Introduction to Pediatric Neoplasms

FCDS EDUCATIONAL WEBCAST SERIES
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Program Outline

- Introduction
- Types of Pediatric Neoplasms
- Signs and Symptoms
- Causes and Risk Factors
- MPH Rules – Solid Tumors
- MPH Rules – Heme/Lymph Neoplasms
- Staging Pediatric Tumors
- Collaborative Stage Data Collection System
- Treatment Options
- Future Webcasts
- Q&A

Introduction

Introduction

**Graph: EIR Cell-Adjusted Incidence and US Mortality**

All Childhood Cancers Under 20 Years of Age, Both Sexes, All Races, 1975-2007

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Relative Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years and younger</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>10 years and younger</td>
<td>75-90%</td>
</tr>
<tr>
<td>10 to 15 years</td>
<td>50%</td>
</tr>
<tr>
<td>Adolescents aged 15 to 19</td>
<td>15-25%</td>
</tr>
</tbody>
</table>

Introduction

**Graph: Five-Year Relative Survival Rates for Acute Lymphoblastic Leukemia in Children Under 15 Years, 1995-2005**

Building on 50 Years of Cooperative Research

<table>
<thead>
<tr>
<th>Pediatric Clinical Trial Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 and younger</td>
</tr>
<tr>
<td>10 and younger</td>
</tr>
<tr>
<td>10 to 15</td>
</tr>
<tr>
<td>Adolescents aged 15 to 19</td>
</tr>
</tbody>
</table>
Introduction

Building on 50 Years of Cooperative Research

1940s
Remission achieved in pediatric leukemia patients using an antifolate drug, aminopterin

1950s
- 6-mercaptopurine treats pediatric acute lymphoblastic leukemia
- Combination chemotherapy introduced by NCI researchers
- NCI begins funding pediatric cooperative clinical trials

1960s
- Dactinomycin first used to treat Wilms tumor
- National Wilms Tumor Study Group formed and multi-modality therapy first used in pediatric patients (surgery, radiation, chemo)
- Prophylaxis of occult central nervous system leukemia markedly improves outcome for children with ALL
- Laminar airflow technology creates "sterile rooms" for chemotherapy patients
1970s

- Intergroup Rhabdomyosarcoma Study Group Committee pioneers repetitive-course, multi-agent chemotherapy for advanced rhabdomyosarcoma
- First successful bone marrow transplant (BMT) for leukemia
- Knudson describes the 2-hit hypothesis for retinoblastoma to describe genetics and heredity of cancer

1980s

- First tumor-suppressor gene, in retinoblastoma, is cloned
- MYCN identified as a target of genomic amplification in neuroblastoma
- Adjuvant chemotherapy improves relapse-free survival for pediatric osteosarcoma
- Different treatment for lymphoblastic lymphoma vs other lymphomas are realized
- Platinum-based chemo improves response rates in pediatric germ cell tumors
- National Marrow Donor Program begins

1990s

- Autologous BMT and 13-cis-retinoic acid improve survival for neuroblastoma
- Characteristic fusion genes identified for pediatric solid tumors
- Combined ifosfamide and etoposide improve outcomes for Ewing sarcoma
- Long-term survival rates of 80-90% achieved for advanced Burkitt lymphoma
- Genetic test for thyroid cancer enables prophylactic thyroidectomy before age 2
- NCI-funded Childhood Cancer Survivors Study begins
Introduction

Building on 50 Years of Cooperative Research

2000s

- Four legacy research groups merge as the Children's Oncology Group (COG)
- COG publishes long-term follow-up guidelines for pediatric cancer survivors
- Imatinib added to intensive chemotherapy improves early outcomes for Ph+ ALL
- 5-year survival rates for children with cancer (age 0-14 years) approach 80%
Children's Oncology Group

Children's Oncology Group
The world's childhood cancer experts

[Image of map and icons]

http://cancer.gov/

Childhood Cancer Survivor Study

- Diagnosis 1970-1986
- 20,000 person cohort
- Survival at least 5 years
- Chance for long-term effects increase over time
- > 70% at least 1 chronic illness related to treatment
- > 25% have 3 or more chronic illnesses related to tx

[Image of children]

http://cancer.gov/

Childhood Cancer Survivor Study

- Kidney Disease
- Second Cancers
- Cognitive Dysfunction
- Cardiovascular Disease
- Endocrine Abnormalities
- Musculoskeletal Conditions

