LONG-TERM FOLLOW-UP FOR SURVIVORS OF CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCERS

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OBJECTIVES

• Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFU Guidelines)

• Screening recommendations for asymptomatic survivors of childhood, adolescent, or young adult cancer presenting for routine exposure-based medical follow-up.

• Ongoing issues related to the long-term follow-up needs of this patient population, and the role of the pediatric oncology long-term follow-up centers

• Individualized survivorship care plans for each childhood cancer survivor to serve as a “road map” for providing risk-based, long-term follow-up care in the community setting.
CANCER FACTS: UNITED STATES

Each year:
• 1.5 million people are diagnosed with cancer
• 0.5 million die from cancer

Five year survival rates:
• 68% for adults
• 81% for children
CANCER IN CHILDREN

Distribution - All ages

- Leukemia
- Lymphoma
- Brain Tumor
- Soft tissue sarcoma
- Germ cell
- Bone
- Neuroblastoma
- Renal
- Retino
- Hepato
- Carcinoma
- Other
CANCER IN CHILDREN

- Leukemias, Brain tumors, Lymphomas
- 2nd leading cause of death 1-14yrs
- 12,400 cases per year
CANCER FACTS: UNITED STATES

• 12 million people alive with a history of cancer

• By 2010, 1 in every 250 young adults will be a survivor of childhood cancer

• By 2020, there will be 2 million cancer survivors annually
CHRONIC AND LATE EFFECTS OF TREATMENT

- Physical/Medical
- Psychological
- Social
- Spiritual
The large majority of cancer survivors function very well in their lives. Even those who function well may have needs for surveillance or specific problems that are not observable and require a full evaluation to detect.
LATE EFFECTS

• Health condition persisting or developing 5 or more years from cancer diagnosis
• Commonly reported by cancer survivors
• Reported to impact almost any aspect of health
• Includes life- threatening to life- altering events
• Contribute to cancer- related morbidity
• Predispose to early mortality
SPECTRUM OF LATE EFFECTS

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

Second Cancers
- Second Neoplasms
- Benign
- Malignant of Offspring

Fertility and Reproduction
- Fertility
- Health Organ Function

Organ Function
- Cardiac
- Pulmonary
- Renal
- Endocrine
- Gastrointestinal
- Vision/Hearing
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System

Endocrine

Pulmonary

Cardiovascular

Liver/GI

Kidneys/Bladder

Derm/MSK

SMN

Cognitive/Learning

Psychosocial

Mental Health Disorders

Fatigue

Seizures

Neuropathies

Cataracts

Ototoxicities

Dental Caries

Tooth/Root Agenesis

Chronic Sinusitis
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System

Endocrine

Pulmonary

Cardiovascular

Liver/GI

Kidneys/Bladder

Derm/MSK

SMN

Poor Growth/GHD
Thyroid Problems
Adrenal Insufficiency
Ovary and Testes
Early Puberty
Hypogonadism
Infertility
Osteopenia
Obesity
Metabolic Syndrome
SCREENING FOR ENDOCRINE EFFECTS

- Review history for constitutional symptoms suggesting endocrinopathy.
- Monitor growth & pubertal development.
  - Physical exam for height, weight, BMI, Tanner stage
  - Menstrual history
- Obtain bone age in poorly growing children.
- Obtain LH, FSH, and estradiol/testosterone if growth/puberty is accelerated.
- Obtain free T4 and TSH yearly.
- Refer for endocrine consultation.
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System
Endocrine
Pulmonary
Cardiovascular
Liver/GI
Kidneys/Bladder
Derm/MSK
SMN

Pulmonary Toxicity
Fibrosis
Interstitial Pneumonitis
Restrictive Disease
Obstructive Disease
Impaired Diffusion
SCREENING FOR PULMONARY ISSUES

• Pulmonary function tests (PFT) – these should be obtained immediately following completion of therapy, at entry to long-term follow-up and as needed based on symptoms

