- **Classification of bone tumors:**
  - Age-gender-bone-site related classification.
  - Behavioral classification:
    | Code | Description                                      |
    |------|--------------------------------------------------|
    | 0    | Benign                                           |
    | 1    | Unknown behavior (whether benign or malignant)   |
    | 2    | Non-invasive/ in situ                            |
    | 3    | Primary malignant                                |
    | 6    | Metastatic tumors                                |
    | 9    | Unknown whether the malignant tumor is primary or metastatic |
  - Histogenesis-based classification:
    - Bone-forming tumors:
      - Benign: osteomas (slow-growing benign tumors composed of compact cortical type of bone), osteoid-osteoma, osteoblastoma.
      - Malignant: osteosarcoma.
    - Cartilage-forming tumors:
      - Benign: enchondroma (composed of well-differentiated hyaline cartilage), enchondromatosis, osteochondroma, chondroblastoma, chondromyxoid fibroma.
      - Malignant: chondrosarcoma.
    - Giant cell tumors (osteolastomas): producing lytic multiloculated lesion of the bone.
    - Bone marrow tumors: Primitive Neuroectodermal Tumors of Childhood (PNET) or also known as Ewing sarcoma, lymphoma, leukemia, myeloma.
    - Vascular tumors:
      - Benign: hemangioma, lymphangioma, hemangioendothelioma, hemangiopericytoma.
      - Malignant: angiosarcoma.
    - Other connective tissue tumors:
      - Benign: desmoplastic fibroma, infantile myofibromatosis, muscle and adipose tissue tumors.
      - Malignant: fibrosarcoma, malignant fibrous histiocytoma.
    - Other primary tumors: lymphomas, adamantinoma of long bone, peripheral nerve tumors, xanthoma, fibrocatilagenous mensenchymoma.
    - Metastatic tumors.
  - Tumor-like lesions of the bone (all of them produce lytic lesions of the bone)
    - Fibrous dysplasia.
    - Metaphyseal fibrous defect (non-ossifying fibroma):
      - Benign tumor of childhood occurring in the metaphysis of long bones (commonly femur & tibia) and characteristically regress thereafter.
    - Eosinophilic granuloma.
    - Bone cysts:
      - Aneurysmal bone cyst.
      - Simple (unicameral) bone cyst.
      - Subchondral cyst.
      - Ganglion cyst of bone.

- **Principles in the diagnosis of bone tumors:**
  - Age of the patient (adult vs child).
  - Bone involved.
  - Specific anatomic location: epiphysis, metaphysis, diaphysis, cortex, medulla, periosteum.
  - Radiological appearance:
    - Onion skin of Ewing sarcoma.
- **Sunburst of osteosarcoma.**
- **Codman’s triangle.**
- **Histogenesis of tumor:** developmental, defective, neoplastic… etc.
- **Biopsy procedure and microscopic appearance.**
- **Immunohistochemistry, cytogenetics, molecular studies.**
- **Tumor-like conditions.**
- **Clinical-radiological-pathological correlation.**

### Presentation of bone tumors:
- **Clinical presentation:** asymptomatic, pain, functional limitations of movements, local swelling, pathological fracture, vertebral collapse, metastasis.
- **Radiological appearance.**
- **Laboratory findings:**
  - $↑$ serum alkaline phosphatase: secreted by osteoblasts in carcinoma of the breast and lung.
  - $↑$ serum acid phosphatase: secreted by neoplastic cells of prostatic carcinoma.

### Pathogenesis of bone tumors:
- **Most malignant bone tumors arise de novo** (starting from the beginning) but some tumors arise within pre-existing conditions.
- **There are some predisposing benign bone lesions which can transform to malignancy such as:**
  - Paget’s disease.
  - Chondromatosis (benign cartilage-forming tumor).
  - Osteochondromatosis.
  - Fibrous dysplasia (tumor-like lesion).
  - Osteofibrous dysplasia.
- **Malignant bone tumors can also be caused by exposure to radiation such as:**
  - Radium: in watch makers.
  - External therapeutic radiation.
- **Following prosthesis in hip replacement.**
- **Genetic implication:**
  - Ewing’s sarcoma: t(11,22) and t(21,22).
- **Pathogenesis of osteosarcoma:**
  - Rb suppressor gene: especially in children treated with chemotherapeutic alkylating agents for retinoblastoma and other malignancies.
  - Mutation in p53 gene.
  - Amplification of MDM2, CDK-4, PRIM.
  - Overexpression of MET and POS

### Giant cell tumors of bone (details):
- **Locally aggressive, potentially malignant tumors characterized by the presence of osteoclastic giant cells in a background of proliferating mononuclear cells.**
- These tumors usually originate at the junction between epiphysis and metaphysis of long bones (especially in humerus, distal end of the radius, knee area and fibula).
- **Pathogenesis:** two lineages of mononuclear stromal cells:
  - Non-neoplastic macrophage monocyte system.
  - Cells with chromosomal abnormalities and molecular alterations in oncogens (TP53 and c-myc).
- **Osteosarcoma (details):**
  - Arises proximal to the knee (but any other metaphysis can be affected).
  - There will be bone destruction and neoplastic bone formation due to the mutations which will result in the pathogenesis of this disease (mentioned above).

- **Gross appearance:**
  - **Variable:** depending on the amount of neoplastic bone which is found, cartilage, stroma and blood vessels.
  - **Cut surface:** combination of hemorrhagic, cystic, soft and bony areas.

- **Microscopy:**
  - Malignant osteoblasts forming malignant osteoid and tumor bone (which is woven and lack structural arrangement).
  - There are also malignant giant cells and malignant cartilage.
  - Immunohistochemistry: malignant cells stain for alkaline phosphatase and osteonectin.

- **Spread:**
  - **Direct into:** bone marrow, periosteum, epiphysis and joint space.
  - **Direct to nearby structures:** muscle, nerve or soft tissue.
  - **Blood stream metastasis to lungs.**

- **Juxtacortical osteosarcoma:**
  - Variant of osteosarcoma occur on periosteal surface of bone particularly lower posterior metaphysic of femur.
  - Low-grade lesion which does not invade the cortex or medulla of bone but grows externally to the shaft.
  - No Codman’s triangle because the periosteum is not elevated.

- **Ewing’s sarcoma (PNET):**
  - Occurs as midshaft or metaphyseal lesion.
  - Tends to parallel the distribution of red marrow.
  - Tumor cells are rich in glycogen.
  - Onion-skin appearance: represents alternate circumferential discontinuous layer of periosteal new bone and lytic bone.

- **Metastatic bone tumors:**
  - Commonest malignant bone tumors.
  - Mostly carcinomas (thyroid, breast, lung, kidneys and prostate).
  - Carried by blood stream.
  - Commonly vertebral column and end of long bones.