

## Review Article

# PRACTICAL ATTITUDE IN THE ESTABLISHMENT OF DIAGNOSIS AND THERAPEUTICAL OPTIONS IN OSTEOSARCOMA

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### Abstract

In Romania, the malignant bone tumors affect on average 37 children and adolescents annually: 60% are osteosarcomas, 24% Ewing sarcomas and 16% other types of sarcomas, which are rarely met as far as the frequency is regarded. The maximum incidence for the newly diagnosed patients is situated between 10 and 20 years old, but the appearance of new cases below 5 years old, as well as over 50 years old can also be met.

Unfortunately, most of the patients with osteosarcoma present to the specialty physician very late, being diagnosed in II B Enneking stage, when the tumor has already exceeded the cortical bone and has a high degree of malignancy. A part of these patients present occult metastases, which are less than 2 mm in diameter, undetectable in the CT and MRI explorations. Their evolution confirms this presumption and the patients do not benefit from the expected effects of the therapeutic protocol. At present, the therapeutic program of the osteosarcomas presupposes a cytostatics preoperative treatment, en bloc oncological resection and osteoplastic or osteoarthroplastic reconstruction, followed by postoperative chemotherapeutical treatment for a year. The chemotherapy and surgical treatments allow the saving of the limbs and, sometime, even the saving of the life. The cases of some cured patients who had the chance of being precociously diagnosed and treated are well known.

At the international level, many personalities in the medical field have been distinguished, persons who have theoretically and practically approached the field of bone tumors: R. Kotz, M. Campanacci, F. Enneking, M. Mercuri, E. Greenfield, A. Meyers, R. Capanna, G. Bacci, etc. In Romania, D. Stănculescu, C. Zaharia, Al. Pesamosca, D. Antonescu, M. Socolescu, N. Gorun, etc., have brought special contributions in this field. Currently, the progresses obtained by applying the chemotherapy protocols have raised the survival rate to over 5 years to 80%. The present preoccupations are oriented towards the designing of new therapeutic protocols, but mostly towards the administration of chemotherapy agents which have high specificity and low toxicity rates. In perspective, the actual researches will be able to establish the genetic therapy through induction or inhibition, which will have as a final result the cure of the patients.

**Key-words:** *osteosarcoma, exploration, chimiotherapy, en bloc oncological resection, endoprosthesis, osteoplastic reconstruction*

### Rezumat

În România, tumorile osoase maligne afectează, în medie, 37 de copii și adolescenți anual: 60% sunt osteosarcoame, 24% sarcoame Ewing și 16% alte tipuri de sarcoame, mult mai rare ca frecvență. Incidența maximă pentru pacienții nou diagnosticați se înregistrează între 10 și 20 de ani, însă nu este exclusă apariția de cazuri noi sub vârsta de 5 ani, cât și peste 50 de ani. Din păcate, majoritatea pacienților cu osteosarcom se adresează târziu medicului de specialitate, fiind diagnosticați în stadiul II B Enneking, când tumora a depășit corticala osoasă și are grad înalt de malignitate. O parte din acești pacienți prezintă metastaze oculate, mai mici de 2 mm în diametru, nedetectabile la explorările CT și IRM. Evoluția lor confirmă această prezumție și pacienții nu beneficiază de efectele scontate ale protocolului terapeutic. Actualmente programul terapeutic al osteosarcomelor constă în tratament preoperator cu citostatice, rezecție oncologică în bloc și reconstrucție osteoplastică sau osteoartroplastică, urmate de tratament chimioterapic postoperator timp de un an. Tratamentul chimioterapic și cel chirurgical permit salvarea membrelor și uneori chiar salvarea vieții. Sunt cunoscute cazurile unor pacienți vindecați, care au avut șansa să fie diagnosticați și tratați precoce.

Pe plan internațional s-au remarcat, abordând teoretic și practic domeniul tumorilor osoase, personalități medicale precum R. Kotz, M. Campanacci, F. Enneking, M. Mercuri, E. Greenfield, A. Meyers, R. Capanna, G. Bacci, etc. În România contribuții deosebite în acest domeniu și-au adus D. Stănculescu, Al. Pesamosca, D. Antonescu, M. Socolescu, C. Zaharia, N. Gorun, etc.

