- **Introduction:**
  - Cancer is the most common cause of death from diseases in childhood but notice that most of them are not carcinomas (in contrast to cancers in adults).
  - **Most common childhood cancers are:** leukemias, lymphomas, brain tumors, neuroblastoma and Wilm’s tumor.
  - **Causes of childhood cancers:** often unknown but patients might have genetic predisposition + environmental factors which playing a role.
    - **Wiskott-Aldrich syndrome:** which is characterized by thrombocytopenia, eczema and deficiency in T and B-cell immunity. It is associated with leukemia and lymphoma.

- **Leukemias:**
  - **Acute Lymphocytic Leukemia (ALL):**
    - It is the most common childhood cancer. Notice that ALL represents 80% of childhood leukemias and is occurring between the age of 2-6 years and more in males.
    - **Etiology:** unknown but might be associated with chemotherapy, ionizing radiation, genetic syndromes (Down syndrome), chemical agents or immunodeficiency diseases (ataxia telangiectasia).
Classifications:

- **Clinical features**: fever, bone or joint pain, pallor, bruising, hepatosplenomegaly and lymphadenopathy. Testicular involvement might occur.

Diagnosis:

- *Suggested by*: CBC which shows anemia and thrombocytopenia. WBCs are increased in 1/3 of patients, normal in 1/3 of patients and decreased in 1/3 of patients.
- *Confirmed by*: bone marrow evaluation which shows replacement by lymphoblasts.

Prognostic factors:

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>1-9 years</td>
<td>&lt; 1 or &gt; 9 years</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Whites</td>
<td>Blacks</td>
</tr>
<tr>
<td><strong>WBCs</strong></td>
<td>&lt; 50,000 cells/mm³</td>
<td>&gt; 50,000 cells/mm³</td>
</tr>
<tr>
<td><strong>Ploidy</strong></td>
<td>Hyperploidy</td>
<td>Low ploidy</td>
</tr>
<tr>
<td><strong>Organ involvement</strong></td>
<td>None</td>
<td>Organomegaly</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>CALLA (+)</td>
<td>CALLA (-)</td>
</tr>
<tr>
<td><strong>Chromosomal translocation</strong></td>
<td>None</td>
<td>t(9,22)</td>
</tr>
</tbody>
</table>

Management: there are three stages

- **Induction of remission**
  - To destroy as many cancer cells as possible
  - Intrathecal methotrexate is given to all children.
  - Corticosteroids, L-asparaginase and vincristine are used
  - Remission is induced in 95% of patients
Consolidation
- Intrathecal methotrexate is continued
- Cranial irradiation for high-risk children but after 5 years to avoid neuropsychological effects.

Maintenance
- Daily and periodic chemotherapy during remission for up to 3 years


- Complications of treatment (tumor lysis syndrome):
  - Hyperuricemia: renal insufficiency
  - Hyperkalemia: cardiac arrhythmias.
  - Hyperphosphatemia: hypocalcemia and tetany.

✓ Prognosis: long-term survival in 85% of patients.

- Acute myelogenous leukemia (AML):
  ✓ It represents 20% of childhood leukemias.
  ✓ Etiology: unknown but might be associated with chemotherapy, ionizing radiation or Down syndrome.
  ✓ Classification:
    - M1: acute myeloblastic leukemia (no maturation).
    - M2: acute myeloblastic leukemia (some maturation).
    - M4: acute myelomonocytic leukemia.
    - M5: acute monocytic leukemia.
    - M6: erythroleukemia.
    - M7: acute megakaryocytic leukemia.

✓ Clinical features: fever, bone or joint pain, pallor, bruising and hepatosplenomegaly. Lymphadenopathy and testicular involvement are uncommon.

✓ Investigations: pancytopenia (↓Hb, ↓platelets, ↓WBCs) or leukocytosis + DIC

✓ Diagnosis:
  - Suggested by: clinical features and myeloblasts with Auer rods on peripheral blood smear.
  - Conformation: bone marrow biopsy.