[Image of children]

http://cancer.gov/

Long-Term Active Follow-Up is CRITICAL...
Childhood Cancer Survivor Study

- **Pediatric Cancer Registries**
  - COG – Childhood Cancer Research Network
  - CDC NPCR – National Childhood Cancer Registry
  - FAPTP – Florida Consortia Pediatric Cancer Registry
  - Cancer Site/Type Specific Registries
  - Bone Marrow Donor Registries
  - National Children’s Study
  - Other

http://cancer.gov/
Major Types of Pediatric Neoplasms

<table>
<thead>
<tr>
<th>Childhood Cancer Incidence Rates (SEER) by ICCC Group 2001-2004 – All Sex, All Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Brain/CNS</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Soft Tissue</td>
</tr>
<tr>
<td>Germ Cell</td>
</tr>
<tr>
<td>Bone</td>
</tr>
<tr>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Retinoblastoma</td>
</tr>
</tbody>
</table>

Note: Rates are per 1,000,000 population

http://cancer.gov/
Major Types of Pediatric Neoplasms

Source: The Simpsons – Homer Brain X-Ray

Major Types of Pediatric Neoplasms

Source: http://www.montekids.org/services/neurosurgery/neurologicaldisorders/brain_tumor/

Major Types of Pediatric Neoplasms

Source: http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/anatomy.html

Major Types of Pediatric Neoplasms

Source: http://www.sbo.edu/states/lsbhbooks/pathphys/endocrine/hypopit/anatomy.html
### Major Types of Pediatric Neoplasms

<table>
<thead>
<tr>
<th>Ewing Family of Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PNET</strong></td>
</tr>
<tr>
<td><strong>Brain/CNS</strong></td>
</tr>
<tr>
<td><strong>pPNET</strong></td>
</tr>
<tr>
<td><strong>Soft Tissue</strong></td>
</tr>
<tr>
<td><strong>Askin Tumor</strong></td>
</tr>
<tr>
<td><strong>Soft Tissue</strong></td>
</tr>
<tr>
<td><strong>Ewing Sarcoma</strong></td>
</tr>
<tr>
<td><strong>Bone</strong></td>
</tr>
<tr>
<td><strong>Ewing Sarcoma</strong></td>
</tr>
<tr>
<td><strong>Extra Osseous</strong></td>
</tr>
<tr>
<td><strong>Soft Tissue</strong></td>
</tr>
</tbody>
</table>

### Major Types of Pediatric Neoplasms

- **Langerhans Cell Histiocytosis**
- **Retinoblastoma**
- **Neuroblastoma**
- **Wilms Tumor**
- **Melanoma**
Major Types of Pediatric Neoplasms

Signs and Symptoms
- Continued, unexplained weight loss
- Headaches, often with early morning vomiting
- Increased swelling or persistent pain in bones, joints, back, or legs
- Lump or mass, especially in the abdomen, neck, chest, pelvis, or armpits
- Development of excessive bruising, bleeding, or rash
- Constant infections
- Whitish color behind the pupil
- Nausea which persists or vomiting without nausea
- Constant tiredness or noticeable paleness
- Eye or vision changes which occur suddenly and persist
- Recurrent or persistent fevers of unknown origin

Causes and Risk Factors
- Genetic Abnormalities
- Ionizing Radiation Exposure
- History of Chemotherapy and/or Radiation Therapy
- Infectious Agents Including Prenatal Infection
  - HIV
- Environmental Including Parental Exposure
  - Toxins
  - Solvents
  - Pesticides
  - Magnetic Fields
- Cancer Predisposition Syndromes
  - Down Syndrome
  - Li-Fraumeni Syndrome
  - Neurofibromatosis
  - Gorlin Syndrome
Causes and Risk Factors

MPH Rules – The Basics

1. Is the condition reportable?
2. How many cases do I abstract?
3. How do I code the primary site?
4. How do I code the histology?
5. How do I code the grade?

MPH Rules – Solid Tumors

- Identify the Primary Site

- Use Multiple Primary Rules
  - General Rules
  - Site-Specific Rules
    - Brain – Malignant
    - Brain – Benign/Borderline
    - Melanoma
    - Kidney
    - N/A – breast, colon, head & neck, lung, urinary system
MPH Rules – Solid Tumors

- Histology Coding Rules
- What Drives Treatment Decisions?
- Pediatric Pathology – Characteristics and Terminology
- Tumor Characteristic Testing
- Tumor Marker Testing
- Genetic Testing
- Profile

MPH Rules – Heme/Lymph Neoplasms

- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia
- Chronic Myeloid Leukemia
- Myeloid Leukemia Associated with Down Syndrome
- Langerhans Cell Histiocytosis – solitary/multifocal
Staging Pediatric Tumors

