Cancer Survivorship: Pediatrics Leading the Way ... And Still Evolving

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Age-specific Cancer Incidence

Data Source: SEER 2010
Common Childhood Cancers

- Leukemia
- CNS tumor
- Lymphoma
- Sarcoma
- Wilms
- NB
- Other
Survival of Childhood Cancers
Ages 0-19 years

Data Source: SEER 2010
Childhood Cancers: Survivorship Statistics

• Estimate 13,500 newly diagnosed cases annually

• 2010, estimated 379,100 survivors living in US

• 1 in 750 in the US is a childhood cancer survivor
Spectrum of Health-related and Quality of Life Outcomes

Growth & Development
- Skeletal maturation
- Linear growth
- Intellectual function
- Emotional/social maturation
- Sexual development

Organ Function
- Fertility
- Health of offspring
- Sexual functioning

Carcinogenesis
- Sexual development
- Sexual functioning
- Subsequent neoplasms
- Recurrent primary cancer

Psycho-social
- Mental health
- Education
- Employment
- Insurance
- Social interactions
- Chronic symptoms
- Physical & body image

Recurrent primary cancer
- Subsequent neoplasms

Childhood & Adolescent Cancer
- Mental health
- Education
- Employment
- Insurance
- Social interactions
- Chronic symptoms
- Physical & body image

Cardiac
- Endocrine
- GI/Hepatic
- Genitourinary
- Musculoskeletal
- Neurologic
- Pulmonary

Chronic symptoms
- Employment
- Insurance
- Social interactions
- Physical & body image

Recurrent primary cancer
- Subsequent neoplasms

Sexual development
- Sexual functioning
- Health of offspring
- Fertility

Subsequent neoplasms
- Sexual development
- Sexual functioning
- Health of offspring
- Fertility

Sexual functioning
- Health of offspring
- Fertility

Health of offspring
- Fertility

Fertility
- Health of offspring

Fertility & Reproduction
- Fertility
- Health of offspring

Endocrine
- GI/Hepatic
- Genitourinary
- Musculoskeletal
- Neurologic
- Pulmonary

GI/Hepatic
- Genitourinary
- Musculoskeletal
- Neurologic
- Pulmonary

Genitourinary
- Musculoskeletal
- Neurologic
- Pulmonary

Musculoskeletal
- Neurologic
- Pulmonary

Neurologic
- Pulmonary

Pulmonary

Robison and Hudson
Nature Rev Cancer
2014
Factors to be Considered in Risk of Late Effects

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

CT S RT
At Schneider Children’s Medical Center of Israel, a cancer survivors follow up clinic was established 35 years ago by Prof. Rina Zaizov.
Pregnancy outcome in women who received doxorubicin for malignancy in childhood is generally favorable. However, those with baseline left ventricular dysfunction should be considered at increased risk for worse pregnancy outcome and further deterioration in myocardial function. 


Survivors of childhood ALL treated with cranial radiation require prolonged surveillance because of a high incidence of late meningiomas. Early detection, when the tumor is still small, facilitates resection and may reduce complications.


Half of the survivor sample reported subjective feelings that their illness experience had impaired their achievement in several domains. Quality of life is considered an important outcome parameter in terms of clinical decision making as well as in guiding preventive and supportive intervention efforts.


Childhood brain tumor survivors are at increased risk of late endocrine effects, particularly those treated with cranial radiation and diagnosed at a younger age. The frequency of hormonal deficits increases with time, warranting lifelong surveillance.

Horm Res Paediatr. 2011;76(2):113-22

Endocrine complications and components of the metabolic syndrome in survivors of childhood malignant non-brain solid tumors.


Risk factors for endocrine complications and parameters of the metabolic syndrome in patients who underwent hematopoietic stem cell transplantation during childhood and adolescence -A retrospective cohort analysis.

Bone Marrow Transplant. 2006 Jun;37(12):1109-17
Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin’s lymphoma: an analysis from the St Jude Lifetime Cohort Study

*Lancet Oncol* 2016
Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium

Clin Oncol 34. 2016
A meta-analysis of the neuropsychological effects of chemotherapy in the treatment of childhood cancer

*Pediatr Blood Cancer* 2016

- Children diagnosed with cancer, who received chemotherapy, demonstrated *deficits in attentional capacity* ($g=-0.277$).