• Chest radiograph

• CT scan of the chest based on symptoms and findings on PFTs and chest radiograph

• Quantitative ventilation-perfusion scintigraphy – blood flow to ventilated alveoli has proved most useful in quantifying radiation injury to the lungs.
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System
Endocrine
Pulmonary
Cardiovascular
Liver/GI
Kidneys/Bladder
Derm/MSK
SMN

Cardiomyopathies
Congestive Heart Failure
Arrhythmias
Valvular Disease
Vascular Disease
Atherosclerotic Disease
Myocardial Infarction
Moyamoya
Stroke
Dyslipidemia
Metabolic Syndrome
SCREENING FOR CARDIOVASCULAR INJURY

- Detailed history yearly
- EKG for evaluation of QTc interval at baseline
- ECHO or MUGA for evaluation of systolic function at baseline, then periodically based on:
  - Age at treatment
  - History of chest radiation
  - Cumulative anthracycline dose
## RECOMMENDED SCREENING

### Recommended Frequency of Echocardiogram or MUGA Scan

<table>
<thead>
<tr>
<th>Age at Treatment</th>
<th>Radiation with Potential Impact to the Heart</th>
<th>Anthracycline Dose</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year old</td>
<td>Yes</td>
<td>Any</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;200 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>1–4 years old</td>
<td>Yes</td>
<td>Any</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;100 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥100 mg/m² to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>≥5 years old</td>
<td>Yes</td>
<td>&lt;300 mg/m²</td>
<td>Every 2 years</td>
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<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;200 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 mg/m² to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>Any age with decrease in serial function</td>
<td></td>
<td></td>
<td>Every year</td>
</tr>
</tbody>
</table>

Adapted from: COG Survivorship Guidelines. [http://www.survivorshipguidelines.org](http://www.survivorshipguidelines.org), with permission.
OTHER CONTRIBUTING FACTORS

**Medical**
- Congenital heart disease
- Hypertension
- Obesity
- Dyslipidemia
- Diabetes
- GH deficiency
- Ovarian failure
- Pregnancy

**Behavioral**
- Smoking
- High dietary fat
- Sedentary lifestyle
- Isometric exercise
- Recreational drugs
  - Cocaine
  - Ephedra

**Familial**
- Dyslipidemia
- Premature coronary artery disease
- Diabetes
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System

Endocrine

Pulmonary

Cardiovascular

Liver/GI

Liver Toxicity
Hepatic Fibrosis
Cirrhosis
Veno-Occlusive Disease
Cholelithiasis
Functional Asplenia
GI Strictures
Bowel Obstruction
Fistulas / Strictures

Kidneys/Bladder

Derm/MSK

SMN
LATE EFFECTS OF CANCER THERAPY

- Brain/Cranium/Nervous System
- Endocrine
- Pulmonary
- Cardiovascular
- Liver/GI
- Kidneys/Bladder
- Derm/MSK
- SMN

Renal/ GU Toxicity
  - Tubular
  - Glomerular
- Renal Insufficiency
- Hypertension
- Hemorrhagic Cystitis
- Bladder Fibrosis
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System
Endocrine
Pulmonary
Cardiovascular
Liver/GI
Kidneys/Bladder
Derm/MSK
SMN

Alopecia
Skin Fibrosis
Premature Aging
Osteonecrosis
Exostosis
Limb Loss / Dysfunction
Hypoplasia
Limb length discrepancy
MSK growth disorders
Scoliosis / Kyphosis
Fractures
LATE EFFECTS OF CANCER THERAPY

Brain/Cranium/Nervous System
Endocrine
Pulmonary
Cardiovascular
Liver/GI
Kidneys/Bladder
Derm/MSK
SMN

Bone Cancer
Breast Cancer
CNS Cancer
Thyroid Cancer
Skin Cancer
Leukemia
Lymphoma
Bladder Cancer
Colorectal Cancer
SECONDARY MALIGNANCIES

