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Review Article

BONE TUMORS: MORPHO-BIOLOGIC AND EVOLUTION GUIDELINES BEFORE ANATOMOPATHOLOGICAL EXAMS

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Abstract

Bone tumors represent an ongoing challenge for the physician, who can remain in control of the disease only by means of comprehensive knowledge of clinical presentation, evolution, staging, pathology and possible responses to treatment. Although some malignant bone tumors are life-threatening, for many types the average outcome has improved due to the application of adjuvant chemotherapy and limb reconstruction. Survival rates for reconstruction associated with chemotherapy can now match those for radical amputation. The development and improvement of staging systems, based on biological activity and the extent of tumor invasion, allow the physician to select the most effective treatment program.

The aggressiveness of a tumor can be measured by its mitotic activity, its degree of cellular differentiation and the amount of necrosis. This histopathological grading best reflects the tumor's biological activity, its prognosis and guides the choice of treatment; it is the key to an effective treatment.

Keywords: *benign bone tumor, malignant bone tumor, staging*

Rezumat

Tumorile osoase reprezintă o continuă provocare adresată medicului, în care acesta poate controla situaţia numai printr-o cunoaştere completă a aspectelor clinice, evoluţiei naturale, stadiilor de evoluţie, histopatologiei şi răspunsului la tratament.

Deşi unele tumori osoase maligne constituie o ameninţare asupra vieţii, prognosticul multora din ele s-a îmbunătăţit în condiţiile aplicării unei chimioterapii adjuvante sau în urma asocierii chimioterapiei cu procedee de reconstrucţie, obţinându-se rate ale supravieţuirii altădată posibile doar prin amputaţii radicale.

Dezvoltarea şi îmbunătăţirea actuală a sistemului de stadializare, având la bază activitatea biologică şi extinderea tumorii, au permis aplicarea de către medic a mai multor scheme terapeutice eficace.

Comportamentul agresiv al tumorilor poate fi demonstrat prin activitatea mitotică histologică a tumorii, gradul de diferenţiere celulară şi /sau gradul necrozei tisulare. Acest „grading" histologic reflectă cel mai bine activitatea biologică a tumorii, prognosticul şi indică cele mai bune modalităţi de tratament, reprezentând cheia unui tratament eficace.

Cuvinte-cheie: *tumoră osoasă benignă, tumoră osoasă malignă, stadializare*

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Generalities

Tumors are masses of newly formed tissue that form by abnormal cellular proliferation. This pathological pattern of growth exceeds the development rate of normal tissue and persists after the disappearance of inductive factors; thus, tumors are said to be biologically autonomous from the body.

Unlike cell proliferation in inflamed and regenerating tissue, which is integral to the processes of defense and adaptation, tumor proliferation is primitive, unbounded and not only useless, but actively damaging to the body. This observation is first attributed to Galen, who distinguished physiological, inflammatory or reparatory swellings from those "against nature", where he included tumors. The term "tumor" comes from the Latin word *tumor*, which defined any type of swelling, regardless of its nature – neoplastic, inflammatory, hyperplastic or vascular.

Today, the word tumor is a synonym for neoplasia (from Greek *neos* – new, and *plassis* - growth), and defines the development of tissue featuring new characteristics, different from the ones of the host organism (Ackerman, 1964; Robbins, 1974).

Bone tumors are an important group of lesions that, because of their variability, incidence and severity, represent an important part of children's surgical pathology. Some are malignant, others are benign, and some can regress spontaneously [15] (*Figure no. 1*). Rarely, tumors can have both malignant and benign features, so-called "borderline" tumors [6,13] (*Figure no. 2*).

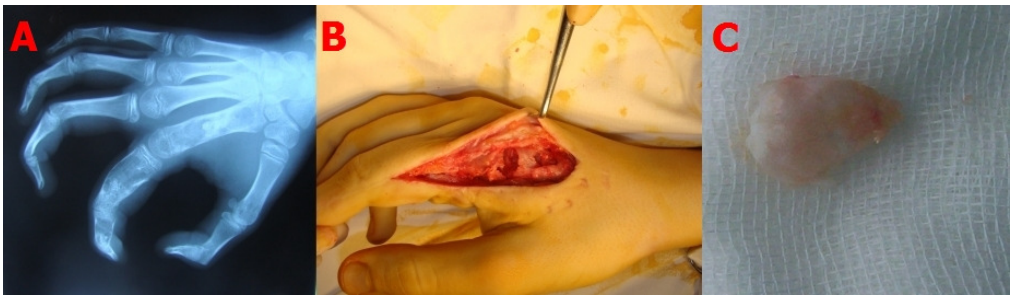

Figure no.1: Chondromyxoid fibroma.

