Pediatric oncology review

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Leukemia's

- Acute lymphoblastic leukemia: 75%.
- Acute myeloid leukemia: 20%.

- Chronic myeloid leukemia constitute 3% of all childhood leukemia and consist of:
  - Chronic myeloid leukemia (CML) usually Philadelphia chromosome positive > 99%
  - Juvenile myelomonocytic leukemia (JMML) should be negative for Philadelphia chromosome.
Etiology

- Increased incidence with the following genetically determined conditions:
  - Shwachman–Diamond syndrome
  - Ataxia telangiectasia
  - Li–Fraumeni syndrome (germ line p53 mutation) liable for leukemia, osteosarcoma, colon and breast cancer
  - Diamond–Blackfan anemia
  - Kostmann disease
  - Bloom syndrome
Clinical importance of immunological characterization

Eighty-five percent of children with common ALL (usually pre-B-cell ALL) are HLADR and CD10 positive, which indicates a good prognosis.

Infantile ALL:

- often high WBC
- massive hepatospleenomegally
- high rate of CNS involvement
- poor response to treatment
- CD10 negative leukemia
- t(4;11)
Children with T-cell ALL are characterized by:

- older age (peak at 10 years of age)
- with a ratio of boys to girls of 4:1
- blacks
- high initial leukocyte count
- mediastinal involvement
- high rate of CNS involvement
- testicular involvement
Figure 17-1 Schematic Representation of Human Lymphoid Differentiation. (A) Hypothetical schema of marker expression and gene rearrangement during normal B-cell ontogeny. (B) Hypothetical schema of marker expression and gene rearrangement during normal T-cell ontogeny.

<table>
<thead>
<tr>
<th>Chromosomal Abnormalities</th>
<th>Event-Free Survival</th>
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<tbody>
<tr>
<td>Hyperploidy</td>
<td></td>
</tr>
<tr>
<td><em>Trisomies of chromosomes 4,10,17</em></td>
<td>89% 8 yr EFS</td>
</tr>
<tr>
<td><em>Tel /AML1 Fusion positive</em></td>
<td>86% 5 yr EFS</td>
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<tr>
<td>Hypodiploidy, &lt;45 chromosomes</td>
<td>39% 8 yr EFS</td>
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<tr>
<td>MLL-rearranged</td>
<td></td>
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<tr>
<td>Infants (0–12 months)</td>
<td>37% 4 yr EFS</td>
</tr>
<tr>
<td>Non infants (&gt;12 months)</td>
<td>50% 8 yr EFS</td>
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<tr>
<td>t(9;22)</td>
<td>39% 8 yr EFS*</td>
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</table>

*Studies have shown a 3 year EFS of 80% using intensive chemotherapy with Imatinib.*
<table>
<thead>
<tr>
<th>Factor</th>
<th>Favorable</th>
<th>Intermediate</th>
<th>Unfavorable</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>1–9</td>
<td>≥10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1 and MLL+</td>
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<td>White blood cell count (&lt;(10^9)/L)</td>
<td>&lt;50</td>
<td>≥50&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Immunophenotype</td>
<td>Precursor B cell</td>
<td>T cell&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Genetics</td>
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<td>Diploid</td>
<td>t(9;22)/BCR-ABL1</td>
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<td></td>
<td>Trisomies 4, 10 and 17</td>
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<td></td>
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<tr>
<td></td>
<td>t(12;21)/ETV6-CBFA2</td>
<td></td>
<td></td>
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<tr>
<td>CNS status</td>
<td>CNS1</td>
<td>CNS2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CNS3</td>
</tr>
<tr>
<td></td>
<td>Traumatic spinal tap with blasts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD (end of induction)</td>
<td>&lt;0.01%</td>
<td>0.01% to 0.99%</td>
<td>≥1%</td>
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</tbody>
</table>

<sup>a</sup>These factors used to carry an unfavorable prognosis; however, outcome has improved with risk-directed contemporary therapy.

*Abbreviation:* MRD, minimal residual disease.

Acute Myeloid Leukemia

The following inherited disorders are predisposing factors:

- Down syndrome
- Fanconi anemia
- Kostmann syndrome
- Bloom syndrome
- Diamond–Blackfan anemia
Secondary AML can evolve from:

- Myelodysplastic syndromes and myeloproliferative syndromes
- Exposure to ionizing radiation.

