson: 1902-1994
Erik Erikson’s Stage of Psychosocial Development

🌟 Adolescence (age 13-19yrs): Identity
🌟 Young Adulthood (20-39yrs): Intimacy
🌟 Middle Adulthood: (25-64yrs): Generativity
Challenges of a Young Adult Cancer Survivor: Psychological

_water_bottle
Prevalence of symptoms among adult survivors of childhood cancers:
- Learning/memory problems: 26.9%
- Anxiety: 13.1%
- Depression: 15.8%
- Somatization: 19.3%

Huang et al. 2013.
Primary and Secondary Prevention Strategies have reduced late mortality from childhood cancers

Still much work to be done

Specific issues of emotional importance
- Fertility
- Psychosocial