A: Proximal and middle phalanges of index and the second metacarpus show lacunar areas alternating with radio-opaque, irregular images, bone septa and punctiform ossifications on X-rays.
B. The translucid and gellatinous tumoral tissue is surgically removed and the resulted defect is filled with BMP containing bone putty.
C: Macroscopic aspect of the chondromyxoid fibroma (resection sample).

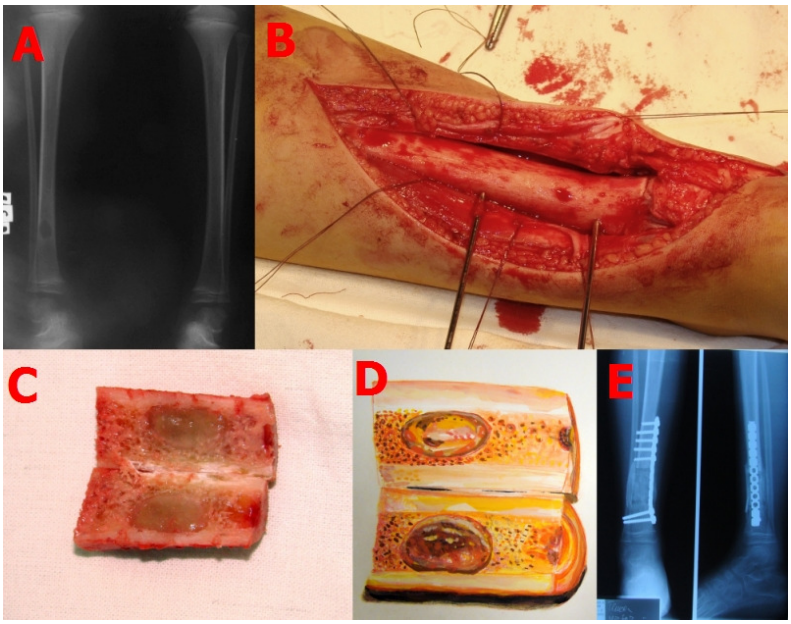

Figure no. 2: Eosinophilic granuloma located in the distal third of the tibia.

A: The X-rays of the calf show a lacunar space in the areolar spongeous tissue. There is no sclerous contour to properly delimit and the cortical bone is not affected.
B: The affected cortical surface looked pale, with reduced bleeding intraoperatively.
C. Segmental resection of the tibia: the osteotomies were performed 3 cm proximal and distal to the lacunar space. The resected segment exposed the tumor entrapped between the two cortices; resection margins are distant from the tumor formation.
D: The drawing clearly shows the tumor margins and the presence of adjacent spongy tissue.
E: The resected segment was replaced with cortical-cancellous bone grafts from the bone bank, and the tibia was fixed and stabilized with a reconstruction plate.

Bone tumors can be classified by their biological behavior, their ability to grow and breach natural barriers, which are:

- The capsule: a layer of bone or fibrous tissue surrounding the tumor;
- The reactive zone: a result of the proliferation of mesenchymal (reactive bone or fibrous) tissue, new vessels and inflammatory cells, formed between the capsule and normal bone;
- Bone cortex;
- Periosteum;
- Joint cartilage.

Benign tumors

Benign tumors have the following characteristics:

Growth:

- Strictly local, slow growth;
- Lack of infiltration in healthy tissue;
- Favorable evolution;
- No metastases.

Morphology:

- Strict delimitation from neighboring tissues, either by the basement membrane (epithelial tumors), or by a fibrous capsule (mesenchymal tumors);
- Well differentiated, both at the tissue and cellular level, resembling the source tissue;
- Cells morphologically similar to normal ones;
- Rare to absent mitoses, always in a typical pattern; most dividing cells do so by amitosis, resulting in an expansive growth pattern;
- Low vascularity.