În prezent, progresele obținute prin aplicarea protocoalelor chimioterapice au crescut rata supraviețuirii peste 5 ani până la 80%. Preocupările actuale sunt orientate în conceperea unor noi protocoale terapeutice, dar mai ales în administrarea unor agenți chimioterapici care posedă specificitate ridicată și toxicitate scăzută. În perspectivă, cercetările actuale vor putea stabili terapia genetică prin inducție sau inhibiție care să aducă vindecarea pacienților.

**Cuvinte cheie:** *osteosarcom, explorare, chimioterapie, rezecție oncologică în bloc, endoprotezare, reconstrucție osteoplastică,*

## **GENERALITIES**

The osteogenic sarcoma is the most frequent form of primitive malignant bone tumor that develops from the mesenchymal cells, which directly or indirectly form the osteoid tissue and the neoplastic tissue [1], through the rapid growth of the tumor towards the cartilaginous stage of development.

This tumor annually affects approximately 22 children and adolescents in Romania. Most frequently, the diagnosis is established between 12 and 18 years old. 30% of these patients present detectable metastases and it is assumed that there are micrometastases or occult metastases in the other cases too. 560 children and adolescents are diagnosed with this affection in USA each year.

The tumor is most frequently localized in the areas of rapid growth of the bones. This way, the tumors most frequently affect the adjacent metaphyses of the knee (distal femur, proximal tibia) and, rarely, the proximal humerus.

## **PRESUMPTIVE DIAGNOSIS**

### **Clinical approach**

Sarcomatous lesions frequently appear at the level of the long bones metaphysis and the first symptom that draws the attention is the local pain. Unfortunately, this symptom is signalled at 2-3 years from the debut of the histopathological lesions.

During the 1980s, the rate of mortality due to osteogenic sarcoma was extremely high in Romania, on average, the patient presenting (to the medical centers in the most advanced stages of the disease) to be diagnosed at 6 weeks to 6 months from the debut of the disease [2]. In the last 4 decades, the preoccupations oriented towards the establishment of a precocious diagnosis and the improvement of the evaluation techniques have led to a raise in the addressability, to a part of the patients suffering from this affection, earlier than 3 months from the appearance of the first symptoms.

These pains have an unregulated character, they can appear suddenly, synchronized with the physical efforts, or they can induce discomfort due to their persistence during the night, sometimes leading to insomnia. The local pain is initially intermittent, subsequently becoming constant and more intense. It is possible that in children and adolescents, the patient or the parents interpret the presence of pain as the consequence of some minor traumatisms, which are usual during childhood.

Due to the localization near the joints, most of the times the antalgic position of the adjacent joints appears.

Most frequently, the patients with these affections present to the physician when the swelling appears, which, unfortunately, is a sign of tumor progress. At a couple of months from the appearance of the swelling, the local modification of the skin can be observed: glossy aspect, apparent thinning, edema, accentuation of the vascular network. The local temperature can be high. As the tumor grows in size, the swelling accentuates, the tumor becomes more evident, and the limitation of the joint mobility appears, accompanied by the marked atrophy of the muscles.

In the advanced stages of the osteosarcoma, the alteration of the general state is also present. The patient becomes apathetic, with a diminished appetite, characteristic features of the neoplastic intoxication.

The pathological bone fracture occurs in 13% of the cases and aggravates the evolution of the disease. The presence of the pulmonary metastases is asymptomatic in the initial state and presents signs of respiratory insufficiency in the final stage.

#### Imagistic approach

Any patient, who presents to the physician with a pain localized in the metaphysis area of the long bones, must be evaluated from a clinical and imagistic point of view in order to establish an oriented diagnosis, which will be confirmed by biopsy.

*The X-ray* for the bone structure in two incidences, in the initial state, highlights a typical aspect determined by the destruction of the osteoblasts.