• Leading cause of death was recurrence of original cancer – 58% of all deaths after 5 years

• Standardized Mortality Ratios for other causes of death:
  Cause of Death Among 5-year Survivors
  – New Cancer 15.2 13.9-16.6
  – Cardiac 7.0 (5.9-8.2)
  – Pulmonary 8.8 (6.8-11.2)
  – Other Medical Causes 3.1 (2.7-3.5)
<table>
<thead>
<tr>
<th>Malignant Neoplasm</th>
<th>Predisposing Factor</th>
<th>Other</th>
<th>Signs and Symptoms</th>
<th>Recommended Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone or soft-tissue sarcoma</td>
<td>Radiotherapy (RT)</td>
<td>Doses &gt;3,000 cGy; adolescents</td>
<td>Pain or mass in irradiated area</td>
<td>Radiograph, other imaging, baseline every 5 years or if symptoms arise</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td></td>
<td>Familial and bilateral cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis (NF)</td>
<td></td>
<td>Diagnosis based on clinical findings; influence of RT not established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>Retinoblastoma</td>
<td>Bilateral and familial cases</td>
<td>Change in sleep pattern</td>
<td>Neuroimaging baseline, then if symptoms arise</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>RT</td>
<td>Younger children at greater risk</td>
<td>Seizures, headaches, altered mental status</td>
<td></td>
</tr>
<tr>
<td>NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neviod basal cell carcinoma syndrome</td>
<td>Ionizing RT increases risk and shortens latent period</td>
<td>Enhanced thyroid, nodules</td>
<td>Ultrasound baseline, then if symptoms, ^31^I scan</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>RT</td>
<td>Younger children at greater risk</td>
<td>Enlarged thyroid, nodules</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>RT</td>
<td>Preadolescent females; interaction with family history (?)</td>
<td>Breast mass</td>
<td>Mammo gram at age 25, every 2 years to age 40, than every year, biopsy if mass present</td>
</tr>
<tr>
<td>Skin</td>
<td>RT</td>
<td>Ionizing RT increases risk and shortens latent period</td>
<td>New lesion or change in skin color or texture</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Neviod basal cell carcinoma syndrome</td>
<td></td>
<td>Risk associated with ultraviolet light</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xeroderma pigmentosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>Alkylating agents</td>
<td>Dose response, melphalan&gt;nitrogen mustart&gt;cyclophosphamide; associated with chromosome 5 and 7 abnormalities</td>
<td>Pallor, bruising, fatigue, petechiae</td>
<td>Complete blood count annually</td>
</tr>
<tr>
<td>Epipodophyllotoxins</td>
<td>Associated with 11q23 abnormality; schedule or dose dependent (?)</td>
<td></td>
<td></td>
<td>Bone marrow evaluation for symptoms</td>
</tr>
<tr>
<td>NF</td>
<td></td>
<td>Juvenile chronic myelogenous leukemia (JCML) most common; cutanomas; may develop monosomy 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Childhood Cancer Survivor Study (CCSS)
#### Risk of SMN by Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Obs.</th>
<th>Exp.</th>
<th>Standardized Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>802</td>
<td>135</td>
<td>6</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>277</td>
<td>32</td>
<td>8.7</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>80</td>
<td>14</td>
<td>5.8</td>
</tr>
<tr>
<td>NBL</td>
<td>33</td>
<td>5</td>
<td>6.9</td>
</tr>
<tr>
<td>Kidney</td>
<td>35</td>
<td>7</td>
<td>4.8</td>
</tr>
<tr>
<td>ALL</td>
<td>132</td>
<td>30</td>
<td>4.4</td>
</tr>
<tr>
<td>OGS</td>
<td>46</td>
<td>11</td>
<td>4.2</td>
</tr>
<tr>
<td>CNS - Astro</td>
<td>43</td>
<td>10</td>
<td>4.3</td>
</tr>
<tr>
<td>CNS - Medullo</td>
<td>19</td>
<td>3</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Friedman, JNCI 2010

University of Minnesota Cancer Center
IS THERE A RISK OF SMN 20 YRS AFTER ORIGINAL DIAGNOSIS?