- The following chemotherapy agents are associated with secondary AML:
  - Cyclophosphamid
  - Anthracyclins
  - Etoposide (VP16)
CLINICAL MANIFESTATIONS

- subcutaneous nodules or “blueberry muffin” lesions (especially in infants)
- infiltration of the gingiva (especially in monocytic subtypes) M5
- disseminated intravascular coagulation (especially indicative of APL) M3
- masses, known as chloromas or granulocytic sarcomas. typically are associated with a t(8;21) translocation. M2
<table>
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<th>FAB classification of acute myelogenous leukemia</th>
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<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
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<td>M7</td>
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### Table 17-22  Relationship Among Immunologic Surface Markers with FAB Subtypes of Acute Myeloblastic Leukemia

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<tr>
<th>FAB Subtype of AML</th>
<th>HLA-DR</th>
<th>CD11b</th>
<th>CD13</th>
<th>CD14</th>
<th>CD15</th>
<th>CD33</th>
<th>CD34</th>
<th>Glycophorin</th>
<th>CD41</th>
<th>CD42</th>
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<tr>
<td>M1/M2</td>
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<tr>
<td>M3/M3V</td>
<td>+</td>
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<tr>
<td>M4/M5</td>
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</table>
Favorable cytogenetics:

- t(8;21) AML M2
- Inversion (16) or t(16;16) AML M4
- t(15;17) AML M3
- Down syndrome: usually AML M7 with fibrosis and t(1;22)
Adverse cytogenetics:

- Monosomy 5 or del (5q)
- Monosomy 7
- Complex karyotype
- *FLT3* mutation

**current survival rate of 60-70% with modern therapy**
APL AML M3

- Is a rare subtype of AML that is characterized by maturation arrest at the promyelocyte stage and the classic chromosomal translocation t(15;17)

- Many patients with APL present with DIC that requires urgent and aggressive management.

- The treatment of APL has been revolutionized by the ability to target the PML-RARA fusion with ATRA, which induces differentiation of the blasts

- ATRA should be started quickly when APL is suspected.

- Survival rate 90%.
Chronic Myelogenous Leukemia:

- CML is a clonal disorder of the hematopoietic tissue that accounts for 2-3% of all cases of childhood leukemia.

- Approximately 99% of the cases are characterized by a specific translocation, t(9;22).

- The presenting symptoms of CML are nonspecific and can include fever, fatigue, weight loss, anorexia, and splenomegaly.

- The diagnosis is suggested by a high white blood cell count with mild anemia and thrombocytosis (chronic phase).
Typically, the chronic phase terminates 3-4 yr. after onset, when the CML moves into the accelerated or “blast crisis” phase.

At this point, the blood counts rise dramatically and the clinical picture is indistinguishable from acute leukemia.

Neurologic symptoms from hyper-leukocytosis, which causes increased blood viscosity with decreased CNS perfusion.

Imatinib (Gleevec) and dasatinib, are agents designed specifically to inhibit the BCR-ABL tyrosine kinase.

HSCT is curative in 80% of cases.
Juvenile Myelomonocytic Leukemia (JMML)

- affects children younger than 2 years of age.
- present with rashes, lymphadenopathy, splenomegaly, and hemorrhagic manifestations.
- Philadelphia chromosome should be negative.
- Monocytosis and less than 20% blast in BM.
- neurofibromatosis type 1 and Noonan syndrome.
- Cure only by Stem cell transplantation.
LYMPHOMA

- Lymphoma is the third most common cancer among U.S. children (age 14 year or younger)

- It is the most common cancer in adolescents, accounting for >25% of newly diagnosed cancers in persons 15-19 year old.

- The 2 broad categories of lymphoma, Hodgkin lymphoma (HL) and non- Hodgkin lymphoma (NHL), have different clinical manifestations and treatments.
Hodgkin Lymphoma

- Hodgkin lymphoma (HL) is a malignant process involving the lymphoreticular system that accounts for 6% of childhood cancers.

- HL is the most common malignancy in adolescents (15-19 year of age)

- Infectious agents may be involved, such as human herpes virus 6, cytomegalovirus, and Epstein-Barr virus (EBV).