✓ Management: bone marrow transplantation once remission is induced.

✓ Prognosis:
  - Aggressive chemotherapy is effective in 50% of patients.
  - Bone marrow transplantation is curative in 70% of patients.
Chronic Myelogenous Leukemia (CML):
- It is the least common type of leukemia and is more common in males.
- Classification:
  - **Adult-type CML**:
    - More common
    - In older children and adolescents
  - **Juvenile CML**:
    - Less common (often fatal)
    - In infants and children < 2 years
  - Philadelphia chromosome (reciprocal translocation between chromosomes 9 and 22 producing BCR-ABL fusion protein)
  - **Clinical features**: massive splenomegaly and extremely high WBCs (>100,000 cells/mm³)
  - **Management**: induction of remission with imatinib and bone marrow transplantation
  - Philadelphia chromosome is absent
  - **Clinical features**: fever, petechiae and purpura, suppurative lymphadenopathy, WBCs < 100,000 cells/mm³ and chronic eczema-like facial rash
  - Management: bone marrow transplantation

- **Brain tumors**:
  - They are the 2nd most common childhood cancer and the most common solid tumors.
  - Classification:
    - **Histology**
      - Glial cell tumors (most common): including astrocytomas. High-grade tumors in supratentorial region (cerebrum). Low-grade tumors in infratentorial region (cerebellum)
      - Primitive Neuroectodermal Tumors (PNETs): 2nd most common and including medulloblastoma which is arising from cerebellum.
      - Ependymomas: 3rd most common
      - Craniopharyngiomas: 4th most common
    - **Grade**
      - High-grade: aggressive; proliferating cells
      - Low-grade: less aggressive; more differentiated cells
    - **Location**
      - Infratentorial region (most common): medulloblastoma
      - Supratentorial region: astrocytomas
  - **Clinical features**:
    - Initial non-specific symptoms: Headache, vomiting, drowsiness/irritability, ataxia, change in behavior, seizures and head tilt
    - Physical examination: Enlarged head circumference or bulging of fontanel in infants, nytagmus, papilledema, cranial nerves abnormalities
    - Features associated with specific tumors
      - **Optic glioma**: diminished vision, visual filed deficits and strabismus
      - **Craniopharyngioma**: growth retardation, delayed puberty, visual disturbances and diabetes insipidus.
  - **Diagnosis**: Brain CT or MRI. CSF is obtained during surgery for staging and assessment of tumor markers.
  - **Management**: surgery is the principle of treatment. Almost all brain tumors are radiosensitive. Chemotherapy can be added.
  - **Prognosis**:
    - **Astrocytomas**
      - Low-grade: > 75% survival
      - High-grade: 35% survival at 3 years
    - **PNETs**
      - > 75% survival if majority of tumor can be resected with no metastasis.
    - **Brainstem gliomas**
      - Poorest prognosis
**Lymphoma:**
- It is the 3rd most common childhood cancer.

**Hodgkin’s disease:**
- It is cancer of antigen-processing cells in lymph nodes or spleen.
- It is associated with EBV infection and occurs in older children and adolescents.
- Clinical features: gradual onset of painless supraclavicular or cervical lymphadenopathy.
- Diagnosis: it is made by lymph node biopsy which shows Reed-Sternberg cell (a large multinucleated cell with abundant cytoplasm).
- Staging: it is done by Ann Arbor system with four main stages each being subclassified to A (refers to lack of systemic symptoms) or B (refers to presence of systemic symptoms: fever, night sweats and weight loss).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of ≥ 2 lymph nodes on the same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph nodes on both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of ≥ 1 extralymphatic organ or tissue</td>
</tr>
</tbody>
</table>

**Management:** chemotherapy and radiation. Late complications of therapy are:
- Male sterility (most common).
- Growth retardation.
- Hypothyroidism (10-20%)
- Secondary malignancies.