Benign tumors are never accompanied by neoplastic intoxication phenomena or by paraneoplastic syndromes. The complications that can arise are mostly local and rarely regional (by compression, strangulation or stenosis). The behavior of benign tumors can be predicted from their clinical, radiological ant histopathological features and can fall into three groups: inactive, active and aggressive tumors. Active and aggressive tumors can cause local destruction, despite their inability to metastasize [1, 2].

Inactive (stationary or latent) benign bone tumors

They are completely surrounded by a capsule of mature fibrous tissue or cortex-like bone, remain local and do not distort the bone they're located in. The reactive zone is minimally represented and the histological features are benign: low division rate, well differentiated cells, absence of hyperchromatism, anaplasia or pleomorphism (*Figure no. 3*).

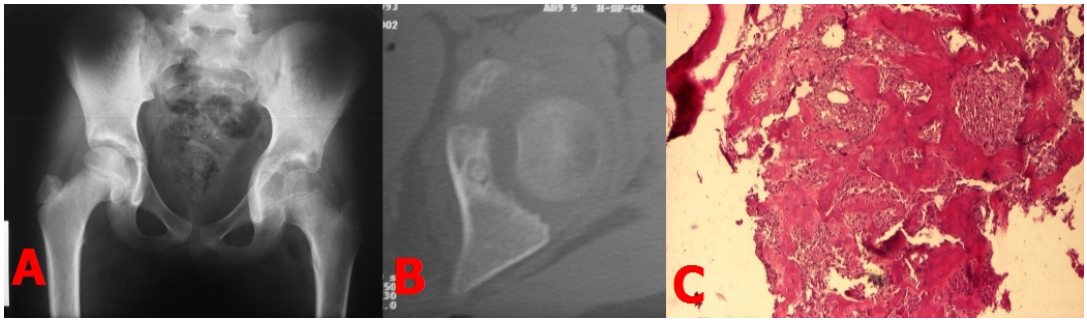

Figure no. 3: Osteoid osteoma with exceptional location, on the internal side of the acetabulum.

A: The X-rays do not allow a certain diagnosis.
B: Suggestive symptoms, nocturnal pains awaking the patient required a CT scan. The presence of a circumferential areolar space (nidus) certifies the diagnosis of acetabular osteoid osteoma.
C: The histological examination confirmed the diagnosis of osteoid osteoma (nidus: proliferation of osteoblasts with osteoid production, connective-vascular stroma, fibrous-vascular areas, sclerotic bony tissue) (MD Augustina Enculescu's series).

Active benign bone tumors

They are usually asymptomatic. Unlike the former, they continue to grow and can distort the cortex or joint cartilage, while still being encapsulated in mature fibrous tissue or trabecular rings (more effective than a cortical shell). The inside of the capsule can be irregular, giving the tumor a lobulated appearance. Surrounding the tumor is a thin reactive zone (*Figure no. 4,* next page). The symptoms are minimal and, occasionally, these tumors can cause pathological fractures and disjunctions [3].

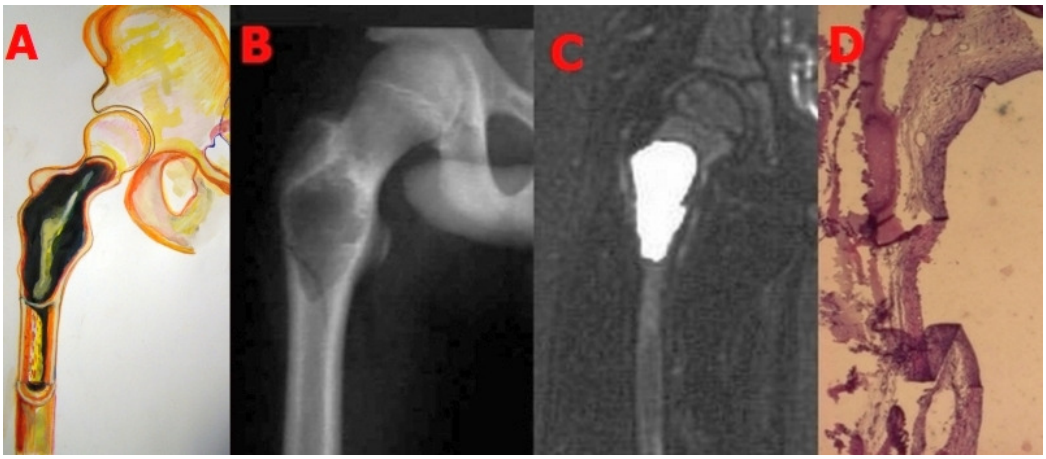

Figure no. 4: Simple bone cyst.