- Infection with EBV confers a 4-fold higher risk of developing HL and may precede the diagnosis by years.
The Reed-Sternberg (RS) cell, a pathognomonic feature of HL, is a large cell (15-45 μm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL.

Patients commonly present with painless, nontender, firm, rubbery, cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement.

Extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration.
Systemic symptoms, classified as B symptoms that are considered important in staging, are unexplained fever >38°C (100.4°F), weight loss >10% total body weight over 6 months, and drenching night sweats.

Less common and not considered of prognostic significance are symptoms of pruritus, lethargy, anorexia, or pain that worsens after ingestion of alcohol.
Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should undergo chest radiography CXR to identify the presence of a large mediastinal mass before undergoing lymph node biopsy and anesthesia.

Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies.
evaluation includes history, physical examination, and imaging studies, including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and positron emission tomography (PET) scan.

- Bilateral BM biopsy in advanced stage

- Bone scan if bone pain or high ALP

- A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax. This determines “bulk” disease and becomes prognostically significant.
Classical Hodgkin lymphoma: usually CD15 and 30 positive

**HL types:**
- Nodular lymphocyte predominance
- Classical Hodgkin lymphoma
- Lymphocyte rich
- Mixed cellularity
- Nodular sclerosis
- Lymphocyte depletion
Prognosis

With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an event-free survival (EFS) of 85-90% and an overall survival (OS) at 5 year of >95%.

Patients with advanced-stage disease have slightly lower EFS (80-85%) and OS (90%).

Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of bulky nodal disease.
Chemotherapy and radiation therapy are both effective in the treatment of HL.

Treatment of HL in pediatric patients is risk adapted and involves the use of combined chemotherapy with or without low-dose involved-field radiation therapy based on response.

ABVD, COPP regimens.

Brentuximab vedotin: new targeted therapy as anti CD30.
Patients whose disease relapses >12 months after chemotherapy alone or combined modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60-70%.

A myeloablative autologous stem cell transplantation in patients with refractory disease or relapse within 12 months of therapy results in a long-term survival rate of only 40-50%.
Non-Hodgkin Lymphoma

- Non-Hodgkin lymphoma (NHL) accounts for approximately 60% of lymphomas in children.

- Pediatric NHL is usually high grade and aggressive.

- Although more than 70% of patients present with advanced disease, the prognosis has improved dramatically.

- Survival rates of 90-95% for localized disease and 70-95% with advanced disease.
The 4 major pathologic subtypes of childhood and adolescent:

- Lymphoblastic lymphoma (LBL)
- Burkitt lymphoma (BL) CD19, CD20, and CD22
- Diffuse large B-cell lymphoma (DLBCL) CD19, CD20, and CD22
- Anaplastic large cell lymphoma (ALCL) CD30

- Children with BL and DLBL commonly have a t(8;14) translocation (90%) (C-myc).
- Patients with ALCL commonly have a t(2;5) translocation (90%), anaplastic lymphoma kinase (ALK).
The clinical manifestations of childhood and adolescent NHL depend primarily on pathologic subtype and sites of involvement.

Approximately 70% of patients with NHL present with advanced disease (stage III or IV), including extranodal disease with bone marrow and central nervous system (CNS) involvement.
BL commonly manifests as abdominal (sporadic type) or head and neck (endemic type) tumor and can metastasize to the bone marrow or CNS.

DLBCL commonly manifests as either an abdominal or mediastinal primary and, rarely, disseminates to the bone marrow or CNS.

ALCL manifests either as a primary cutaneous manifestation (10%) or as systemic disease (90%) with dissemination to liver, spleen, lung, or mediastinum.
Recommended laboratory and radiologic testing includes complete blood cell count; measurements of electrolytes, lactate dehydrogenase, uric acid, calcium, phosphorus, blood urea nitrogen, creatinine.

- bone marrow aspiration and biopsy; lumbar puncture with cerebrospinal fluid cytology.

- chest radiographs; and neck, chest, abdominal, and pelvic CT scans and PET scan.
The primary modality of treatment for childhood and adolescent NHL is multiagent systemic chemotherapy with intrathecal chemotherapy.

