Pediatric Cancer Survivorship: Late Health Effects, Risk-Based Screening, and Optimizing Care Delivery

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Cancer Survivorship Division
Disclosures

• I have no financial interest or other relationship with any manufacturer/s of any commercial products.
Objectives

- Discuss the long-term health conditions commonly experienced by survivors of childhood cancer.
- Explore ways in which treatment should be tailored individually to each patient to reduce long-term consequences.
- Review measures for the monitoring, prevention and management of long-term health conditions in childhood cancer survivors.
- Explore strategies to facilitate collaborative long-term, interdisciplinary care for survivors of childhood cancer.
Emerging Survivor Population

- >84% of children diagnosed with cancer will achieve 5-year survival.
- 1 in 750 individuals in the U.S. is a childhood cancer survivor.
- 500,000 childhood cancer survivors are estimated to be living in the U.S.

Howlader et al, SEER Cancer Statistics Review 1975-2012
Childhood cancer survivors experience increased mortality risk compared to the U.S. population.

Survivor Mortality

- Childhood cancer survivors experience increased mortality risk compared to the U.S. population.
- By 30 years from cancer diagnosis, chronic health conditions surpass recurrent or progressive disease as the leading cause of death.

## Late Effects of Cancer Treatment

<table>
<thead>
<tr>
<th>Cohort Size/Citation</th>
<th>( \geq 1 ) Problem</th>
<th>( \geq 2 ) Problems</th>
<th>Severe Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>58%</td>
<td>32%</td>
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<tr>
<td>Eur J Cancer 1998;24:694-8</td>
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<tr>
<td>288</td>
<td>69%</td>
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<td>21%</td>
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<td>AJPHO 1994;16:143-52</td>
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<tr>
<td>96</td>
<td>69%</td>
<td>36%</td>
<td>30%</td>
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<tr>
<td>Cancer 2000;88:1687-95</td>
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<tr>
<td>10,397</td>
<td>67%</td>
<td>33%</td>
<td>33%</td>
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<td>NEJM 2006;355:1572-82</td>
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<tr>
<td>1,713</td>
<td>95.5%</td>
<td>–</td>
<td>80.5%</td>
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<td>JAMA 2013;309:2371-2381</td>
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Modified from Bhatia 2006
Cumulative Incidence vs. Cumulative Burden

Cardiovascular Conditions in SJLIFE Hodgkin Lymphoma Survivors


Cumulative Burden of Chronic Conditions in Childhood Cancer Survivors

<table>
<thead>
<tr>
<th>Attained Age</th>
<th>Grade 1-5</th>
<th>Grade 3-5</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Survivors</td>
<td>Controls</td>
</tr>
<tr>
<td>30</td>
<td>7.7</td>
<td>2.0</td>
</tr>
<tr>
<td>50</td>
<td>17.1</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Bhakta, et al Lancet 2017

Grades 3-5 Chronic Health Conditions

Bhakta et al, Lancet 2017
Factors Influencing Survivor’s Health Outcomes

- Survivorship education or training
- Survivorship experience
- Practice style
- Perceptions regarding preventive care
- Access to survivorship resources
- Knowledge or access to individual survivor health history

- Age at treatment and attained age
- Sex, race or ethnicity
- Familial or genetic factors
- Pre- or co-morbid conditions
- Health behaviours
- Cognitive or developmental status
- Health knowledge
- Health risk perceptions
- Self-efficacy
- Insurance or health care access

- Histology or involved sites
- Biology or response
- Treatment
- Surgery
- Chemotherapy
- Radiotherapy
- Transplantation
- Transfusion
- Treatment events

- Financing and payment policies
- Organization and affiliation of providers
- Data systems and information sharing
- Models of survivorship care
- Insurance coverage and benefits supporting survivorship care (especially preventive and psychosocial services)
- Community resources
- Survivorship advocacy activity