A: Graphical representation illustrating Beck's triad (physis integrity, smooth lesional contour and clear, transparent lacunar area);
B: Radiological appearance suggestive for bone lacuna, in the cervical and trochanteric area, relatively well defined;
C: MRI image clearly outlines the bone lacuna, reiterating the smooth contour;
D: Microscopic examination confirmed the presumptive clinical and imagistic diagnosis by the presence of a fibrous and vascular membrane, collagen fibers, capillaries, arterioles and veinules, hemosiderin deposits, lymphocytes and osteoid tissue (MD Augustina Enculescu's series).

Aggressive benign bone tumors

These tumors have the aggressive behavior of low grade cancers, extending finger-like projections into normal surrounding tissues. The reactive zone forms a capsule or a pseudocapsule surrounding the growing lesion. Although this pseudocapsule doesn't hinder tumor growth, it limits the extension of tumor nodules in healthy tissue. Aggressive tumors cause the destruction and resorbtion of surrounding bone and infiltrate adjacent bone and compartments (*Figure no. 5*). Unlike the former, these have a high division rate, but are made of highly differentiated cells (*Figure no. 6*). In contrast with their evolution, the cytological features are benign. They are often symptomatic and are associated with pathological fractures [5].

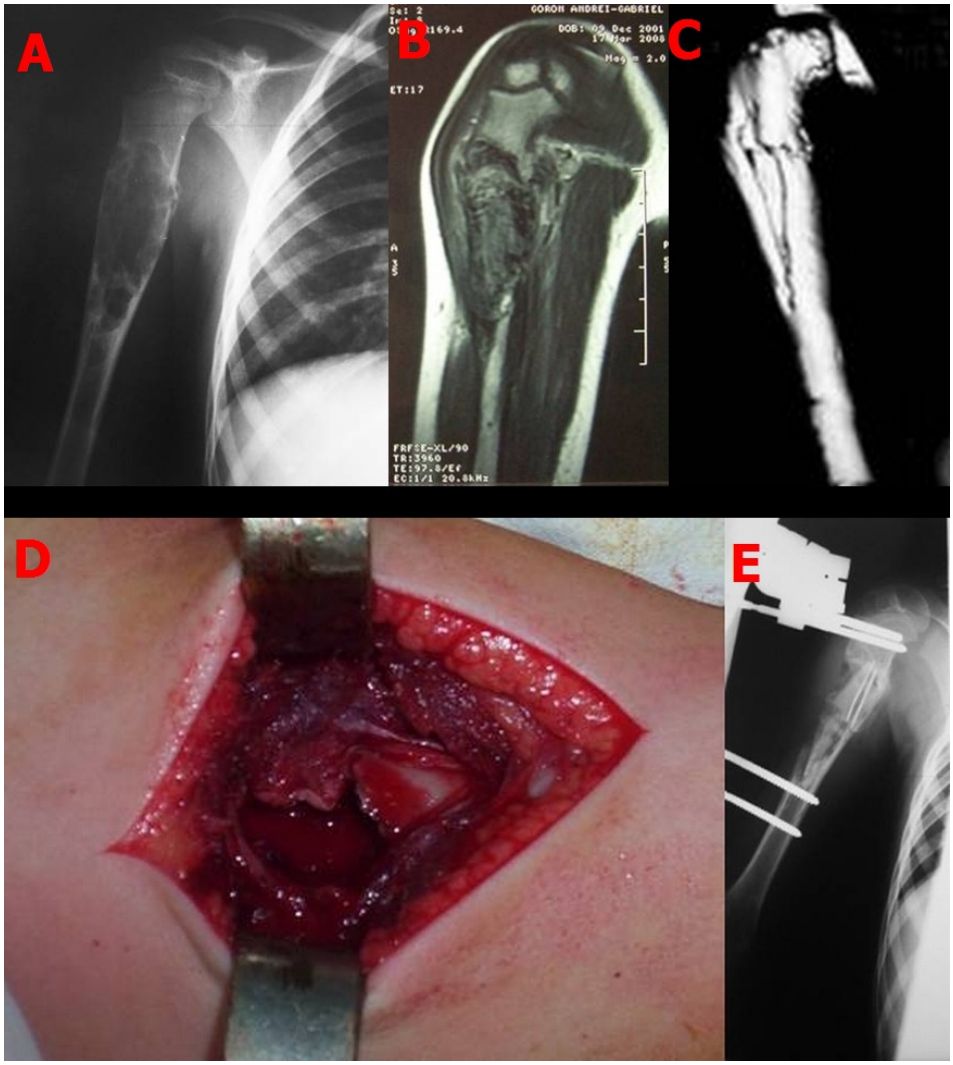

Figure no. 5: Non-ossifying fibroma.

A: The radiological image does not allow to distinguish a benign tumor from a malignant one. The radiolucent area is disposed in the proximal metaphyseal-diaphyseal humerus having a fenestrated shape with cortical bursting and imminent fracture risk.
