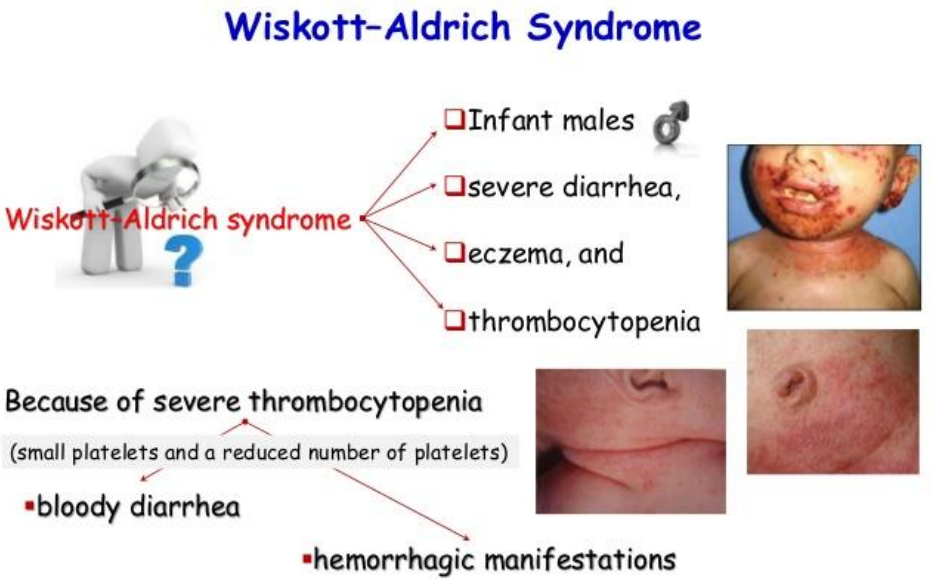
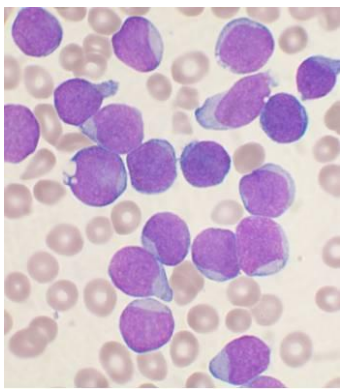
- **Introduction:**
  - Cancer is the most common cause of death from diseases in childhood but notice that most of them are not carcinomas (in contrast to cancers in adults).
  - **Most common childhood cancers are**: leukemias, lymphomas, brain tumors, neuroblastoma and Wilm's tumor.
  - **Causes of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



    - ✓ X-linked lymphoproliferative disease: it is associated with EBV and might result in lymphoma.
    - ✓ Infectious diseases: EBV associated with Burkitt's lymphoma; HIV is associated with Kaposi's sarcoma.
    - ✓ Environmental factors: prior chemotherapy and ionizing radiation.
  - **Genetic disorders and their association with childhood cancers:**

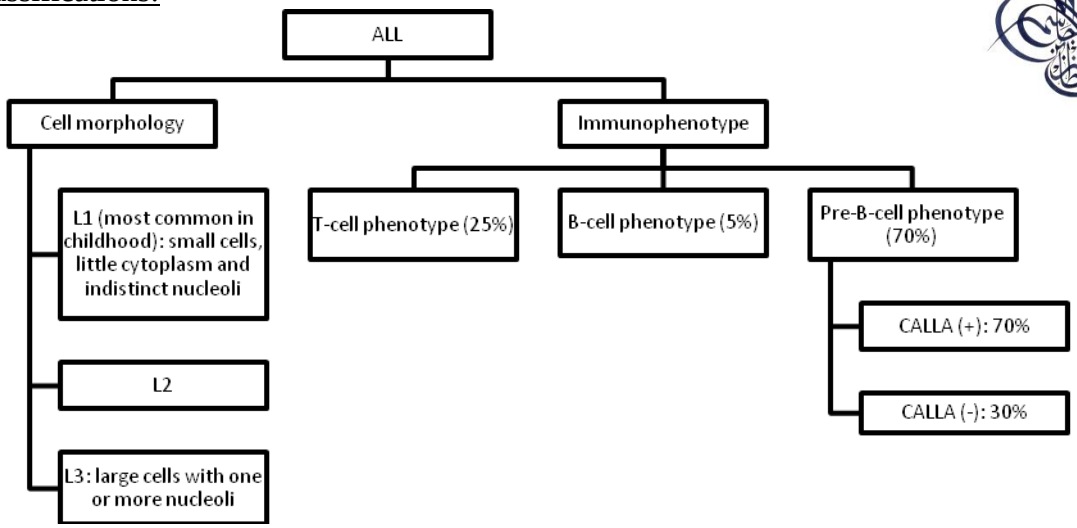
Down syndrome	Leukemia and lymphoma
Tuner syndrome	Gonadoblastoma
Trisomy 13	Leukemia and teratoma
Trisomy 18	Wilm's tumor and neurogenic tumors
Klinefelter syndrome	Breast cancer, germ cell tumors and leukemia