Newly diagnosed patients, especially those with BL and LBL, are at high risk for TLS.

These patients require vigorous hydration, frequent electrolyte monitoring, and either a xanthine oxidase inhibitor (allopurinol, 10 mg/kg/day PO divided into 3 doses daily) or recombinant urate oxidase (rasburicase, 0.2 mg/kg/day IV once daily for up to 5 days).
Pediatric BL and DLBCL are treated with similar chemotherapy regimens, which are designed for mature B-NHL.

Localized disease, multiagent chemotherapy is given over a 6 weeks to 6 months period. 4 year OS of 99%.

Advanced disease is usually treated with a 4-6 months of multiagent chemotherapy. OS of 79-90%.

Rituximab is a monoclonal antibody directed at CD20 that improves outcome in patients with B-NHL (BL and DLBL)
The best results in LBL have been obtained using the NHL-BFM 90 protocol, which uses therapeutic approaches similar to those for childhood acute leukemia.

ALL like therapy (2-3 years of chemotherapy)

OS 80-90%
For patients who present with localized disease, surgical resection alone is sufficient.

The majority of patients, however, have advanced disease, which requires multiagent chemotherapy.

Various chemotherapy regimens have been studied with similar outcomes and survival ranging from 70-79%.
Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the second most common malignancy in childhood and adolescence.

The overall mortality among this group approaches 30%.

Patients with CNS tumors have the highest morbidity primarily neurologic of all children with malignancies.

Outcomes have improved over time with innovations in neurosurgery and radiation therapy as well as the introduction of chemotherapy as a therapeutic modality.
The classic triad of headache, nausea, and vomiting as well as papilledema is associated with midline or infratentorial tumors.

Torticollis may occur in cases of cerebellar tonsil herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors.

tumors of the brainstem region may be associated with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g., hemiparesis, hyperreflexia, clonus).
Supratentorial tumors are more commonly associated with lateralized deficits, such as focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry.

Infants with supratentorial tumors may present with premature hand preference.

Optic pathway tumors manifest as visual and/or afferent oculomotor disturbances, such as decreased visual acuity, nystagmus, and/or visual field defects.
These are some syndromes associated with CNS tumors:

- Neurofibromatosis type 1 (autosomal dominant)
- Neurofibromatosis type 2 (autosomal dominant)
- Von Hippel–Lindau (autosomal dominant)
- Tuberous sclerosis (autosomal dominant)
- Li-Fraumeni (autosomal dominant)
- Turcot (autosomal dominant)
Treatment

- Treatment is multidisciplinary and includes the pediatric oncologist, pediatric neurosurgeon or other surgical subspecialist, and most often radiation oncologist.
Neuroblastoma

- Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system.

- Neuroblastoma is the most common extracranial solid tumor in children and the most commonly diagnosed malignancy in infants.

- The tumors may resemble other small round blue cell tumors, such as rhabdomyosarcoma, Ewing sarcoma, medulloblastoma and non-Hodgkin lymphoma.
Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the MYCN (N-myc) proto-oncogene and tumor cell DNA content, or ploidy.

Amplification of MYCN is strongly associated with advanced tumor stage and poor outcomes.

Loss of heterozygosity of 1p, 11q, and 14q, and gain of 17q, are commonly found in neuroblastoma tumors and are also associated with worse outcomes.

Hyperdiploidy confers better prognosis if the child is younger than 1 year of age at diagnosis.
Neuroblastoma may develop at any site of sympathetic nervous system tissue.

Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia.

The most common sites of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin.
Metastatic disease can cause fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and periorbital ecchymoses (racoon eyes).

Neuroblastoma originating in the superior cervical ganglion can result in Horner syndrome.

Paraneoplastic syndrome of autoimmune origin, Opsoclonus–myoclonus–ataxia syndrome, in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination, and cognitive dysfunction.
Tumor markers, including catecholamine metabolites homovanillic acid and vanillylmandelic acid, are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis.

A pathologic diagnosis is established from tumor tissue obtained by biopsy.