Robison and Hudson, Nat Rev Cancer 2014
Late Effects as Stimulus for Change

Musculoskeletal

Cardiac

Subsequent cancers
# Finding the Balance: Cost of Cure

## Cumulative Doses Associated with Long-Term Sequelae in Comparable Pediatric Hodgkin Regimens (mg/m²)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stanford V + Radiation</th>
<th>GPOH-HD 2002 ± Radiation</th>
<th>HLHR13 ± Radiation</th>
<th>RC 59704 Rapid Responders + Radiation (Males)</th>
<th>RC 59704 Slow Responders + Radiation (Both)</th>
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</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>150</td>
<td>160</td>
<td>160</td>
<td>340</td>
<td>280</td>
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<tr>
<td>Bleomycin</td>
<td>30</td>
<td>120</td>
<td>80</td>
<td>120</td>
<td>80</td>
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<tr>
<td>Etoposide</td>
<td>360</td>
<td>1250</td>
<td>1250</td>
<td>2400</td>
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<tr>
<td>Cyclophosphamide</td>
<td>2000</td>
<td>4000</td>
<td>4800</td>
<td>4800</td>
<td>7600</td>
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<td>Procarbazine</td>
<td>3000</td>
<td>3000</td>
<td>2800</td>
<td>2800</td>
<td>4480</td>
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<td>Dacarbazine</td>
<td>3000</td>
<td>3000</td>
<td>2240</td>
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<td>5600</td>
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<tr>
<td>Mechlorethamine</td>
<td>18</td>
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<tr>
<td>Brentuximab vedotin</td>
<td></td>
<td></td>
<td>16.8</td>
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<tr>
<td>Prednisone</td>
<td>1120</td>
<td>4200</td>
<td>4200</td>
<td>2240</td>
<td>4480</td>
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</table>

*Flerlage, personal communication*
Finding the Balance: Cost of Cure

Cumulative Doses Associated with Long-Term Sequelae in Comparable Pediatric Hodgkin Regimens (mg/m²)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Doxorubicin (mg/m²)</th>
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<tbody>
<tr>
<td>Stanford V</td>
<td>150</td>
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<td>GPOH-HD 2002</td>
<td>160</td>
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<tr>
<td>HLHR13</td>
<td>160</td>
</tr>
<tr>
<td>CCG 59704</td>
<td>340</td>
</tr>
</tbody>
</table>

Rapid Responders
- BEACOPP + Radiation (Males)
- BEACOPP+ABVD

Slow Responders
- BEACOPP + Radiation (Females)
- BEACOPP


Heart Failure

- RT + anthracycline
- Anthracycline alone
- RT alone
- No RT or anthracycline
- Sibling

Cumulative Doses Associated with Long-Term Sequelae in Comparable Pediatric Hodgkin Regimens (mg/m^2)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Radiation</th>
<th>Rapid Responders</th>
<th>Slow Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford V GPOH-HD 2002</td>
<td>+ Radiation ± Radiation</td>
<td>BEACOPP+ABVD</td>
<td>BEACOPP+ABVD</td>
</tr>
<tr>
<td>HLHR13</td>
<td>± Radiation</td>
<td>BEACOPP+ABVD</td>
<td>BEACOPP+ABVD</td>
</tr>
<tr>
<td>CCG 59704</td>
<td></td>
<td>+ Radiation (Males)</td>
<td>+ Radiation (Both)</td>
</tr>
</tbody>
</table>

Rapid Responders: OEPA/COPDaC ± Radiation
Slow Responders: AEPA/CAPDaC ± Radiation


Finding the Balance: Cost of Cure

Mantle Radiation  
Involved Field Radiation  
Involved Node Radiation

Temporal Trends in Mortality and Morbidity

- Strategies of lowering treatment exposures have led to reductions in survivor *mortality* over time.

Strategies of lowering treatment exposures have led to reductions in survivor mortality over time.

• Strategies of lowering treatment exposures have led to reductions in survivor morbidity over time.

Gibson et al, *Lancet Oncol* 2018
Late Effects and Impact on Survivors

• Medically complex population with diverse healthcare needs.
• At risk for adverse psychosocial and medical outcomes.

Model for Care Across the Cancer Continuum

Primary Interventions
- Risk-adapted therapy considering cancer- and host-related factors

Secondary Interventions
- Health education
- Health screening/surveillance
- Risk-reducing interventions

- Cancer Diagnosis
- Pediatric Health Care
- Long-Term Survival
- Adult Health Care
- Survivor Health & Quality of Life

Modified from Hudson, Cancer 2005
Emergence of Cancer Survivorship

• 1986 – National Coalition for Cancer Survivorship
  – Change perspective from “cancer victim” with “cancer survivor”
  – Influence government agencies and policymakers

• 2005 – Institute of Medicine Publication Essential Aims for Survivorship Care
  – Prevention of recurrent/new cancer and late effects
  – Cancer surveillance (progression, recurrence, or secondary)
  – Assessment of medical and psychosocial late effects
  – Intervention for consequences of cancer and its treatment
  – Coordination between specialists and primary care providers to ensure survivors' health needs are met
Institute of Medicine, 2005 Recommendation:

“Patients completing primary treatment should be provided with a comprehensive care summary and follow-up plan that is clearly and effectively explained.”
Survivorship Care Plans

- Diagnostic (cancer) information
- Cumulative treatment exposures
- Clinical events and status
- Transfusion history
- Family history
- Cancer-related health risks
- Health behaviors modifying risks
- Risk-based screening recommendations
Institute of Medicine, 2005 Recommendation:

“Health care providers should use systematically developed evidence-based clinical practice guidelines, assessment tools, and screening instruments to identify and manage late effects of cancer and its treatment.”
Clinical Practice Guidelines

- **Exposure-based**
  - Includes screening and counseling based on specific chemotherapy, radiation doses/volumes and surgery

- **Disease-based**
  - Focuses on modalities and health concerns related to a specific malignancy (e.g., NCCN breast, prostate)

- **Organ-system based**
  - Considers specific organ systems affected by cancer or cancer therapy

- **Symptom-based**
  - Targets symptoms common to many cancer diagnoses and treatment (e.g., fatigue, sleep, cognition)
Children’s Oncology Group Survivorship Guidelines

- survivorshipguidelines.org
- Updated every 5 years
- Comprehensive literature search and grading of evidence
Children’s Oncology Group Survivorship Guidelines

- Evidence linking late effects with therapeutic exposures
- Screening recommendations based on expert clinical experience
- Allows identification of high-risk categories
- Matches magnitude of risk with intensity of screening

- [survivorshipguidelines.org](http://survivorshipguidelines.org)
- Updated every 5 years
- Comprehensive literature search and grading of evidence
- Consensus based recommendations – hybrid of evidence and expert opinion

Organized around risk-based exposure, including corresponding offending agents
Children’s Oncology Group Survivorship Guidelines

- Organized around risk-based exposure, including corresponding offending agents
- Pertinent late effects are individually listed

<table>
<thead>
<tr>
<th>CHEMOTHERAPY</th>
<th>POTENTIAL LATE EFFECTS</th>
<th>PERIODIC EVALUATION</th>
<th>HEALTH COUNSELING/FURTHER CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEC 33</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anthracycline Antibiotics</td>
<td>Cardiac toxicity</td>
<td>HISTORY:</td>
<td></td>
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<tr>
<td>Daunorubicin</td>
<td>Cardiomyopathy</td>
<td>Shortness of breath</td>
<td>HEART HEALTH</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Subclinical left ventricular dysfunction</td>
<td>Dyspnea on exertion</td>
<td>Cardiac Risk Factors</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Congestive heart failure</td>
<td>Chest pain</td>
<td>Diet and Physical Activity</td>
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<tr>
<td>Idarubicin</td>
<td>Anemia</td>
<td>Palpitations</td>
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<tr>
<td>Mitoxantrone</td>
<td></td>
<td>Yearly</td>
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<tr>
<td>Dose Conversion</td>
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</tbody>
</table>

**ANTHRACYCLINE ANTIBIOTICS (CONT)**

- **HEALTH LINKS**
  - Heart Health
  - Cardiac Risk Factors
  - Diet and Physical Activity

- **COUNSELING**
  - Cardiac: appropriate weight, blood pressure, and heart-healthy diet.
  - Regular exercise in patients without symptoms and should be encouraged for patients with normal or mildly impaired left ventricular function.

- **SCREENING**
  - ECG (or comparable imaging to evaluate cardiac function)

- **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION**
  - ECHO (or comparable imaging to evaluate cardiac function)

**Additional Information**

Although Mitoxantrone technically belongs to the anthracycline class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.
Suggested evaluations are outlined pertinent to the exposure and degree of risk.