B: The MRI scan reveals the tumoral expansion in the adjacent tissue, preserving a contour delimited to the periosteum and muscular tissue.
C: 3D CT reconstruction shows a discontinuity in the bone contour and an incomplete fracture line.
D: A thinned cortical, fractured over an area of 3 x 2.5 cm is obvious and the brownish and jelly content was removed intraoperatively. The remaining cavity was cauterized and filled with cortical and cancelous bone allograft.
E: To avoid spontaneous fractures, an external fixator stabilizes the tumoral focus.

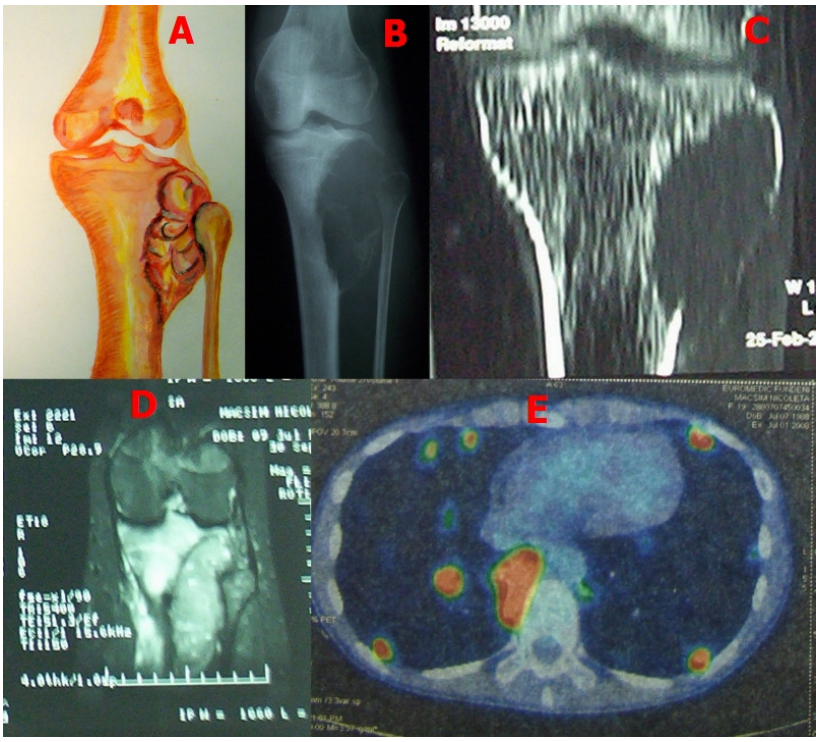

Figure no. 6: Giant cell tumor (stage III, malignant)

A. Relevant drawing for macroscopic aspect and local and regional extent.
B, C: On X-ray and tomography, the tumor included half of the proximal end of tibia, has no smooth contour, the proximal physis being destroyed and invaded the epiphysis. The lateral cortex is completely destroyed and the fibular head is invaded.
D: MRI clearly reveals the degree of extension in the soft tissues. Lateral calf muscles in the proximal third are totally invaded next to the subcutaneous cellular tissue.
E: PET exam shows multiple lung metastases.

Malignant tumors

The main feature of these tumors is their ability to colonize distant locations in the body, or metastasis. The essential characteristics of malignant bone tumors are:

Growth:

- Infiltrative, invasive and destructive growth pattern, with no clear line of demarcation between the tumor and healthy tissue (*Figure* no. 7);
- Non-encapsulated;
- Tendency for recurrence and metastasis;
- Rapid growth rate.