Neuroblastoma can be diagnosed without a primary tumor biopsy if small round blue tumor cells are observed in bone marrow samples and the levels of vanillylmandelic acid or homovanillic acid are elevated in the urine.
<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>STAGE</th>
<th>AGE</th>
<th>MYCN AMPLIFICATION</th>
<th>PLOIDY</th>
<th>SHIMADA</th>
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stage 4S refers to neuroblastoma in children younger than 1 year of age with dissemination to liver, skin, and/or bone marrow without bone involvement

Stage 4S neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy
The usual treatment for children with low-risk neuroblastoma is surgery for stages 1 and 2 and observation for stage 4S with cure rates generally >90% without further therapy.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. with cure rates generally >80% without further therapy.
Children with high-risk neuroblastoma have long-term survival rates between 25% and 35% with current treatment that consists of:

- intensive chemotherapy
- high-dose chemotherapy with autologous stem cell rescue
- surgery
- radiation
- 13-cis-retinoic acid as differentiating agent.
Wilms Tumor

- Wilms tumor (WT), also known as nephroblastoma, is the most common primary malignant renal tumor of childhood.

- WT accounts for 6% of pediatric malignancies and more than 95% of kidney tumors in children.

- Approximately 75% of the cases occur in children younger than 5 years with a peak incidence at 2-3 year of age. It can arise in 1 or both kidneys; the incidence of bilateral WTs is 7%.

- WT is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies (WAGR), Beckwith- Wiedemann syndrome and Denys-Drash syndrome.
The most common initial clinical presentation for WT is the incidental discovery of an asymptomatic abdominal mass by parents while bathing or clothing an affected child.

Hypertension is present in approximately 25% of tumors at presentation and has been attributed to increased renin activity.

Abdominal pain, gross painless hematuria, and fever are other frequent findings at diagnosis.

Patients might have polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor or factor VII deficiency.
Prognostic factors for risk-adapted therapy include age, stage, tumor weight, and loss of heterozygosity at chromosomes 1p and 16q.

Histology plays a major role in risk stratification of WT. Absence of anaplasia is considered a favorable histologic finding.

Despite some adverse risk factors that decrease prognosis (metastases, unfavorable histology, recurrent disease, and loss of heterozygosity of both 1p and 16q), most children with WT have a very favorable prognosis.

Overall, the survival of children with WT approaches 90%.
Soft Tissue Sarcomas

- Rhabdomyosarcoma accounts for more than 50% of soft tissue sarcomas.

- Rhabdomyosarcoma is thought to arise from the same embryonic mesenchyme as striated skeletal muscle although a large percentage of these tumors arise in areas lacking skeletal muscle (e.g., bladder, prostate, vagina).

- These tumors may occur at virtually any anatomic site but are usually found in the head and neck (25%), orbit (9%), genitourinary tract (24%), and extremities (19%); retroperitoneal and other sites account for the remainder of primary sites.

- Small round cell tumors that includes Ewing sarcoma, neuroblastoma, and non-Hodgkin lymphoma.
Three major histological types:

- The embryonal type accounts for approximately 60% of all cases and has an intermediate prognosis.

- The botryoid type, a variant of the embryonal form in which tumor cells and an edematous stroma project into a body cavity like a bunch of grapes, is found most often in the vagina, uterus, bladder, nasopharynx, and middle ear.

- The alveolar type accounts for approximately 25-40% of cases and carry the poorest prognosis with a characteristic t(2;13).
The most common presenting feature of rhabdomyosarcoma is a mass that may or may not be painful.

Origin in the nasopharynx may be associated with nasal congestion, mouth breathing, epistaxis, and difficulty with swallowing and chewing.

Orbital primary tumors are usually diagnosed early in their course because of associated proptosis, periorbital edema, ptosis, change in visual acuity, and local pain.

Other symptoms depend on the site involved.
Prognosis

- Prognostic factors include age, stage, histology, and primary site.

- Among patients with resectable tumor and favorable histology, 80-90% have prolonged disease-free survival.

- Unresectable tumor localized to certain favorable sites, such as the orbit, also has a high likelihood of cure.

- Approximately 65-70% of patients with incompletely resected tumor also achieve long-term disease-free survival.
Patients with disseminated disease have a poor prognosis; only approximately 50% achieve remission.

Treatment is multidisciplinary and includes the pediatric oncologist, pediatric surgeon or other surgical subspecialist, and most often radiation oncologist.