- Wilms Tumor Study Group Staging
- International Neuroblastoma Staging System
- Children’s Oncology Group Neuroblastoma Risk Grouping
- Intergroup Rhabdomyosarcoma Study Staging System
- Soft Tissue Sarcoma Tumor Pathological Grading System
- FNCLCC Grading System
- TNM Staging System

Collaborative Stage Data Collection System

CS Core Data Items and Site Specific Factors Used to Derive
- AJCC Cancer Staging
- TNM 6th edition
- TNM 7th edition
- Clinical Stage
- Pathologic Stage
- Best Combined Stage
- T, N, and M Core Elements
- Anatomic/Prognostic Stage Group
- SEER Summary Stage 1977
- SEER Summary Stage 2000

NO Pediatric-Specific Staging Schema or SSFs
Staging is often Site/Type Specific or Clinical Trial-Specific
Solid Tumor Staging

- Wilms Tumor
  - Stage I – 45%
    - Tumor is limited to the kidney
    - Tumor is completely resected.
    - The renal capsule is intact.
    - Tumor is not ruptured or biopsied prior to removal.
  - Stage II – 20%
    - Tumor is completely resected.
    - The tumor extends beyond the kidney as evidenced by any of the following:
      - There is regional extension of the tumor (i.e., penetration of the renal sinus capsule).
      - Blood vessels in the nephrectomy specimen outside the renal parenchyma with tumor
  - Stage III – 21%
    - Residual non-hematogenous tumor present following surgery confined to the abdomen
  - Stage IV – 11%
    - Hematogenous metastases (lung, liver, bone, brain)
    - Lymph node metastases outside the abdominal-pelvic region are present
  - Stage V – 5%
    - Bilateral involvement by tumor is present at diagnosis
Brain Tumor Staging

Leukemia Staging

Lymphoma Staging

Source: [http://cancer.gov](http://cancer.gov) – Pediatric Non-Hodgkin Lymphoma NCI PDQ for Health Professionals
**Treatment**

**Treatment Options – Basic Concepts**

- Surgery
- Chemotherapy
- Radiation Therapy
- Hormonal Therapy
- Combination Therapy
- Continuation Therapy
- Bone Marrow/Stem Cell Transplant

Image Source: [http://greenplanetparadise.com](http://greenplanetparadise.com) and [http://avinoamlerner.com](http://avinoamlerner.com)

**Treatment Options – Basic Concepts**

- Pre-Induction Risk Assessment
- Induction Therapy
- Post-Induction Assessment
- Re-Induction Therapy
- Intensification/Consolidation Therapy
- Post-Consolidation Assessment
- BMT/Stem Cell Transplant
- Maintenance Therapy
- Maintenance Assessment
Treatment Options – Basic Concepts

- Risk-Based Treatment – Pre-Induction Risk
  - Patient Characteristics
    - Age at Diagnosis
    - WBC Count at Diagnosis
    - CNS Involvement
    - Gender
  - Neoplasm Characteristics
    - Morphology
    - Immunophenotype
    - Cytogenetics
  - Genetic Characteristics of Neoplasm
    - Philadelphia Chromosome Translocation
    - MLL Translocations
    - CRLF2 and JAK Mutation

- Risk-Based Treatment – Induction Failure
  - Patients at highest risk of induction failure:
    - T-cell phenotype (especially without a mediastinal mass).
    - B-precursor ALL with very high presenting leukocyte counts.
    - 1s23 rearrangement.
    - Older age.
    - Philadelphia chromosome

- Risk-Based Treatment – ReInduction/Consolidation
  - Re-Induction
  - Intensification
  - Consolidation

- Risk-Based Treatment – Sanctuary Sites
- Risk-Based Treatment – Maintenance Therapy

Source: [http://cancer.gov – Pediatric Lymphoid Neoplasm NCI PDQ for Health](http://cancer.gov)
Treatment Options – Basic Concepts


Treatment Options – Lymphoid Neoplasms

- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Chronic Lymphocytic Leukemia
- Acute Lymphocytic Leukemia
- Other Lymphoid Neoplasm

Source: Mosaic Rainbow and Woodland Forest – http://www.etsy.com

Treatment Options – Lymphoma

Source: http://cancer.gov – Pediatric Hodgkin Lymphoma NCI PDQ for Health Professionals
Treatment Options – Lymphoma

<table>
<thead>
<tr>
<th>Chemotherapy (No. of Courses)</th>
<th>Radiation (Yr)</th>
<th>Stage</th>
<th>No. of Patients</th>
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<tr>
<td>COPP (6–8)</td>
<td></td>
<td>II</td>
<td>36</td>
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<td>COPP (6–8) + IFRT</td>
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<td>II</td>
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<tr>
<td>COPP (6–8) + IFRT</td>
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<td>III</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td>COPP (6–8) + IFRT + ABVD</td>
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Source: [Pediatric Hodgkin Lymphoma NCI PDQ for Health Professionals](http://cancer.gov)