- These deficits are noted in the context of relatively unaffected performance in other domains.

- When examining potential moderators, those tested more than 5 years after completion of treatment demonstrated better attentional performance than those tested within 5 years of treatment completion.

- These deficits in attentional capacity have implications related to the academic success of these children.

- Given the potential for remediation strategies within this domain, neuropsychological assessment can be an integral aspect of long-term care plans of survivors of childhood cancer.
Risk of Severe Neurocognitive Impairment in ALL Survivors: Effect of Age at Diagnosis and Dose of CRT

Krull et al, J Clin Oncol, 2013
Endocrine and metabolic disturbances in survivors of hematopoietic stem cell transplantation in childhood and adolescence

The endocrine system of a growing child is an exquisitely sensitive target for the cytotoxic effects of the high-dose chemotherapy and radiation that are often administered before HSCT.

We found that endocrine and metabolic complications were extraordinarily common in our patients, with a prevalence of 65.2%.

This number is likely to increase as the cohort continues to mature.

The FORUM study – an attempt to omit radiation
St. Jude Lifetime Cohort

Childhood Cancer Survivor Study

- 37,000 5-Year Survivors
- Hospital-based Treatment Data
- Biological samples (>90%)
Childhood Cancer Survivor Study

- Retrospective cohort assembled in 1994
- 5-yr survival
- Leukemia, lymphoma, CNS, bone, Wilms’, NBL, soft-tissue sarcoma
- Diagnosis **1970-1986**
- Age <21 yr at diagnosis
- Detailed treatment data
- Biological samples
- Wide range of outcomes

```
20,720  Eligible

20,720  Eligible
- Lost  \( (n = 3017) \)

17,703  Contacted

17,703  Contacted
- Refusal  \( (n = 3189) \)

14,372  Participants
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Late Mortality Among 5+ Year Survivors
Childhood Cancer Survivor Study
(N=20,483)

Cumulative cause-specific mortality

## Cause-Specific Late Mortality within CCSS

### Non-recurrent, non-external

<table>
<thead>
<tr>
<th></th>
<th># deaths</th>
<th>SMR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cancer</td>
<td>470</td>
<td>15.2</td>
<td>(13.9-16.6)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>176</td>
<td>7.0</td>
<td>(5.9-8.2)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>67</td>
<td>8.8</td>
<td>(6.8-11.2)</td>
</tr>
<tr>
<td>Other causes</td>
<td>166</td>
<td>2.6</td>
<td>(2.3-3.0)</td>
</tr>
</tbody>
</table>

Mertens AC et al, JNCI 100:1368, 2008
Cumulative Incidence of Chronic Health Conditions in Survivors, by Grade (n = 10,397)

Cumulative Incidence

YRS since diagnosis

Grade 1-5

Grade 3-5

Cumulative Incidence of Chronic Conditions: Grades 3-5

Armstrong et al, 2013
### High yield conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosed Before study</th>
<th>Identified by screening</th>
<th>Available therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary dysfunction</td>
<td>8%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Low BMD</td>
<td>10%</td>
<td>23%</td>
<td>Calcium supp.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>30%</td>
<td>10%</td>
<td>Thyroid replacement therapy</td>
</tr>
<tr>
<td>Iron overload</td>
<td>none</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>13%</td>
<td>23%</td>
<td>Auditory amplification</td>
</tr>
</tbody>
</table>

- Asymptomatic nature in early stage
- Fairly long latency
Pre-existing conditions, screening yield, and overall prevalence for high-yield (≥ 10%) screening tests.
St. Jude Lifetime Cohort (SJLIFE)

Cohort Characteristics

1713 Adult Survivors
Median Age 32 years (range 18-60)
Median time from Diagnosis 25 years (range 10-47)
51% Female
87% Caucasian

Hudson/Ness et al, JAMA, 2013
At SJLife
Before SJLife
Screened → 417 251 1214 685 1062 1127 1422 1536 920 1142 1437 1410 113 1375 640

Yield (%) from Risk-Based Screening
Yield (%) from Risk-Based Screening
Most childhood cancer survivors are not followed at a cancer center

Conclusions

- Survivors of childhood cancer are a vulnerable population:
  - Overall death rate is 8 times greater than general population
  - More than 70% of survivors will develop at least one chronic medical condition by 30 yrs from diagnosis of their cancer
  - At age 45 yrs, ~80% will have a serious/disabling or life-threatening chronic health condition
- Late effects are determined largely by the individual’s therapeutic exposures
- Risk for late effects increases over time
- Lifelong surveillance required for those at risk
Transition and transfer of childhood cancer survivors to adult care: A national survey of pediatric oncologists

Pediatr Blood Cancer 2016

Pediatric oncologists are responsible for ensuring that adolescent and young adult childhood cancer survivors have the knowledge and skills necessary to manage their follow up care in adult healthcare systems.