Other soft tissue sarcomas are synovial sarcoma (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%).
Neoplasms of Bone

- Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, followed by Ewing sarcoma.

- In children younger than 10 years of age, Ewing sarcoma is more common than osteosarcoma.

- Both tumor types are most likely to occur in the second decade of life.
<table>
<thead>
<tr>
<th>FEATURE</th>
<th>OSTEOSARCOMA</th>
<th>EWING FAMILY OF TUMORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Second decade</td>
<td>Second decade</td>
</tr>
<tr>
<td>Race</td>
<td>All races</td>
<td>Primarily whites</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1.5:1</td>
<td>1.5:1</td>
</tr>
<tr>
<td>Cell</td>
<td>Spindle cell–producing osteoid</td>
<td>Undifferentiated small round cell, probably of neural origin</td>
</tr>
<tr>
<td>Predisposition</td>
<td>Retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy</td>
<td>None known</td>
</tr>
<tr>
<td>Site</td>
<td>Metaphyses of long bones</td>
<td>Diaphyses of long bones, flat bones</td>
</tr>
<tr>
<td>Presentation</td>
<td>Local pain and swelling; often, history of injury</td>
<td>Local pain and swelling; fever</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>Sclerotic destruction (less commonly lytic); sunburst pattern</td>
<td>Primarily lytic, multilaminar periosteal reaction (“onion-skinning”)</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Ewing sarcoma, osteomyelitis</td>
<td>Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma</td>
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<tr>
<td>Metastasis</td>
<td>Lungs, bones</td>
<td>Lungs, bones</td>
</tr>
<tr>
<td>Treatment</td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Ablative surgery of primary tumor</td>
<td>Radiotherapy and/or surgery of primary tumor</td>
</tr>
<tr>
<td>Outcome</td>
<td>Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival</td>
<td>Without metastases, 60% cured; with metastases at diagnosis, 20-30% survival</td>
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</table>
The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation.

Patients are taller than their peers of similar age.

There are 4 pathologic subtypes of conventional high-grade osteosarcoma: osteoblastic, fibroblastic, chondroblastic, and telangiectatic.
Pain, limp, and swelling are the most common presenting manifestations of osteosarcoma.

Because these tumors occur most often in active adolescents, initial complaints may be attributed to a sports injury or sprain.

Any bone or joint pain not responding to conservative therapy within a reasonable time should be investigated thoroughly.

Additional clinical findings may include limitation of motion, joint effusion, and tenderness.
When osteosarcoma is suspected, the patient should be referred to a center with experience in managing bone tumors.

The biopsy and the surgery should be performed by the same surgeon so that the incisional biopsy site can be placed in a manner that will not compromise the ultimate limb salvage procedure.

With chemotherapy and surgery, the 5-yr disease-free survival rate of patients with nonmetastatic extremity osteosarcoma is 65-75%.
Twenty percent to 30% of patients who have limited numbers of pulmonary metastases also can be cured with aggressive chemotherapy and resection of lung nodules.

Complete surgical resection of the tumor is important for cure.

Usually radioresistant tumors

The current approach is to treat patients with preoperative chemotherapy (neoadjuvent) in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately.
Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy.

It is important to resume chemotherapy (adjuvant) as soon as possible after surgery.

Lung metastases present at diagnosis should be resected by thoracotomies at some time during the course of treatment.

Active agents currently in use in multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.
Ewing sarcoma

- Ewing sarcoma, an undifferentiated sarcoma of bone, also may arise from soft tissue.

- The term Ewing sarcoma family of tumors refers to a group of small, round cell, undifferentiated tumors thought to be of neural crest origin that generally carry the same chromosomal translocation.

- This family of tumors includes Ewing sarcoma of bone and soft tissue and peripheral primitive neuroectodermal tumor. (PNET)
- small, round, blue cell tumors

- CD99 staining is usually positive in Ewing sarcoma.

- A specific chromosomal translocation, t(11;22), is found in most of the Ewing sarcoma.
Symptoms of Ewing sarcoma are similar to those of osteosarcoma.

Pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue are common presenting symptoms.

Ewing sarcoma often is associated with systemic manifestations, such as fever and weight loss.

Fever of unknown origin
standard neoadjuvant chemotherapy for Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide

Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy.