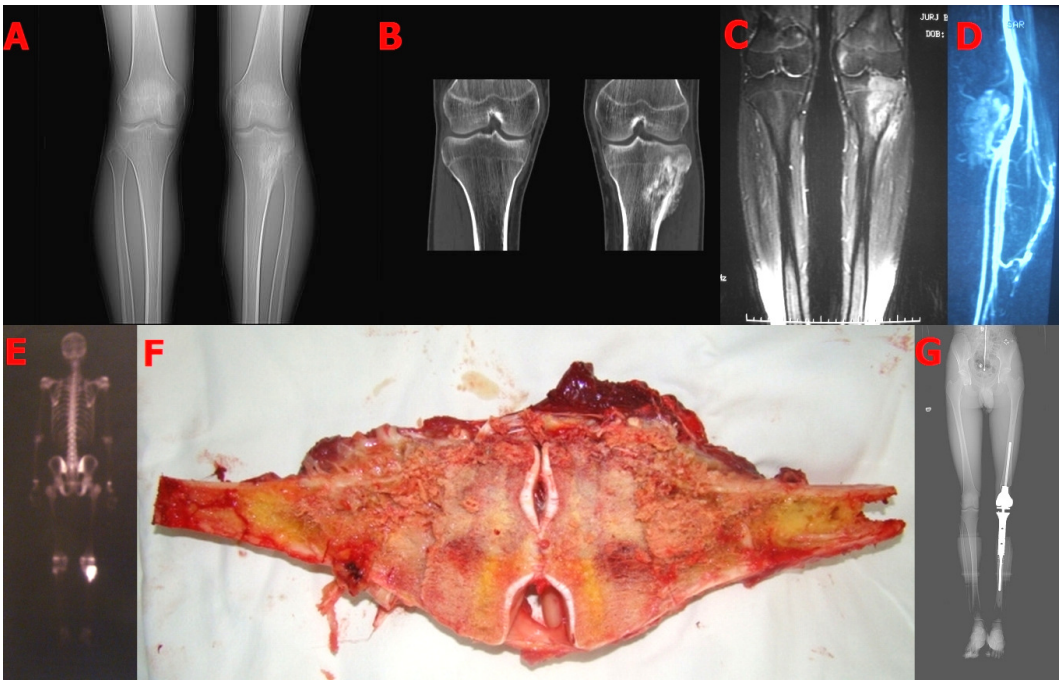

Figure no. 7: Proximal tibia osteogenic osteosarcoma

A: The upper extremity of left tibial bone has multiple eccentric structural changes and central cotton-like or cloud-like densities. The extension through the cortex gives the image of "sunburst" due to periosteal reaction;
B: The CT scan shows a diffuse tumor with expansive character, central calcifications, incomplete destruction of the lateral cortex and periosteal reaction;
C. MRI scan shows the extracortical expansion limits and more obvious the invasion of the physis;
D: The arteriography reveals a neo-formation area, with tributary vessels from the posterior tibial artery. Artery is not included in the tumoral extension;
E: Scintigraphic whole-body scan shows hypercaptation in the upper part of the left tibia;
F: "En bloc" oncological resection piece sectioned longitudinally. Macroscopically the tumoral tissue appears pinkish-brown, centrally located in the metaphysis and extended in the epiphysis and extracortically. The centromedular extension limit is represented by a modified areolar tissue and a yellow "cap"-like matter;
G: Osteoartroplastic reconstruction of the left tibia with modular endoprosthesis with femoral component.

Histopathology:

- Made of malignant cells, which are derived from normal cells, but irreversibly altered, with a certain degree of autonomy from the body's self-regulation mechanisms; they feature numerous different properties from normal cells;

- Cells are usually atypical;
- Well vascularized.

Function:

- Increased proliferation capacity;
- Decreased intercellular adhesion;
- Capacity for locomotion.

Malignant tumors are associated with neoplastic intoxication and paraneoplastic syndromes. Cancer is essentially a cellular disease, associating genetic, metabolic and functional anomalies of neoplastic cells. Cancer-causing agents directly or indirectly affect the cellular genetic material and are able to transform normal cells into malignant ones. The malignant phenotype of a cell is an irreversible, acquired set of features that is transmitted to the next generation of cells.