Usually, it appears in the metaphysis area as a result of the trabecular structure disappearance, a defective area eccentrically disposed, with an anfractuous contour. In the intermediary state, radiopaque centers of various sizes appear in the defective area as a result of the formation of a new neoplastic bone. In the extraosseous growth stage, the cortical has been invaded and the X-ray image shows its destruction. The touching and the invading of the periosteum lead to the formation of some bone spikes, which have the aspect of “sunrise” / “fire herbs”. These bone spikes form along the vessels that go from the periosteum to the cortical. The extension of the tumor stretches the periosteum and a periosteum bone spike appears at the periphery, forming the so-called Codman triangle.

In the case of fracture appearance, the X-ray examination highlights a solution of bone continuity in the area of osteogenic or osteolitical destruction. The X-ray evaluation offers valuable information regarding the state of evolution of the tumor and its extension.

*The CT Scan* has the property of clearly evidencing the destruction of the bone around the tumor and better delineates the cortical erosion areas, aspects that can facilitate the differentiation from the benign bone tumors. It is a useful exploration because it can give information regarding the integrity of the cortical and the bone mineralization. It also evidences the invasion of the growth cartilage and the epiphysis; in the cases in which the tumor does not invade the growth cartilage, the epiphysis can be preserved.

The CT Scan is more valuable than the X-ray in detecting the pulmonary metastases. All the patients affected by osteosarcoma must benefit from the CT exploration. The dynamics evaluation allows the establishing of the initial appearance of the metastases or the moment of the ulterior relapses. The metastases usually appear at the periphery of the lung, looking like some well-delimited little nodules, with a high density.

*MRI* is an investigation that evaluates more efficiently than the CT the osteogenic sarcoma, showing the extension of the tumor in the soft tissues, the degree of invasion of the neurovascular axis, the extension towards the bone marrow and the presence of the necrotic areas inside the bone.

*$^{99m}\text{Tc}$  bone scintigraphy* marks the tumoral area, which has an intense vascularisation and an increased metabolic activity. It evidences the distance metastases and allows the detection of the tumors locally extended in discontinuous form, when the CT scan is done concomitantly.

*The angiography* delineates the report between the tumor and the vascular-nervous axis, better than the MRI. At the evaluation of the arterial precocious phase, we can measure the dimensions of the active tumor (with the neoformation blood vessels). The late venous phase evidences the total dimensions of the tumor, which appears at the arteriography looking like a “red tumor”.

*The arteriography* establishes the limits of the en bloc oncological resection.

The evaluation of the osteogenic sarcoma by the *angio-CT scan* or the *angio-MRI*, eloquently illustrates the relations between the vascular structures, the tumor and the bone. They allow the establishment of a preoperative therapeutic attitude: of conservation of the limb and endoprosthesis, of en bloc resection followed by the implant of the distal segment in the proximal one or amputation.

*Positron Emission Tomography (PET)* represents a relatively recent introduced tool, which deals with the investigation of the patients with malign bone tumors. Due to the high costs, this investigation is rarely used, being very important in establishing the evolution state of the osteosarcoma and the monitoring of the postoperative evolution. The presence of some metastatic outbreaks, revealed at the PET scan put the physician in a delicate position; the continuation of the treatment with chemotherapy can be an inefficient gesture. Most of the time, in this situation, amputation is the only resort, being easily realized, the patient should be convinced that this intervention is the most useful in the case given.

## **ORIENTED DIAGNOSIS – biological parameters**

Laboratory investigations of a patient with osteosarcoma have to comprise the usual blood analyses, the determination of the lung and renal functions and the urinalysis test. The alkaline phosphatase can be a test that allows the appreciation of the evolution of the osteogenic sarcoma. By monitoring the alkaline

phosphatase, we can observe its decrease after tumor ablation and its increase in the case of local relapse or the appearance of metastases.

The immunological exploration is not infallible. The anti-sarcoma antibodies can be determined by hemagglutination or precipitation reactions. The anti-sarcoma serum antibodies increase after the tumor ablation and decrease with the relapse and the appearance of metastases.

## **DIFFERENTIAL DIAGNOSIS**

Before performing the biopsy and the histopathological examination, the oriented and presumptive diagnosis data allow the physician to do an exercise of medical proficiency in which he can take into consideration other diseases that may represent the biological background of the established affection. The differential diagnosis, which is sometimes possible, other times surprising after the biopsy, highlights traumatic, infectious or dysplastic affections, which have a similar aspect in the debut phase:

the exuberant calluses of the stress fractures;

subacute osteomyelitis with a very fast evolution;

acute myositis ossificans;

aneurismal bone cyst;

eosinophilic granuloma.