- **Leukemias:**
  - **Acute Lymphocytic Leukemia (ALL):**

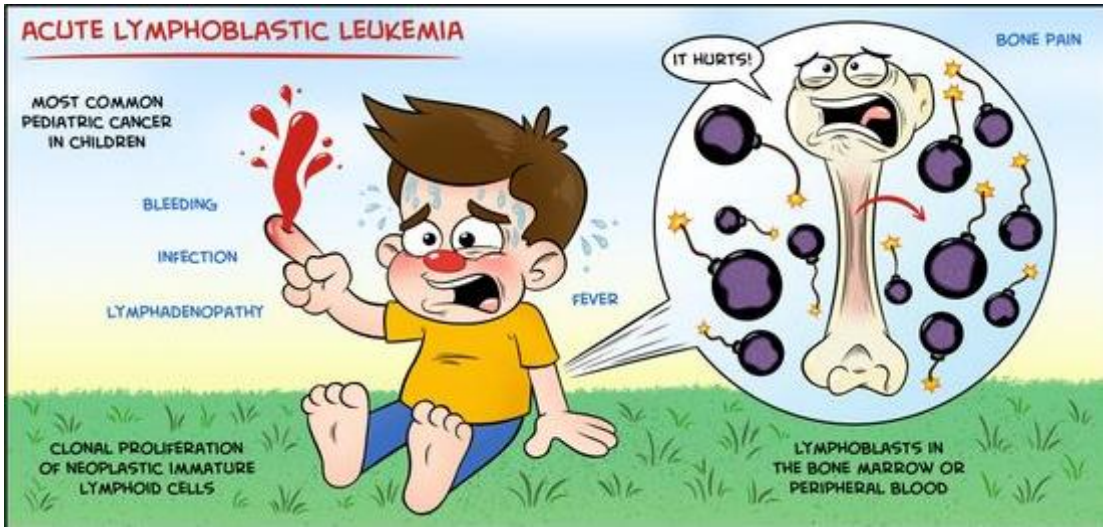


    - ✓ It is the most common childhood cancer. Notice that ALL represents 80% of childhood leukemias and is occurring between the age of 2-6 years and more in males.
    - ✓ Etiology: unknown but might be associated with chemotherapy, ionizing radiation, genetic syndromes (Down syndrome), chemical agents 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:

Prognostic factor	Favorable	Unfavorable
Age	1-9 years	< 1 or > 9 years
Sex	Females	Males
Race	Whites	Blacks
WBCs	< 50,000 cells/mm^3	> 50,000 cells/mm^3
Ploidy	Hyperploidy	Low ploidy
Organ involvement	None	Organomegaly
Immunophenotype	CALLA (+)	CALLA (-)
Chromosomal translocation	None	t(9,22)

- ✓ Management: there are three stages

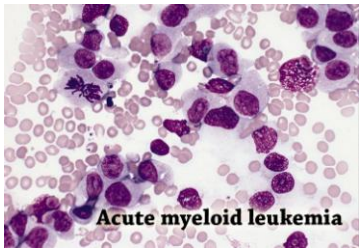
Induction of remission	• To destroy as many cancer cells as possible • Intrathecal methotrexate is given to all children. • Corticosteroids, L-asparaginase and vincristine are used • Remission is induced in 95% of patients

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

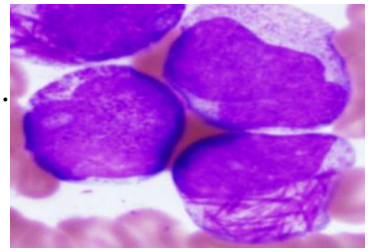
- ❖ *Bone marrow transplantation*: for high-risk children and those who relapse after treatment.
- ❖ *Complications of treatment (tumor lysis syndrome):*
  - ➢ Hyperuricemia: renal insufficiency
  - ➢ Hyperkalemia: cardiac arrhythmias.
  - ➢ Hyperphosphatemia: hypocalcemia and tetany.