## Children’s Oncology Group Survivorship Guidelines

### CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Sec 4</th>
<th>Therapeutic Exposure</th>
<th>Potential Late Effects</th>
<th>Periodic Evaluation</th>
<th>ANTHRACYCLINE ANTIBIOTICS (CONT)</th>
</tr>
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<tbody>
<tr>
<td>33</td>
<td>Anthracycline Antibiotics</td>
<td>Cardiac toxicity, Cardiomyopathy</td>
<td>History: Shortness of breath, Dyspnea on exertion, Orthopnea, Chest pain, Palpitations, Abdominal symptoms (nausea, vomiting)</td>
<td>Health Counseling/Further Considerations: Heart Health, Cardiac Risk Factors, Diet and Physical Activity</td>
</tr>
<tr>
<td></td>
<td>Daunorubicin</td>
<td>Subclinical left ventricular dysfunction, Congestive heart failure, Arrhythmia</td>
<td>Yearly, Yearly, Yearly, Yearly, Yearly</td>
<td>Counseling</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td>Counselling: Maintain appropriate weight, blood pressure, and healthy diet.</td>
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<td></td>
<td>Etoposide</td>
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<td></td>
<td>Regarding exercise: Regular exercise is generally safe and advised for patients who have normal or subclinical function.</td>
</tr>
<tr>
<td></td>
<td>Idarubicin</td>
<td></td>
<td></td>
<td>Survivors with asymptomatic cardiac injury should consult cardiologists to define limits and precautions for physical activity.</td>
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<tr>
<td></td>
<td>Mitoxantrone</td>
<td></td>
<td></td>
<td>Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intense exercise.</td>
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<td>If CRT is interval, consult. Guidelines regarding use of medications that may further impair the QoT should be reviewed.</td>
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### ANTHRACYCLINE ANTIBIOTICS (CONT)

#### HISTORY

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#### PHYSICAL

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#### SCREENING

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#### ECHO (or comparable imaging to evaluate cardiac function)

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#### EKG (include evaluation of QoT interval)

Baseline at entry into long-term follow-up, repeat as clinically indicated.

### ADDITIONAL INFORMATION

Although Mitoxantrone technically belongs to the anthracycline class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.
Suggested evaluations are outlined pertinent to the exposure and degree of risk. Further considerations and the level of evidence (scored according to the National Comprehensive Cancer Network “Categories of Consensus”) are provided.
Institute of Medicine, 2005
Recommendation:

“...qualified organizations should support demonstration programs to test models of coordinated, interdisciplinary survivorship care in diverse communities and across systems of care.”
Adult Survivors’ Medical Visits in Past 2 Years

Years Since Cancer Diagnosis to Baseline Questionnaire

- General Medical Contact
- General Physical Examination
- Cancer-Related Medical Visit
- Cancer Center Medical Visit

What Care Do Survivors Receive?

- 88.8% reported ≥ 1 medical visit during previous 2 years
- Reported care
  - No medical care (11.2%)
  - General medical care (57.3%)
  - General survivor care (13.7%)
  - Risk-based survivor care (17.8%)
Models of Survivorship Care

Treatment of Cancer

Cancer Center Follow-up

Long-Term Follow-Up

Community Follow-up

Shared Care

Specialized LTFU Clinic

Other Models

Adapted from Singer et al, Pediatr Blood Cancer 2013
• Risk of recurrence and late effects
• Type of services to be provided
  - Medical
  - Psychological
  - Social
  - Rehabilitative
  - Financial
• Timing of the services
  - Transition visit at the end of therapy
  - Specified time after completion of treatment
  - Ongoing care
Most Effective Care Delivery Model

- Existing studies vary by disease group, comparative delivery models, and outcomes.

<table>
<thead>
<tr>
<th>Type of Survivorship Intervention</th>
<th>Author and Year</th>
<th>Quality of Life</th>
<th>Depression</th>
<th>Anxiety/Distress</th>
<th>Well-Being</th>
<th>Satisfaction</th>
<th>Resource Use</th>
<th>Adherence to Planned Follow-Up</th>
<th>Disease-Free Period</th>
<th>Overall Survival</th>
<th>Recurrence</th>
<th>Perceptions of Health</th>
<th>Engagement in Health-Promoting Activities</th>
<th>Cancer Survivors' Knowledge</th>
<th>Coordination/Continuity of Care</th>
<th>Unmet Needs</th>
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<tr>
<td>Physician-led</td>
<td>Cannon et al., 2011</td>
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<tr>
<td>Nurse-led</td>
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Halpern et al, J Oncol Pract 2015

- No model has demonstrated superiority in all healthcare environments.
- The preferred model is that which can be implemented within the available resources.
Childhood cancer survivors are at increased risk for chronic health conditions compared to the general population.

Cancer treatment has been modified over time in order to reduce treatment-related exposures that increase risk for adverse health.

Risk-based guidelines provide recommendations regarding care delivery for this medically complex population.

A variety of care delivery models exist and should be adapted to local resource availability.