**Prognosis:** stages I and II (≥ 80% long-term survival).

**Non-Hodgkin’s lymphoma:**
- It is a very aggressive cancer which is more common than Hodgkin’s disease and occurs more in males. It is associated with immunodeficiency conditions (e.g. ataxia telangiectasia, HIV and Wiskot-Aldrich syndrome).
- Classification:

<table>
<thead>
<tr>
<th>Lymphoblastic lymphoma</th>
<th>B-cell origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histology resembles ALL</td>
</tr>
<tr>
<td></td>
<td>Presenting with rapid onset of painless anterior mediastinal mass which might produce SVC-syndrome or airway obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Burkitt’s lymphoma</th>
<th>B-cell origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most common lymphoma in childhood</td>
</tr>
<tr>
<td></td>
<td>It is endemic in Africa and presenting as a jaw mass.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Large-cell lymphoma</th>
<th>B-cell origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enlargement of lymphoid tissue in tonsils, adenoids and Peyer’s patches.</td>
</tr>
</tbody>
</table>
Diagnosis: by lymph node biopsy. It is important to rule-out dissemination by:
analysis of CSF, chest radiograph/CT, abdomino-pelvic CT, bone scan and
bone marrow biopsy and hepatic transaminases.
Management: must be very rapid due to aggressiveness of this tumor. It
includes debulking, chemotherapy and CNS prophylaxis.
Prognosis: best for localized tumor with a cure rate > 90%

- Renal and suprarenal tumors:
  - Neuroblastoma:
    ✓ It is a malignant tumor of neural crest cells arising from: adrenal medulla or
      sympathetic ganglion chain. It is the 2nd most common solid tumor after brain
      tumors with a peak incidence at 5 years of age.
    ✓ 75% occur in abdomen and pelvis; 20% occur in mediastinum; 5% occur in
      the neck.
    ✓ Etiology: unknown but might be associated with deletion in chromosome 1,
      unbalanced translocation between chromosome 1 and 17 or anomalies in
      chromosomes 14 and 22.
    ✓ Clinical features:

Clinical features

- Abdomen and pelvis: firm
  abdominal mass
  crossing the midline,
  abdominal pain
  and anorexia
- Mediastinal: respiratory
  distress and incidental
  radiographic finding
- Cervical: compression of
  trachea and 
  Horner’s syndrome
  (ptosis, miosis and anhidrosis)
- Release of catecholamines:
  flushing, sweating,
  headache and
  hypertension
- Non-specific: fever and
  weight loss
- Acute cerebellar
  atrophy (in 2% of cases): 
  ataxia, opsoclonus and
  myoclonus
- Metastatic disease
  (70% of cases at time of diagnosis):
  hepatomegaly, bone pain/limp,
  peri orbital ecchymosis or skin
  nodule with blueberry muffin
  appearance

Diagnosis: definitive diagnosis is made by positive bone marrow biopsy or
tissue biopsy + elevated urine catecholamines (including VMA and HVA).

Staging (Evan’s system):

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-I</td>
<td>Tumor localized to structure of origin</td>
</tr>
<tr>
<td>Stage-II</td>
<td>Tumor extends beyond structure of origin but no crossing the mid-line</td>
</tr>
<tr>
<td>Stage-III</td>
<td>Tumor crossing the mid-line</td>
</tr>
<tr>
<td>Stage-IV</td>
<td>Metastasis to bone</td>
</tr>
<tr>
<td>Stage-IVS</td>
<td>Tumor at stage I or II with metastasis to organ other than the bone</td>
</tr>
</tbody>
</table>
✓ **Management:**
  - *Surgery only*: for stages I and II.
  - *Chemotherapy*: for metastatic disease (stages IV and IVS).
  - *Radiation*: for advanced disease.

✓ **Prognosis:**
  - *Good*: stages I and II. Notice that there is spontaneous regression – without treatment- for stage-IVS in young infants.
  - *Poor*: stages III and IV.