Microscopic studies allowed the formulation of the general features of cell and tissue anomalies in malignant tumors:

a) Weak or absent cell differentiation, known as anaplasia;
b) Functionally, malignant cells have a profoundly altered metabolism, including: increase of protein and nucleic acid synthesis; decrease of amino acid, purine and pyrimidine metabolism; decreased glycogen and lipid synthesis; quantitative and qualitative alterations of protein synthesis and a particular set of enzymes;
c) Abnormal cell morphology, atypical cell size and shape (pleiomorphism), inversion of the nucleus to cytoplasm ratio, increased number of nucleoli and Barr bodies; basophilic cytoplasm due to increased RNA; increased number of vacuoles; bizarrely shaped mitochondria; numerous free ribosomes ; increased release of lysosomal enzymes in the peritumoral fluid and tissue, increasing tumor invasiveness;
d) Numerous atypical mitoses – bipolar mitoses with randomly oriented spindle axes and multipolar mitoses, with multiple equatorial plates.

The behavior of malignant tumors varies extensively. Some tumors have slow local growth and rare and late-appearing metastases, while others are fast-growing, destructive and often already metastasized at the time of diagnosis (*Figure no. 8*). Like benign tumors, the evolution of malignant tumors can be predicted using correlated clinical, radiological and pathological findings [9, 16].

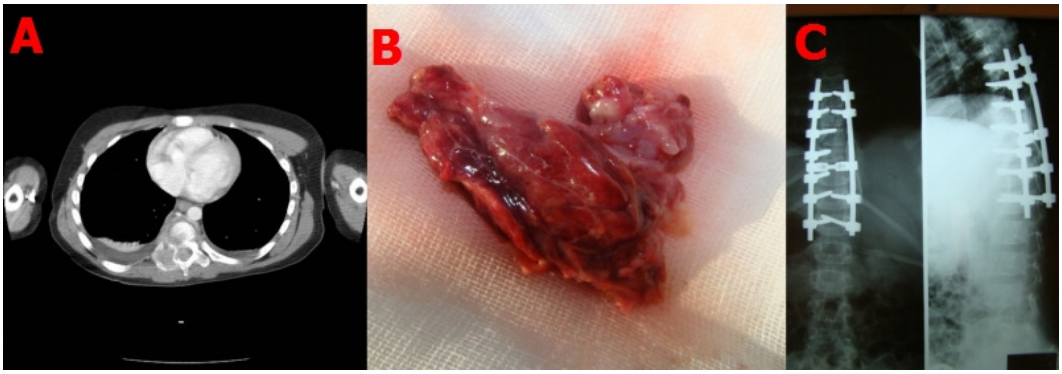

Figure no. 8: Same patient as in figure no. 9 presenting a spinal metastasis one year after pelvic surgery for ganglioneuroblastoma, requiring spinal surgery

A: CT-scan: T10 vertebral lysis with complete hemiarch destruction and vertebral body invasion;
B: Macroscopic aspect of the resected metastasis;
C: Spinal stabilization by posterior spinal implant.

Low grade sarcomas

Low grade sarcomas are tumors that grow slowly, invade local tissue and have a low risk of metastasis. The capsule is interrupted in many points and the thick reactive zone forms a pseudocapsule. Isolated satellite nodules are frequently discovered inside the reactive zone. These sarcomas progressively erode the natural barriers against tumor growth. In time, and especially because of failed excision attempts and recurrences, the risk of evolution to a higher grade sarcoma increases, as well as the risk of the appearance of metastases.

The cytological features of malignancy, anaplasia, pleiomorphism, hyperchromatism, are obvious, but the number of observed mitoses is small. Typical characteristics of malignancy are tumoral necrosis, hemorrhage and varying degrees of vascular invasion. Low grade sarcomas are usually asymptomatic.

High grade sarcomas

This type of tumor rapidly invades the thick reactive zone, making the encapsulation process appear reduced or absent. High grade sarcomas successively breach natural barriers, destroying the bone cortex, joint cartilage and joint capsule. The limit between the lesion and the surrounding bone is diffuse, indicating the capacity for invasion. Satellite nodules appear both within the reactive zone and beyond it, mostly inside the medullar space (***Figure no. 9***).