There is also the possibility that some osteogenic sarcoma forms present similar imagistic signs like the ones of the Ewing sarcoma, fibrosarcoma or the metastatic carcinoma.

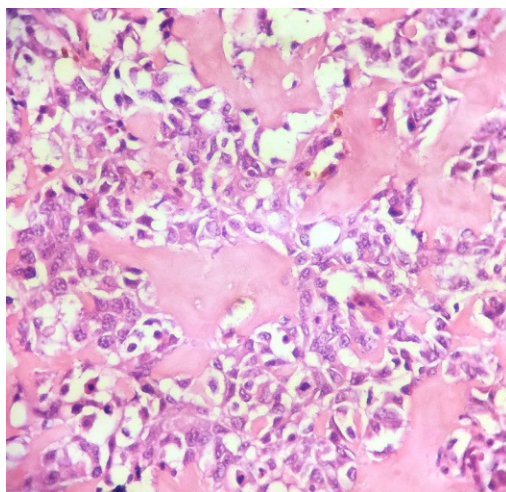
## **ACCURATE DIAGNOSIS**

Biopsy represents an important stage and allows the taking of a sample that has the role of confirming the diagnosis, regardless the value of the diagnosis, which was clinically or imagistically established.

Biopsy will never be considered an excess; on the contrary, a high number of failures, which can endanger the life of the subject, can be due to the lack of the biopsy. In order to do the biopsy of the tumoral tissue, the sampling must be moderated, but enough and always of high quality. The biopsy needs to have the most direct way through the tumor, an area that will subsequently be extirpated en bloc with the tumor [3].

The biopsy has to contain, from the surface to the interior, according to the case, the tumor development state and the macroscopic aspect: tegument, subcutaneous cellular tissue, fascia, muscular tissue, periosteum, cortical and sponge.

The histopathological examination evidences the following: frank sarcomatous stroma, neoplastic osteoid tissue (*fig. 1*). The presence of the neoplastic bone tissue or the osteoid conglomerates is crucial for the diagnosis [4].



*Fig. 1. Conventional osteosarcoma: accentuated cellular pleomorfism and atypical mitoses; osteoid produced by the tumoral cells (Collection Dr. A. Enculescu)*

The careful examination can illustrate the presence of the neoplastic cartilage and the atypical spindle cells.

The immunohistochemical diagnosis completes the histopathological examination, evidencing the presence or the absence of some characteristic



molecules. The osteogenic sarcoma has a positive reaction to anti-vimentin antibodies and a negative reaction to anti-P100 antibodies. The immunohistochemical exam also helps in the differential diagnosis, the detection of the following antigens infirming the osteosarcoma diagnosis:

cytokeratin, membrane epithelial antigen (metastases);

common leukocyte antigen (lymphomas);

neuronal enolase (neuroblastoma);

actin (rhabdomyosarcoma);

VIII factor (angiosarcoma).

## **IMAGISTIC AND HISTOLOGICAL TYPES**

Before mastering the practical attitude used in these cases, the physician must have knowledge about the radiological and histological particularities of different types of osteogenic sarcoma.

The classical conventional osteogenic sarcoma – develops inside the bone, this is why it is also called intramedullary osteosarcoma (conventional).

*The classical conventional osteogenic sarcoma* is the most frequently met, constituting 80% of the osteosarcoma cases. The maximum incidence is between 10 and 25 years old, and, as an exception, it can also appear at any age. It is frequently localised in the metaphyseal area and it is not excluded that it also appears at the diaphysis level. It usually appears at the femur distal extremity and the tibia proximal side (70% of the localisations, in our casuistry). It can also appear at the femur or humerus proximal extremity, fibula, pelvis, spine, hand or leg. The multiple or multicentric forms of osteosarcoma are not excluded.

The face and profile X-ray for the bone structure evidences an osteolitical lesion, with the partial or total erosive destruction of the cortical, according to the evolution state.