• No data on the very long term survivor
• Many state that you are “Cancer Free” at 20 yrs from diagnosis
  • In past return to original population
  • But does the risk continue?
CCSS – Late Cancer Investigation

- 8010 Survivors identified from among 14,363 eligible participants
- 42,063 person years of follow up 20 or more years from original cancer diagnosis
- After 20+ years:
  - Second Malignancy
    - 203 one SMN; 24 >1 SMN
  - Non-melanoma skin cancer: 286 (1+)
  - Meningioma: 53 (1+)
<table>
<thead>
<tr>
<th>Second Neoplasm</th>
<th>O/E Ratio (95% C.I.)</th>
<th>Median time of onset (yrs)</th>
<th>O/E Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SMNs</td>
<td>4.64 (4.29, 5.01)</td>
<td>17.7</td>
<td>5.71 (5.06, 6.45)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4.85 (3.37, 6.98)</td>
<td>9.5</td>
<td>1.47 (0.37, 5.87)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.75 (1.18, 2.60)</td>
<td>18.2</td>
<td>2.66 (1.51, 4.67)</td>
</tr>
<tr>
<td>CNS Tumors</td>
<td>9.33 (7.25, 12.02)</td>
<td>12.1</td>
<td>5.43 (2.72, 10.90)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>14.82 (12.74, 17.24)</td>
<td>21.7</td>
<td>13.50 (11.20, 16.30)</td>
</tr>
<tr>
<td>Bone cancer</td>
<td>14.43 (10.50, 19.84)</td>
<td>9.8</td>
<td>8.25 (2.66, 25.60)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>10.03 (8.00, 12.58)</td>
<td>15.8</td>
<td>9.91 (6.53, 15.0)</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>11.73 (9.71, 14.18)</td>
<td>18.6</td>
<td>10.90 (7.95, 15.0)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.38 (1.68, 3.39)</td>
<td>18.3</td>
<td>2.30 (1.34, 3.94)</td>
</tr>
<tr>
<td>All Other CA</td>
<td>1.87 (1.60, 2.20)</td>
<td>17.0</td>
<td>3.10 (2.44, 3.95)</td>
</tr>
</tbody>
</table>

CCSS – 2007 (unpublished data)
LATE CANCERS SUMMARY

• Risk does not fall, even 20+ years later
• Malignant risk is driven by breast cancer, thyroid cancer and sarcoma
• New carcinomas are emerging.
• Some decrease in leukemia, malignant CNS, ? bone
SCREENING FOR SMN

• Annual complete blood count for those exposed to topoisomerase II poisons, anthracyclines or alkylating agents
• Annual dermatology checks for those exposed to radiation
• Annual thyroid function tests (with ultrasounds if abnormal) for those exposed to thyroid radiation
• Annual mammography with ultrasound or MRI for those exposed to chest/mantle radiation starting at age 25.
• Patients exposed to radiation should be counseled to apply SFP 45 sunscreen liberally and to avoid tobacco smoke.
PSYCHOSOCIAL LATE EFFECTS

- **Mental Health**
  - Depression/mood problems
  - Cancer-related anxiety/fears
  - Post-traumatic stress

- **Education/Vocation**
  - Academic underachievement
  - Vocational limitations
  - Under/unemployment
  - Insurance discrimination
  - Access to Health Care

- **Social Interaction**
  - Family/peer relationships
  - Social withdrawal/isolation

- **Social competence**
  - Ability to live independently
  - Intimacy/marriage/family

- **Health Risking Behaviors**
  - Tobacco/Alcohol/Drugs
  - Medical noncompliance
APPROACH TO RISK BASED CARE