- **Wilm’s tumor (nephroblastoma):**
  - It is the most common childhood renal tumor. It occurs before the age of 5 years old (in 75% of cases). It is associated with:
    - *Beckwith-Wiedemann syndrome* (hemohypertrophy, macoglossia and visceromegaly).
    - *WAGR syndrome* (Wilm’s tumor, Aniridia, Genitourinary abnormalities and mental retardation).
    - *Deletion on chromosome 11*.

✓ **Clinical features**: abdominal mass which rarely crosses the mid-line, abdominal pain (50% of cases), hematuria (25% of cases) and hypertension (25% of cases).

✓ **Diagnosis**: abdominal CT/MRI + tissue biopsy.

✓ **Staging:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-I</td>
<td>Tumor limited to kidney and is completely resectable</td>
</tr>
<tr>
<td>Stage-II</td>
<td>Tumor extends locally but still can be completely resectable</td>
</tr>
<tr>
<td>Stage-III</td>
<td>Residual tumor remains in abdomen</td>
</tr>
<tr>
<td>Stage-IV</td>
<td>Distant metastasis to lungs (most common), liver, brain or bone</td>
</tr>
<tr>
<td>Stage-V</td>
<td>Bilateral renal involvement</td>
</tr>
</tbody>
</table>

✓ **Management**: surgery and chemotherapy. Radiation for advanced diseases (stages III and IV).

✓ **Prognosis**: excellent.

- **Bone tumors:**
  - **Osteogenic sarcoma:**
    - It is a malignant tumor which is producing osteoid (new bone).
    - It is the most common malignant bone tumor and it commonly occurs in adolescent males.
    - **Etiology**: unknown but it is associated with: previous retinoblastoma, Paget’s disease of bone, radiation therapy and fibrous dysplasia.

✓ **Features:**
  - Occurring in metaphysis of long bone. 50% occur near the knee.
  - Most common sites (in order): distal femur, proximal tibia, proximal humerus and proximal femur.
  - Local symptoms: pain and swelling.
  - *X-ray*: sunburst appearance.
  - *Metastasis*: lungs (90%); bones (10%).
Ewing’s sarcoma:
- It is the 2nd most common malignant bone tumor which is occurring in adolescent males.
- Etiology: unknown but in 95% there is chromosomal translocation between chromosomes 11 and 21.
- Features:
  - Occurring in flat bones and diaphysis of tubular bones.
  - Most common sites (in order): axial skeleton (especially pelvis), humerus, femur.
  - Local and systemic symptoms: pain, swelling, fever, weight loss, leukocytosis and ↑ESR.
  - X-ray: onion-skin appearance.
  - Metastasis: lungs (50%); bones (25%); bone marrow (25%).

Diagnosis:
- Suggested by: findings on radiology and MRI.
- Confirmed by: tissue biopsy.

Management: multi-agent chemotherapy followed by surgical excision, when possible.

Prognosis:
- Local disease: 3-5 year survival rate of 80%.
- Metastasis: poor.

Retinoblastoma:
- It is a malignant tumor of sensory retina.
- It is the most common ocular malignancy in childhood and > 95% of cases are diagnosed before 5 years of age.
- Etiology: mutation or deletion of growth suppressor gene on both alleles of chromosome 13. This can be sporadic or inherited as AR.
- Clinical features: leukocoria (white reflex using ophthalmoscope) and strabismus. In addition, calcification of tumor on imaging studies.
- Diagnosis: visual inspection with ophthalmoscope, ocular ultrasound or CT.
- Management:

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large tumors</td>
<td>Poor prognosis; enucleation</td>
</tr>
<tr>
<td>Smaller tumors</td>
<td>External beam radiation</td>
</tr>
<tr>
<td>Very small peripheral tumors</td>
<td>Cryotherapy or laser photocoagulation</td>
</tr>
</tbody>
</table>