✓ 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:



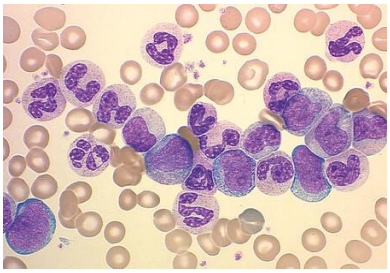
- ❖ *M1*: acute myeloblastic leukemia (no maturation).
- ❖ *M2*: acute myeloblastic leukemia (some maturation).
- ❖ *M3*: acute promyelocytic leukemia (Auer rods common).
- ❖ *M4*: acute myelomonocytic leukemia.
- ❖ *M5:* acute monocytic leukemia.
- ❖ *M6*: erythroleukemia.
- ❖ *M7*: acute megakaryocytic leukemia.

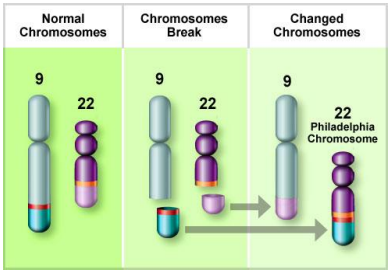


  - ✓ Clinical features: fever, bone or joint pain, pallor, bruising and hepatosplenomegaly. Lymphadenopathy and testicular involvement are uncommon.

  - ✓ 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	Juvenile CML
More common	Less common (often fatal)
In older children and adolescents	In infants and children < 2 years
Philadelphia chromosome (reciprocal translocation between chromosomes 9 and 22 producing BCR-ABL fusion protein)	Philadelphia chromosome is absent
Clinical features: massive splenomegaly and extremely high WBCs (>100,000 cells/mm^3)	**Clinical features**: fever, petechiae and purpura, supparative lymphadenpathy, WBCs < 100,000 cells/mm^3 and chronic eczema-like facial rash
Management: induction of remission with imatinib and bone marrow transplantation	**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

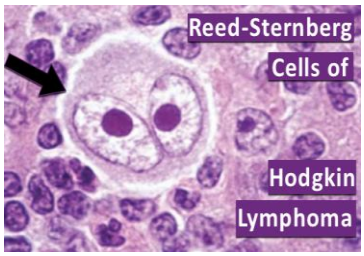
  - **Clinical features:**

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, papilledeme, 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:**

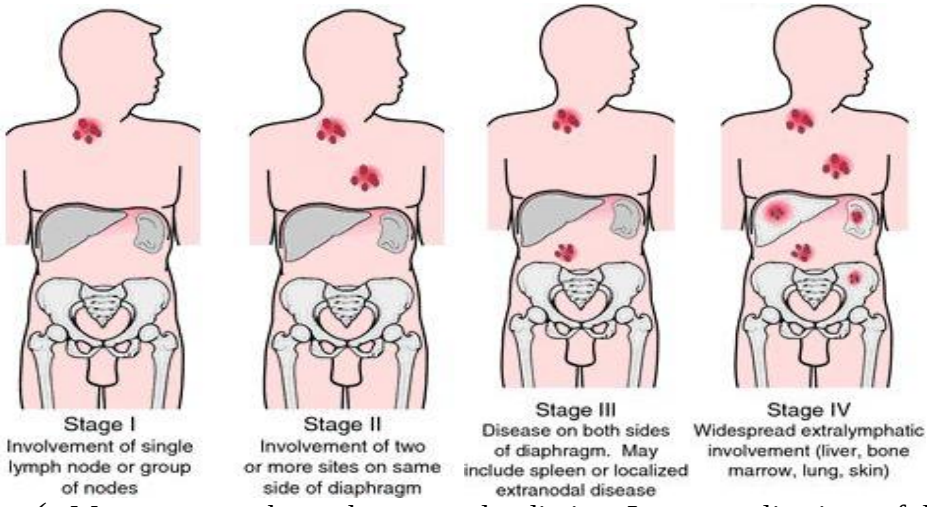
Astrocytomas	**Low-grade**: > 75% survival
	High-grade: 35% survival at 3 years
PNETs	> 75% survival if majority of tumor can be resected with no metastasis.
Brainstem gliomas	Poorest prognosis

