Transitioning Survivors of Childhood Cancer to Adult Endocrine Providers

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Change in Cure Rates of Childhood Cancers by Diagnosis

Hudson MM et al, J Clin. Onc 2014
Childhood Cancers: Survivorship Statistics

- Currently more than 380,000 survivors living in US
- 1 in 530 in the US between ages 20 and 39 yrs is a childhood cancer survivor
- Number of survivors in US will approach 500,000 by 2020
What are the long-term consequences of exposing children and adolescents to radiation therapy and multi-agent chemotherapy?
Spectrum of Health-related and Quality of Life Outcomes

Childhood Cancer Survivor Study

- 37,000 5-Year Survivors
- 1970-99
- Hospital-based
- Treatment data >90%
- Self-report for most outcomes
- Biological samples (7000+)
Factors to be Considered in Risk of Late Effects

- Age
- Gender
- Genetics
- Social
- Other Health
- Lifestyle

CT
RT
S
Radiation-induced abnormalities are, in general, both *dose* and *time* dependent.
## Change in Treatment Characteristics over Time (CCSS)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>1970’s</th>
<th>1980’s</th>
<th>1990s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>57%</td>
<td>77%</td>
<td>58%</td>
<td>41%</td>
</tr>
<tr>
<td>Chest</td>
<td>24%</td>
<td>33%</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>CNS</td>
<td>30%</td>
<td>39%</td>
<td>33%</td>
<td>19%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>23%</td>
<td>33%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%) receiving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>45%</td>
<td>27%</td>
<td>48%</td>
<td>58%</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>52%</td>
<td>43%</td>
<td>55%</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median among receiving)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines (mg/m²)</td>
<td>217</td>
<td>323</td>
<td>251</td>
<td>181</td>
</tr>
<tr>
<td>Alkylating agents (CED* g/m²)</td>
<td>7.7</td>
<td>10.5</td>
<td>7.4</td>
<td>7.2</td>
</tr>
</tbody>
</table>

*CED = cyclophosphamide equivalent dose

Cumulative Incidence of Chronic Health Conditions in Survivors, by Grade (n = 10,397)

Multiple Chronic Health Conditions in Survivors, Grade 3-5

Endocrine and Metabolic Complications

- Among most prevalent late effects in survivors of childhood cancer
- Most often seen in survivors treated with:
  - Radiation to head, neck, or pelvis (e.g., brain tumors, Hodgkin lymphoma, TBI stem cell transplant)
  - High-dose alkylating agents (Hodgkin lymphoma, stem cell transplant)
<table>
<thead>
<tr>
<th>Radiotherapy field</th>
<th>Cancer</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>Whole brain, total-body irradiation, orbital</td>
<td>HPA-related deficiencies (GH, TSH, ACTH, LH, FSH), obesity, diabetes</td>
</tr>
<tr>
<td>Neck</td>
<td>CRT, total-body irradiation, spinal, neck</td>
<td>Hypothyroidism, hyperthyroidism, thyroid nodules, thyroid cancer</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Whole abdomen, flank, para-aortic, total-body irradiation</td>
<td>Insulin resistance, diabetes, fatty liver</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvis, total-body irradiation</td>
<td>Premature ovarian insufficiency, impaired spermatogenesis, Leydig cell failure</td>
</tr>
</tbody>
</table>

HPA=hypothalamic-pituitary axis. GH=growth hormone. TSH=thyroid-stimulating hormone. ACTH=adrenocorticotropic hormone. LH=luteinising hormone. FSH=follicle-stimulating hormone. CRT=cranial radiotherapy. *Risk for outcome can be dose-dependent.

Table 1: Radiation treatment fields and common endocrine outcomes

ALiCCS: Cumulative risk for a first hospital contact for an endocrine disorder (n=31,723)

- Relative risk of endocrine diagnosis was 4.8 (4.6-5.0 95%CI) in survivors compared to controls.

- The prevalence of endocrine disease by the age of 60 years was 43% in individuals diagnosed with cancer when they were 5-9 years old.

Endocrine Complications

- **Hypothalamic-Pituitary Dysfunction**
  - GH deficiency
  - Early puberty
  - LH/FSH, TSH, ACTH deficiencies
  - Hyperprolactinemia
  - Obesity
- **Thyroid abnormalities**
  - Primary hypothyroidism
  - Hyperthyroidism
  - Thyroid neoplasms
  - Hyperparathyroidism?
- **Gonadal dysfunction**
  - Males
    - Infertility
    - Leydig cell failure
  - Females
    - Acute ovarian failure
    - Premature menopause
- **Bone disease**
  - Osteoporosis
  - Osteonecrosis
  - Rickets
- **Metabolic abnormalities**
  - Insulin insufficiency
  - Insulin resistance/metabolic syndrome/DM
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Radiation Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH deficiency</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>LH/FSH deficiency</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>TSH deficiency</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>ACTH deficiency</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>&gt; 40-50</td>
</tr>
</tbody>
</table>
Peak GH According to Hypothalamic Dose and Time After RT