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Treatment Options – Lymphoma

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Source: [Pediatric Hodgkin Lymphoma NCI PDQ for Health Professionals](http://cancer.gov)

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Treatment Options – Myeloid Neoplasms

- Myeloid Leukemia Associated with Down Syndrome
- Chronic Myeloid Leukemia
- Acute Myeloid Leukemia
- Other Myeloid Neoplasm
- MPD/MPS/MDS

Source: [Pediatric Myeloid Neoplasms NCI PDQ for Health Professionals](http://cancer.gov)
About 85% of patients are diagnosed in the chronic phase.

The accelerated phase of CML is characterized by 10% - 19% blasts in the WBC of peripheral blood (WHO).

Note: There are alternative ways to define the accelerated phase proposed by Sokal et al., the International Bone Marrow Transplant Registry, and MD Anderson.

The blast phase, also referred to as blast crisis, is most often defined as >20% blasts WBC of peripheral blood.

Use same basic model as ALL – different agents

Ph+ chronic phase CML is typically treated with a tyrosine kinase inhibitor (TKI).

TKIs include imatinib, nilotinib or dasatinib.

All TKIs are given orally so there will be no “administration” documentation rather the patient will be given prescriptions.

Other treatment options include clinical trial or Hematopoietic Stem Cell Transplant [HSCT].
### Treatment Options – CML/AML

- **Patients** are evaluated for a cytogenetic response
- **Treatment** is based on response
  - **Complete Response** – no Ph+ positive metaphases
  - **Partial Response** – 1-35% Ph+ positive metaphases
  - **Major Response** – 0-35% Ph+ positive metaphases
    - Complete + Partial
  - **Minor** – > 35% Ph+ positive metaphases

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

### Treatment Options – CML/AML

- Patients achieving a complete hematologic response are continued on their current medication at the same dose.
- Patients who fail to achieve a complete hematologic response are evaluated for compliance, drug-drug interaction and possibly mutational status but generally are switched to an alternate TKI as second line treatment.
- Other treatment options include evaluation and discussion of HSCT and clinical trial.

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

### Treatment Options – CML/AML

- **Growth Factors**
  - filgrastim (Neupogen®)
  - pegfilgrastim (Neulasta®)
- **Diuretics** (aldactone, hydrochlorothiazide [HCTZ]), steroids (prednisone 20mg/day x 3 for effusions)
- **Topical steroids** (hydrocortisone cream)
- **Antidiarrheal agents** (loperamide [Imodium®])
- **Analgesics** (acetaminophen, ibuprofen)

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)
Treatment Options – Brain and CNS

Treated Based on Histology and Location

Source: [http://cancer.gov](http://cancer.gov) – Pediatric Brain Tumors NCI PDQ for Health Professionals
Treatment Options – Brain and CNS

Treated Based on Histology and Location

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Pathology Subtype</th>
<th>Staging and Treatment of Seemingly Diagnosed and Resected Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma</td>
<td>Teratoma</td>
<td>Child-related Teratoma Treatment</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Teratoma</td>
<td>Child-related Teratoma Treatment</td>
</tr>
<tr>
<td>Non-Differentiated Glioma</td>
<td>Non-Differentiated Glioma</td>
<td>Kind-related Non-Differentiated Glioma Treatment</td>
</tr>
</tbody>
</table>

Source: [http://cancer.gov](http://cancer.gov) – Pediatric Brain Tumors NCI PDQ for Health Professionals

Treatment Options – Teratoid/Rhabdoid Tumor

- CNS
- Non-CNS
- Both CNS and Non-CNS Involvement
- Rhabdomyosarcoma (see Sarcoma)
- Rhabdoid Tumor of Kidney

Source: [http://cancer.gov](http://cancer.gov) – Atypical Teratoid/Rhabdoid Tumor NCI PDQ for Health Professionals

Treatment Options – Soft Tissue Sarcoma

- Primary Tumor Resection with Negative Margins
- Regional Lymph Node Involvement is Rare
- Radiation Therapy depends upon potential for surgery plus or minus chemotherapy to obtain local control
  - Age
  - Gender
  - Tumor site
  - Tumor size
  - Tumor grade
- Role for Adjuvant Chemotherapy Controversial
  - Vincristine, daunomycin, cyclophosphamide, doxorubicin

Source: [http://cancer.gov](http://cancer.gov) – Pediatric Soft Tissue Sarcoma NCI PDQ for Health Professionals
Treatment Options – Ewing Sarcoma