- **Lymphoma:**
  - **It is the 3rd most common childhood cancer.**
  - **Hodgkin's disease:**



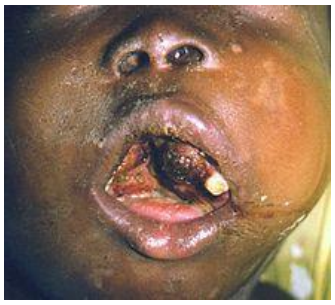
- ✓ It is cancer of antigen-processing cells in lymph nodes or spleen.
- ✓ It is associated with EBV infection and occurs in older children and adolescents.
- ✓ Clinical features: gradual onset of painless supraclavicular or cervical lymphadenopathy.
- ✓ Diagnosis: it is made by lymph node biopsy which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

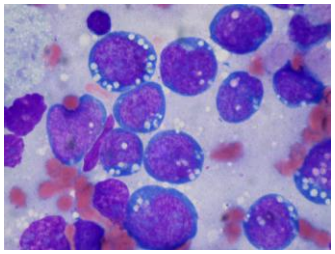
Stage-I	Involvement of a single lymph node
Stage-II	Involvement of ≥ 2 lymph nodes on the same side of diaphragm
Stage-III	Involvement of lymph nodes on both sides of diaphragm
Stage-IV	Diffuse involvement of ≥ 1 extralymphatic organ or tissue



- ✓ 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:

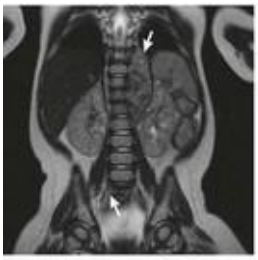
Lymphoblastic lymphoma	• T-cell origin • Histology resembles ALL • Presenting with rapid onset of painless anterior mediastinal mass which might produce SVC-syndrome or airway obstruction
Burkitt's lymphoma	• B-cell origin • Most common lymphoma in childhood • It is endemic in Africa and presenting as a jaw mass.
Large-cell lymphoma	• B-cell origin. • Enlargement of lymphoid tissue in tonsils, adenoids and Peyer's patches.

- ✓ 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%

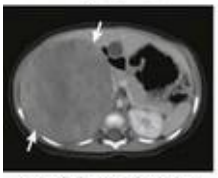
- **Renal and suprarenal tumors:**
  - **Neuroblastoma:**
    - ✓ It is a malignant tumor of neural crest cells arising from: adrenal medulla or sympathetic ganglion chain. It is the 2nd most common solid tumor after brain tumors with a peak incidence at 5 years of age.
    - ✓ 75% occur in abdomen and 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-spcific: 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, periorbital ecchymosis or skin nodule with blueberry muffin appearance