Merchant TE, JCO 2011;29:4776
Cumulative Incidence of Hypothalamic-Pituitary Deficits in Survivors Treated with Cranial Radiation: SJLife Cohort (N=748)

- **GH deficiency**
  - No. at risk (No. failed): 748 (102) 646 (37) 538 (97) 255 (94) 37 (18) 0

- **TSH deficiency**
  - No. at risk (No. failed): 743 (24) 719 (15) 595 (10) 266 (6) 38 (1) 0

- **LH/FSH deficiency**
  - No. at risk (No. failed): 731 (17) 714 (11) 593 (20) 262 (23) 39 (8) 0

- **ACTH deficiency**
  - No. at risk (No. failed): 743 (17) 726 (9) 608 (2) 272 (2) 38 (0) 0

Cumulative Incidence of Growth Hormone Deficiency in Survivors Treated with Cranial Radiation: CCSS

Thyroid Abnormalities

Primary Hypothyroidism
Hyperthyroidism
Thyroid cancer
Among 1791 five year survivors in the CCSS, 34% were diagnosed with at least one thyroid abnormality.

Hypothyroidism was the most common abnormality with a relative risk of 17.1 (p<0.001).

Risk factors for hypothyroidism

- Increasing dose of radiation
- Older age at diagnosis
- Female sex
Probability of developing an underactive thyroid after diagnosis of Hodgkin's lymphoma

N=1,791

Sklar et al, JCEM 85:3227, 2000
Thyroid Cancer Risk By Dose of Radiation to the Thyroid

Veiga et al, Radiation Res 2012;178:365
Thyroid Cancer Risk by dose of Radiation to the Thyroid

Survivors vs Siblings

HR 5.9 (3.0-11.6)
Thyroid Cancer Risk by dose of Radiation to the Thyroid

Prevalence of Premature Ovarian Insufficiency in the CCSS

"High-Risk" Exposures*

Ovarian RT
- Age < 12 yrs ov RT > 15 Gy
- Age >/= 12 yrs, ov RT > 10 Gy

CED > 8 gms/m²

Any pelvic RT + CED > 0

*Modified from COG Guidelines

Prevalence of Premature Ovarian Insufficiency in the CCSS

Risk of Diabetes Mellitus in Survivors

## Risk of DM in CCSS: Multiple Logistic Regression Model

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<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Age &lt;4 dx</td>
<td>2.4</td>
<td>1.3-4.6</td>
</tr>
<tr>
<td>Attained age</td>
<td>1.9</td>
<td>1.2-3.1</td>
</tr>
<tr>
<td>BMI, current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>1.0</td>
<td>ref</td>
</tr>
<tr>
<td>25-29.9</td>
<td>2.0</td>
<td>1.3-3.0</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>4.3</td>
<td>2.9-6.4</td>
</tr>
<tr>
<td>Inactivity</td>
<td>1.5</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>AA</td>
<td>1.5</td>
<td>1.1-2.1</td>
</tr>
<tr>
<td>ABD RT</td>
<td>2.7</td>
<td>1.9-3.8</td>
</tr>
<tr>
<td>TBI</td>
<td>7.2</td>
<td>3.4-15.0</td>
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Meacham et al, Arch Int Med 2009
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Meacham et al, Arch Int Med 2009
Risk of Diabetes Mellitus in Survivors

Trajectory of Medical Follow-up and Development of Chronic Health Conditions Over Time (CCSS)

Prevalence or cumulative incidence *

- Chronic health conditions, any grade
- Cancer-focused visit within past two years

Interval from cancer diagnosis, years

Prevalence or cumulative incidence *

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
0 5 10 15 20 25

* GRADE 1-5 CCFU
Transitioning Survivors of Childhood Cancer: Issues to Consider

• Due to long latency between specific exposures and development of some endocrine complications:
  – Many “at risk” survivors (eg, hx of low dose CRT) without identified endocrine issues, nonetheless, require long-term endocrine surveillance
  – Survivors with known endocrine issues may be at risk for additional endocrinopathies over time

• Survivors at high-risk for non-endocrine co-morbidities

• Subset (eg, BT survivors) cognitively impaired
Barriers to Transitioning Survivors of Childhood Cancer to Adult Providers

• **Survivors**
  – Unaware of, or underestimate future risks
  – Lack of access to specialty care
  – Under-employed and under-insured compared to sibs

• **Providers**
  – Knowledge deficits
  – Discomfort managing disease in cancer patient
  – Difficulty obtaining adequate treatment records
Conclusions

- Endocrine complications highly prevalent among survivors of childhood cancer
- Risk for late effects determined largely by the individual’s therapeutic exposures
- Risk for late effects increases over time
- Lifelong surveillance required for those at risk
http://www.survivorshipguidelines.org/
A Resource for Research

- The **Childhood Cancer Survivor Study** is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.
- Investigators interested in potential uses of this resource are encouraged to visit [www.stjude.org/ccss](http://www.stjude.org/ccss)
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