It is important to resume chemotherapy (adjuvant) as soon as possible after surgery.

Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with irradiation or surgery.
Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children.

Retinoblastoma classically presents with leukocoria, a white pupillary reflex.

Retinoblastoma can be either hereditary or sporadic.

The hereditary form is associated with loss of function of the retinoblastoma gene (RB1) via gene mutation or deletion.

Bilateral involvement in about 25%
The differential diagnosis of retinoblastoma includes other causes of leukocoria:

- persistent hyperplastic primary vitreous
- Coats disease
- vitreous hemorrhage
- cataract
- endophthalmitis from *Toxocara canis*
- choroidal coloboma
- retinopathy of prematurity
- familial exudative vitreoretinopathy.
The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies.

focal therapy (laser photocoagulation or cryotherapy).

Enucleation is performed if there is no potential for the salvage of useful vision.
Hepatoblastoma

- Hepatoblastoma occurs predominantly in children younger than 3 year of age and the median age of diagnosis is 1 yr.

- Hepatoblastomas are associated with familial adenomatous polyposis, Beckwith-Wiedemann syndrome, hemihyperplasia, and other somatic overgrowth syndromes.

- All children with Beckwith-Wiedemann syndrome or hemihyperplasia should be routinely screened with α-fetoprotein (AFP) levels and abdominal ultrasounds.
Hepatoblastoma usually presents as a large, asymptomatic abdominal mass.

The pure fetal histology subtype predicts a more favorable outcome.

Small cell undifferentiated subtype is associated with normal AFP levels and predicts a worse outcome.
A biopsy of liver tumors is necessary to establish the diagnosis.

The AFP levels are elevated in almost all hepatoblastomas.

Treatment of hepatoblastoma is based on surgery and systemic chemotherapy using cisplatin in combination with vincristine and 5-fluorouracil or doxorubicin.
Histiocytosis Syndromes of Childhood

- The childhood histiocytoses constitute a diverse group of disorders.

- They are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte–macrophage system of bone marrow origin.

- Three classes of childhood histiocytosis are defined, based on histopathologic findings.
<table>
<thead>
<tr>
<th>LCH</th>
<th>Langerhans cell histiocytosis</th>
<th>Langerhans-like cells (CD1a-positive, CD207-positive) with Birbeck granules (LCH cells)</th>
<th>Local therapy for isolated lesions; chemotherapy for disseminated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLH</td>
<td>Familial hemophagocytic lymphohistiocytosis</td>
<td>Morphologically normal reactive macrophages with prominent erythrophagocytosis, and CD8-positive T cells</td>
<td>Chemotherapy; allogeneic bone marrow transplantation</td>
</tr>
<tr>
<td></td>
<td>Infection-associated hemophagocytic syndrome†</td>
<td>Characteristic vacuolated lesional histiocytes with foamy cytoplasm</td>
<td>None or excisional biopsy for localized disease; chemotherapy, radiotherapy for disseminated disease</td>
</tr>
<tr>
<td></td>
<td>Associated with albinism syndromes*</td>
<td></td>
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<tr>
<td></td>
<td>Associated with immunocompromised states</td>
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<tr>
<td></td>
<td>Associated with autoimmune/ autoinflammatory states</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Juvenile xanthogranuloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Rosai-Dorfman disease</td>
<td>Hemophagocytic histiocytes</td>
<td>None if localized; surgery for bulk reduction; chemotherapy if organ systems involvement</td>
</tr>
<tr>
<td>Other</td>
<td>Malignant histiocytosis</td>
<td>Neoplastic proliferation of cells with characteristics of monocytes/ macrophages or their precursors</td>
<td>Antineoplastic chemotherapy, including anthracyclines</td>
</tr>
<tr>
<td>Other</td>
<td>Acute monocytic leukemia‡</td>
<td>M5 by FAB classification</td>
<td>Antineoplastic chemotherapy</td>
</tr>
</tbody>
</table>
Two major forms one is familial hemophagocytic lymphohistiocytosis (FHLH), which is an autosomal recessive disorder and represents approximately 25% of patients with HLH.