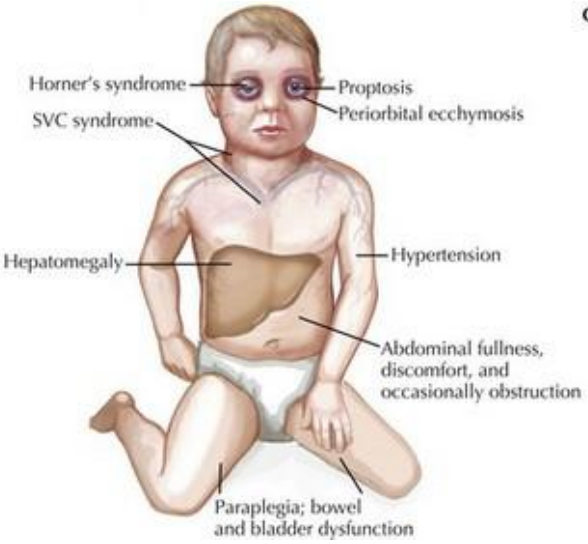


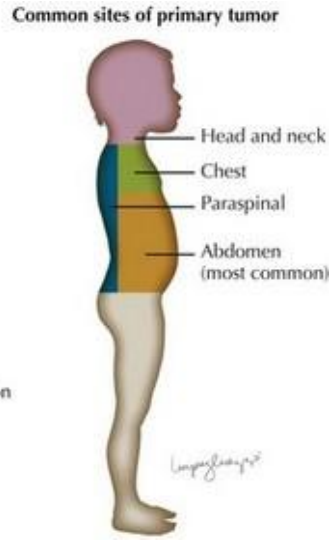
MR image, paraspinal tumor



CT, abdominal tumor

Radiology images courtesy of Lisa States, MD Children's Hospital of Philadelphia





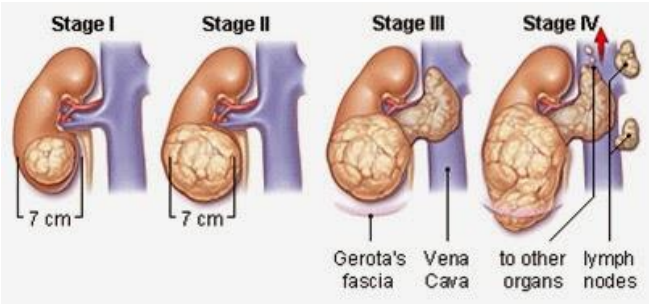
- ✓ Diagnosis: definitive diagnosis is made by positive bone marrow biopsy or tissue biopsy + elevated urine catecholamines (including VMA and HVA).
- ✓ Staging (Evan's system):

Stage-I	Tumor localized to structure of origin
Stage-II	Tumor extends beyond structure of origin but no crossing the mid-line
Stage-III	Tumor crossing the mid-line
Stage-IV	Metastasis to bone
Stage-IVS	Tumor at stage I or II with metastasis to organ other than the bone

- ✓ 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.

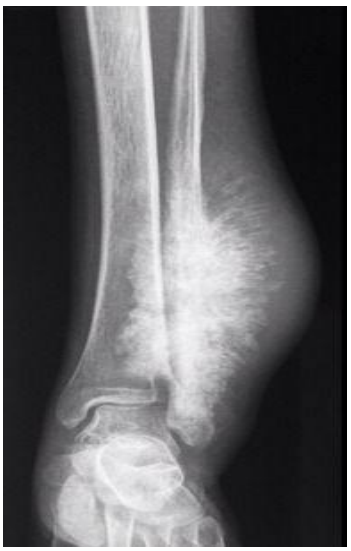
- **Wilm's tumor (nephroblastoma):**
  - ✓ It is the most common childhood renal tumor. It occurs before the age of 5 years old (in 75% of cases). It is associated with:
    - ❖ *Beckwith-Wiedemann syndrome* (hemohypertrophy, macoglossia and visceromegaly).
    - ❖ *WAGR syndrome* (Wilm's tumor, Aniridia, 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:

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



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

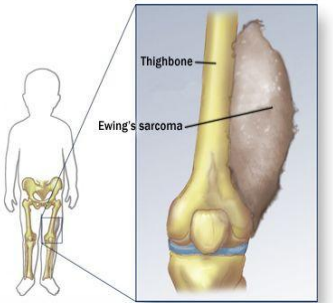
- **Bone tumors:**
  - **Osteogenic sarcoma:**

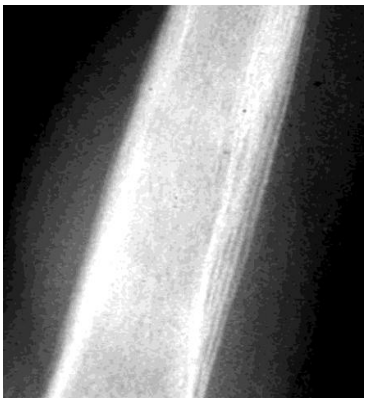


  - ✓ It is a malignant tumor which is producing osteoid (new bone).
  - ✓ It is the most common malignant bone tumor and it commonly occurs in adolescent males.
  - ✓ Etiology: unknown but it is associated with: previous retinoblastoma, Paget's disease of bone, radiation therapy and fibrous dysplasia.
  - ✓ Features:
    - ❖ Occurring in metaphysis of long bon. 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*: sumburst appearance.
    - ❖ *Metastasis*: lungs (90%); bones (10%).

- ✓ Diagnosis:
  - ❖ *Suggested by*: findings on radiology and MRI.
  - ❖ *Confirmed with*: tissue biopsy.
- ✓ Management:
  - ❖ *Surgery*: limb amputation or limb-conserving procedures.
  - ❖ *Chemotherapy (methotrexate).*
  - ❖ *Pulmonary metastasis*: surgical removal.
- ✓ Prognosis: > 60% with addition of chemotherapy.

- **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:**

Large tumors	Poor prognosis; enucleation
Smaller tumors	External beam radiation
Very small peripheral tumors	Cryotherapy or laser photocoagulation