- **Pre-Treatment Factors**
  - Site of Tumor
  - Tumor Size or Volume
  - Age of Patient
  - Gender (favorable girls)
  - Metastases
  - Standard Cytogenetics
  - Detectable Fusion Transcripts
- **Surgery**
- **Chemo** – vincristine, doxorubicin, cyclophosphamide
- **Radiation Therapy**

Treatment Options – Wilms Tumor

- **Preoperative chemotherapy prior to nephrectomy is indicated in the following situations:**[10,17,20-23]
  - Metachronous bilateral Wilms tumor.
  - Wilms tumor in a solitary kidney.
  - Extension of tumor thrombus above the level of the hepatic veins.
  - Tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structures (e.g., spleen, pancreas, colon but excluding the adrenal gland).
  - Pulmonary compromise due to extensive pulmonary metastases.
- **Patients with massive, nonresectable unilateral tumors, bilateral tumors, or venacaval tumor thrombus are candidates for preoperative chemotherapy**

Treatment Options – Wilms Tumor

- **Pre-Surgical Chemotherapy for High Risk Group**
- **Nephrectomy**
- **Chemotherapy**
- **Radiation Therapy**

**Table 4. Standard Chemotherapy Regimens for Wilms Tumor**

<table>
<thead>
<tr>
<th>Regimen Name</th>
<th>Regimen Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Cisplatin, doxorubicin, cyclophosphamide, ifosfamide, vincristine, etoposide</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Cisplatin, doxorubicin, cyclophosphamide, etoposide</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Cisplatin, doxorubicin, cyclophosphamide, etoposide</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Cisplatin, ifosfamide, vincristine, etoposide</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cisplatin, doxorubicin, vincristine, etoposide</td>
</tr>
</tbody>
</table>
Treatment Options – Neuroblastoma

- **Low-Risk Neuroblastoma**
  - Surgery
  - Chemo - carboplatin, cyclophosphamide, doxorubicin, etoposide

- **Intermediate-Risk Neuroblastoma**
  - Surgery
  - Chemo as above x 2 cycles
  - Dose Intensive Multi-Agent Chemo

- **High-Risk Neuroblastoma**
  - Dose Intensive Multi-Agent Chemo as above plus ifosfamide, cisplatin
  - Surgery
- **Response Assessment – then next steps**

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Treatment Options - Retinoblastoma

- **Goals of Treatment**
  - Eradicate the disease to save the patient’s life.
  - Preserve as much vision as possible.
  - Decrease risk of late sequelae from treatment, particularly subsequent neoplasms.

- **Enucleation**
- **Radiation Therapy (beam or brachytherapy)**
- **Local Treatments (Cryotherapy/Laser Therapy)**
- **Chemo – carboplatin, etoposide, vincristine**
- **Subteton (subconjunctival) Chemo - carboplatin**
- **Ophthalmic Artery Infusion Chemo – topotecan, carboplatin**

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Late Effects of Treatment

- **Childhood Cancer Survivors Study**
  - Chance for long-term effects increase over time
  - > 70% at least 1 chronic illness related to treatment
  - > 25% have 3 or more chronic illnesses related to tx
  - Kidney Disease
  - Second Cancers
  - Cognitive Dysfunction
  - Cardiovascular Disease
  - Endocrine Abnormalities
  - Musculoskeletal Conditions
References and Resources

- National Cancer Institute Physician Data Query (PDQ) - Health Professionals
  - Childhood Cancers Fact Sheet
  - Childhood Acute Lymphoblastic Leukemia
  - Childhood Acute Myeloid Leukemia
  - Childhood Brain and Spinal Cord Tumors Overview
  - Childhood Astrocytoma
  - Childhood CNS Embryonal Tumors
  - Childhood CNS Atypical Teratoid/Rhabdoid Tumors
  - Childhood Hodgkin Lymphoma
  - Childhood Non-Hodgkin Lymphoma
  - Ewing Sarcoma
  - Childhood Soft Tissue Sarcoma
  - Childhood Rhabdomyosarcoma
  - Neuroblastoma
  - Wilms Tumor

References and Resources

- NCI Cancer Bulletin, Pediatric Oncology Partnerships are Models for Success, Volume 5/Number 6, March 18, 2008
- Advances in Neuroblastoma Risk Assessment and Treatment, Susan L Cohn, MD, University of Chicago Department of Pediatrics
- Florida Association of Pediatric Tumor Programs (FAPTP)
- Children’s Oncology Group (COG)

Future Pediatric Oncology Webcasts

- Coming Soon!!