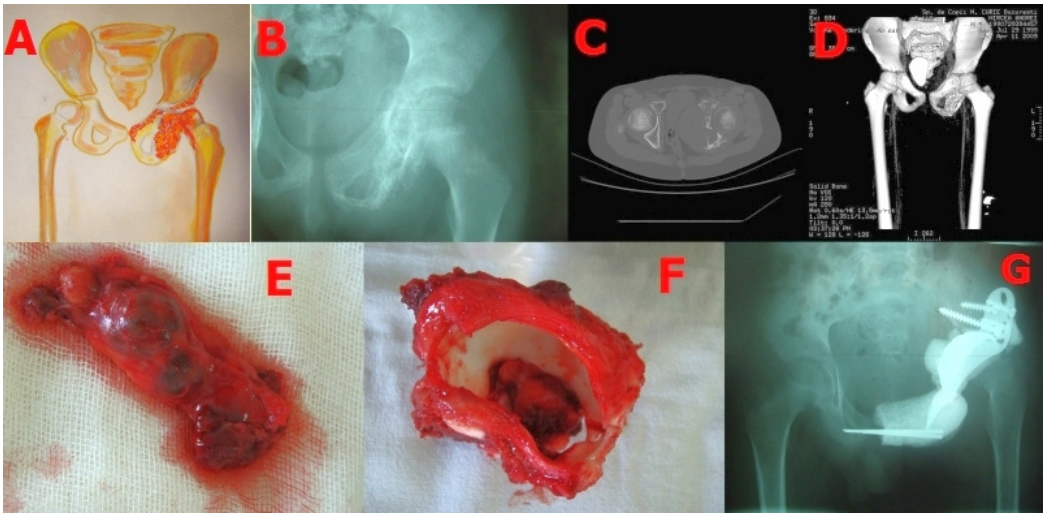

Figure no. 9: Ischial ganglioneuroblastoma extended to the acetabulum.

A. The drawing shows the degree of bone extension from the ischium to the pubis, acetabulum and supraacetabulary in the iliac bone;
B: X-rays are only relevant for the ischial lesions;
C, D: CT-scan sections and 3D CT-scan reconstruction show the tumoral extention and acetabular invasion;
E: Resected lumbo-aortic lymph nodes;
F: The resected acetabulum presents central invasion and a yellowish hyaline cartilage;
G: Reconstruction has been performed with a personalized modular endoprosthesis after the oncological "en-bloc" ganglioneuroblastoma resection.

Besides the malignant features mentioned previously for low grade sarcomas, high grade sarcomas are also characterized by a high rate of cell division and weak cell differentiation.

Staging of bone tumors

Establishing the stage of a bone tumor is done for the purpose of choosing the best treatment course, as well as to quantify the risk of local complications and metastases. Bone tumors can be correctly staged only after in-depth clinical, radiological and pathological investigation. The biopsy must always succeed all the other investigations [11].

The stage of a particular lesion depends on three factors:

- The grade (G), determined by the biological aggressiveness of the tumor [12];
- The anatomical extent of the tumor (T) – whether the tumor is still enclosed in its capsule or the originating compartment;
- The presence or absence of metastases (M).

Staging of benign bone tumors

- Stage I: Inactive, latent tumor;
- Stage II: Active tumor;
- Stage III: Aggressive tumor.

Staging of malignant bone tumors

- Stage I: Reduced degree of invasion;
- Stage II: High degree of destruction;
- Stage III: Metastatic tumor.

Malignant tumors can be divided into intracompartmental and extracompartmental.

Tumors can change from one stage to another: benign stage II tumors often become latent stage I after the end of skeletal growth; positively diagnosed benign tumors can become stage II, II or III sarcomas; malignant tumors can metastasize during or after radiation therapy, after inadequate resections or repeated surgery [4, 10, 14].

According to W. Enneking et al., (1980), muscular-skeletal sarcomas are classified as [7, 8]:

Stage	Grade	Location	Metastases
I A	**Low**	Intracompartmental	No
I B	**Low**	Extracompartmental	No
II A	**High**	Intracompartmental	No
II B	**High**	Extracompartmental	No
III	**Low or high**	Intracompartmental or extracompartmental	Yes

This classification, based on histological grade, extension and the presence of metastases, is only applicable to mesenchymal tumors, not to small cell tumors.

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