Genes are known for 4 of the 5 FHLH syndromes; these mutations affect the ability of T lymphocytes and natural killer cells to synthesize and release perforin and granzymes, thus reducing cytotoxic granule formation.
The other is the infection-associated hemophagocytic syndrome, also called secondary hemophagocytic lymphohistiocytosis.

Noninfectious causes that may trigger secondary HLH include:

- drugs (phenytoin), bone marrow transplantation, chemotherapy, autoimmune diseases, inflammatory bowel disease
- immunodeficiency states (DiGeorge syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, chronic granulomatous disease).
The major forms of HLH, FHLF and secondary HLH, have a remarkably similar presentation consisting of a generalized disease process, most often with fever (90-100%), maculopapular and/or petechial rash (10-60%), weight loss, and irritability.

Children with FHLH generally are younger than 4 years of age, and children with secondary HLH may present at an older age, but both forms are recognized as presenting at any age.

Hepatosplenomegaly (70-100%), lymphadenopathy (20-50%), respiratory distress (40-90%), jaundice, and symptoms of CNS involvement (~50%) that are not unlike those of aseptic meningitis or acute demyelinating encephalomyelitis.
The diagnosis of HLH is established by fulfilling one of the following two criteria:

1. A molecular diagnosis consistent with HLH (e.g., PRF mutations, SAP mutations) or
2. Having 5 of the following 8 signs or symptoms:
   a. Fever
   b. Splenomegaly
   c. Cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dL [or ≤10 g/dL for infants <4 wk of age], platelets <100,000/μL, neutrophils <1,000/μL)
   d. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
   e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
   f. Low or absent natural killer cell cytotoxicity
   g. Hyperferritinemia (≥500 ng/mL)
   h. Elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/mL)
secondary HLH in the presence of a documented infection

treatment of the underlying infection, coupled with supportive
care, is critical.

In FHLH therapy currently includes etoposide, corticosteroids,
cyclosporin, and intrathecal methotrexate.

Nevertheless, even with chemotherapy, FHLH remains
ultimately fatal, often after a relapse of the disease.

Allogeneic stem cell transplantation is effective in curing
approximately 60% of patients with FHLH.
Antimetabolites

Methotrexate:
- Folic acid antagonist; inhibits Dihydrofolate reductase
- ALL, Lymphoma, Medulloblastoma, Osteosarcoma
- Myelosuppression, mucositis, Dermatitis, Hepatitis, Renal and CNS side effects.

6-Mercaptopurine:
- Purine analog, ALL
- Myelosuppression; Hepatitis; mucositis.

Cytosine arabinoside (Ara-C)
- Pyrimidine analog
- ALL, AML, Lymphoma
- Myelosuppression, Conjunctivitis, Mucositis, and Neurotoxicity
Alkylating Agents

Cyclophosphamide and Ifosphamide

- Alkylates guanine; inhibits DNA synthesis
- ALL, lymphoma, sarcoma, brain tumors
- Myelosuppression; hemorrhagic cystitis, neurotoxicity, cardiac toxicity, and secondary malignancy
- The end metabolite is acrolein which is toxic to the bladder epithelium.
- MESNA is used as uroepithelial protection from acrolein.
Antibiotics

Doxorubicin and daunorubicin (anthracyclines)
- ALL, AML, osteosarcoma, Ewing sarcoma, lymphoma, neuroblastoma
- Cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, arrhythmia, and secondary malignancy

Bleomycin:
- Raynaud phenomenon, pulmonary fibrosis.

Dactinomycin:
- Tissue necrosis on extravasation, VOD.
Vinca Alkaloids

Vincristine and vinblastine:


- Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression.
Enzymes

Asparaginase:
- Depletion of asparagine
- ALL, AML
- Allergic reaction;
- pancreatitis,
- hyperglycemia,
- platelet dysfunction, coagulopathy and thrombosis
- encephalopathy, stroke.
Miscellaneous

Cisplatin and carboplatin:

- Inhibits DNA synthesis
- Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors
- Nephrotoxic; myelosuppression, ototoxicity,
- Neurotoxicity, hemolytic uremic syndrome.

Etoposide (VP-16):

- Topoisomerase inhibitor
- ALL, lymphoma, germ cell tumor, sarcoma
- Myelosuppression, secondary leukemia, allergic reaction
QUESTIONS