The most frequent barriers to transfer were:

- perceived attachment to provider (91%),
- lack of adult providers with cancer survivor expertise (86%),
- patient’s cognitive delay (81%),
- unstable social situation (80%)

Oncologists who continue to care for patients older than 25 years are more likely to perceive parents’ attachment to provider (P=0.037) and patients’ social situation as barriers to transfer (P = 0.044).

Although most pediatric oncologists reported transferring AYA cancer survivors to adult care and providing some transition education, they endorse deficits in transition skills, emotional readiness, and institutional resources.
Among patients in whom childhood cancer was diagnosed in the 1970s and 1980s, 18% of those who survived for 5 years died within the subsequent 25 years.

In recent decades, cancer treatments have been modified with the goal of reducing life-threatening late effects.

The strategy of lowering therapeutic exposure has contributed to an observed decline in late mortality among 5-year survivors of childhood cancer.
Lifestyle behavior interventions delivered using technology in childhood, adolescent, and young adult cancer survivors: A systematic review

Pediatr Blood Cancer 2016;00: 1–5

- Studies saw positive effects on motor performance/body coordination, body composition, flexibility, and fitness.

- Data suggest that childhood and AYA cancer survivors consume excess energy and exhibit poor dietary habits after treatment.

- Participation in lifestyle interventions presents a major challenge with the geographically dispersed childhood and AYA cancer survivors.

- Technology based programs will help insure distance to program is not a barrier to participation.
Practical implications:

✓ useful for primary care providers

✓ high yield of certain screening tests demonstrates the need for referral to subspecialists for appropriate interventions

✓ increased awareness of these complications by the specialists.

The incidence of treatment-related complications will likely increase with time from diagnosis

Imperative to continue follow-up of childhood cancer survivors, using standardized recommendations, such as those offered by the COG-LTFU Guidelines.

This study serves as an example of how application of the COG-LTFU Guidelines in a clinical setting can be used to refine them.

The results of this study support the need for additional research to contribute to ongoing refinement of the recommendations for screening frequencies and modalities within the COG-LTFU Guidelines.
Pediatric cancer centers follow three core principles that enhance their patients’ overall care experience.

- **Focus on Families, Not Just Patients:**
  Pediatric cancer centers know that true patient centeredness means having clinicians work in dynamic partnership with sick children’s families.

- **Tailor the Communication:**
  Tailoring language, asking questions, listening without unnecessary interruptions, and using learning aids promote understanding while fostering respect and trust, and medical terms are most effectively explained in simple, rather than technical language.

- **Embrace Play:**
  “Men do not quit playing because they grow old; they grow old because they quit playing.”
  Play can help older patients, ranging from teenagers to the cognitively impaired elderly, see that they are more than their cancers, capable of enjoying a new activity, learning a new skill, or simply experiencing inner calm.

Putting the three principles into practice in adult-care settings requires time, commitment, and sometimes extra cost.

Clinicians should consider some fundamental questions: Who is this patient as a person? Which people matter to this patient? How can I best meet each of their needs.
What Adult Cancer Care Can Learn From Pediatrics

- The recent improvement in adult cancer treatment results in many more long term survivors.

- The growing population of adult cancer survivors carries a significant burden of morbidity, necessitating comprehensive long-term follow-up of these survivors.

- This follow-up should ideally begin at the completion of active therapy, with a documented summary of therapeutic exposures and recommendations for follow-up, thus ensuring standardization of care received by the survivors.

- Better understanding of treatment-related toxicity in pediatrics, has not only guided the design of less toxic therapies, but also the development of treatment summaries, survivorship plans, and efforts to harmonize survivorship guidelines worldwide that could serve as a model for the survivorship care of adult cancer survivors.

- Following the survivors in a systematic way will result in improving their own health, and guide us towards improving the prognosis of many cancer patients in the future.