• Age at treatment
• Sex/race of survivor
• Type/strength of therapy
  – Chemotherapy
  – Radiation therapy
  – Surgery
  – Transplant
  – Transfusions
• Time from treatment
• Type of cancer
• History of relapse
• Family history
• Health habits
  • Tobacco
  • Diet/alcohol
  • Exercise/weight
• Control
  • Sun exposure
COG LONG-TERM FOLLOW UP GUIDELINES

Establishing and Enhancing Services for Childhood Cancer Survivors

LONG-TERM FOLLOW-UP PROGRAM RESOURCE GUIDE

Children's Oncology Group Nursing Discipline Clinical Practice Subcommittee/Survivorship in collaboration with the Late Effects Committee
# Key Content Areas

<table>
<thead>
<tr>
<th>Therapeutic exposures</th>
<th>Recommended Frequency</th>
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</thead>
<tbody>
<tr>
<td>Potential Late Effects</td>
<td>Health Protective Counseling</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Considerations for Further Testing</td>
</tr>
<tr>
<td>Highest Risk</td>
<td>Cancer Screening</td>
</tr>
<tr>
<td>Periodic Evaluations</td>
<td>General Healthcare</td>
</tr>
<tr>
<td>References</td>
<td>References</td>
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</table>

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Potential Late Effects</th>
<th>Risk Factors</th>
<th>Highest Risk</th>
<th>Considerations for Further Testing</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

### Table Notes:
- **Therapeutic Agent**: Commonly used therapeutic agents and their potential side effects.
- **Potential Late Effects**: Common late effects associated with treatments.
- **Risk Factors**: Factors that increase the risk of late effects.
- **Highest Risk**: The highest risk patients based on the severity of side effects.
- **Considerations for Further Testing**: Recommendations for additional testing.
- **References**: Further reading and resources for more detailed information.
# TREATMENT SUMMARY

## Cancer Diagnosis
- **Diagnosis:** Hepatoblastoma
- **Sites involved/stage:** Stage II
- **Date of Diagnosis:** 01/09/2001
- **Age at Diagnosis:** 8 months
- **Date Therapy Completed:** 04/19/2001
- **Relapse(s):** None

## Treatment Center
- **LSUHSC, Children’s Hospital New Orleans, 200 Henry Clay Avenue, New Orleans, LA 70118**
- **Primary Oncologist:** Dr. Lolie Yu
- **Surgeon:** Dr. Charles Hill, Dr. Lui
- **Radiation Oncologist:** None
- **Transplant Physician:** None
- **Long Term Follow-Up:** Dr. Pinki Prasad (504) 896-9740

## Medical Record
- **#:** 0244713

## Family History
- **Cancer:**
- **Other Family History:**
- **Past Medical History:** fever, seizures

## Cancer Treatment Summary
- **Protocol/Treatment:** POG 9645
- **On Study:** Enrolled on study

### Chemotherapy

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Selected Cumulative Dose (units or mg/m²) when Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>13.2 mg/kg or 400 mg/m²</td>
</tr>
<tr>
<td>Vincristine</td>
<td>18 mg/m²</td>
</tr>
<tr>
<td>5-Flourouracil</td>
<td>2400 mg/m²</td>
</tr>
</tbody>
</table>

### Surgery

<table>
<thead>
<tr>
<th>Date</th>
<th>Procedure</th>
<th>Surgeon/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/2000</td>
<td>Partial resection of liver RUQ</td>
<td></td>
</tr>
<tr>
<td>01/12/2001</td>
<td>Portacath placement</td>
<td>Dr. Lui</td>
</tr>
</tbody>
</table>

### Radiation
- None

### Transplant
- None

### Treatment Complications/Late Effects

<table>
<thead>
<tr>
<th>Problem</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech delay</td>
<td></td>
</tr>
<tr>
<td>Concern about high frequency hearing loss</td>
<td></td>
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</tbody>
</table>
THANK YOU
Restore Rebuild Renew

Laissez le bon temps rouler