The classical osteogenic sarcoma initially appears in the medullar cavity, at the level of the metaphysis and, by extension, it penetrates the cortical while invading the periosteum and the adjacent muscle tissue. The tumor has a yellowish appearance and a sandy consistency. The tumor extension limit to the epiphysis is relatively well delimited. The epiphysis remains untouched until an advanced state of the tumor evolution is reached. The hyaline cartilage blocks the intra-articular extension of the tumor. The tumor extends faster to the diaphysis and a conical fat “cork” represents the limit. The extension to the teguments appears extremely rarely (*fig. 2*).



*Fig. 2. A 17-year-old patient with neglected osteogenic osteosarcoma disposed in the third distal of the right femur. A. Clinically, a gigantic tumor with the invasion of the knee joint is evidenced. B. The X-ray image evidences the invasion of the growth cartilage and the soft adjacent tissues. C. The MRI image illustrates the the limit of the medullar conical stopper*

Histopathological diagnosis is established based on the presence of some spindle and polyhedral malign mesenchymal cells, with pleomorphic nuclei and, here and there, on the presence of mitoses. The histological evaluation must establish if a bone or osteoid tissue is produced in the tumor in order to establish the diagnosis.

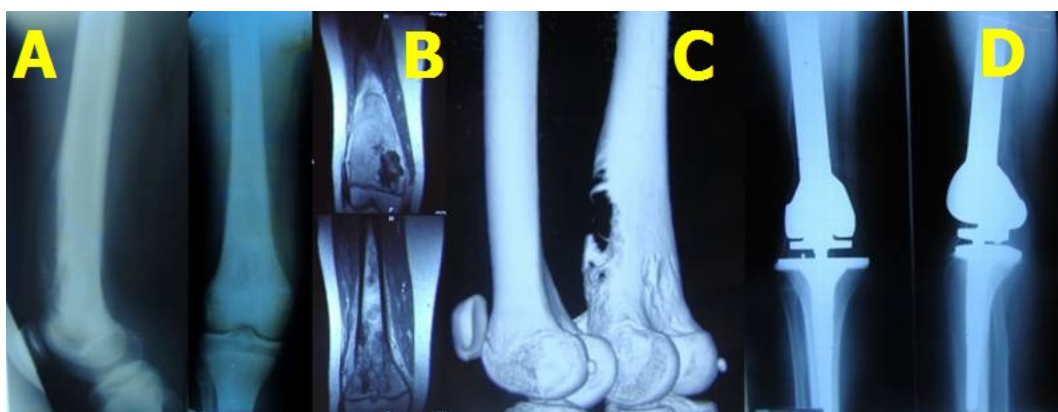
WHO classifies the intramedullary sarcomas according to the predominant extracellular matrix in the osteogenic sarcomas:

osteoblastic, in which the bone or osteoid types of tissue (50%) prevail;

chondroblastic, in which the hyaline cartilage with a high degree of differentiation (25%) prevails;

fibroblastic, with spindle cells characterized by a high degree of differentiation (25%).

Another form is *the classical osteogenic sarcoma with small cells*. This is a rare option, with a 1.5% frequency of the total cases of osteosarcoma. It appears at an age similar to the one of conventional classical osteosarcoma and it is localised at the level of the distal femur. The X-ray shows an eccentric defective area, with different degrees of sclerosis. The MRI has an aspect similar to Ewing sarcoma, with a circle-like extension in the soft tissues (*fig. 3*).



*Fig. 3. A. From the point of view of the X-ray examination the destruction of the anterior femoral cortical can be determined in the third distal and anarchical condensation reactions can be seen predominantly in the metaphysis area. B. The MRI examination illustrates the partial invasion of the soft parts and an area of tumor necrosis eccentrically disposed in the metaphysis area. C. The 3D-CT reconstruction shows the extension of the tumor to the anterior side, with the destruction of the bone cortical. D. Modular endoprosthesis after the en bloc oncological resection and osteoplastic reconstruction*

Histopathologically, little, round malignant cells are present. This tumor's characteristic is the osteoid production and the presence of a twisted pathological cells population. Like the Ewing sarcoma, the little cells osteosarcoma is positive for CD99. The histological differentiation between the little cells osteosarcoma, the Ewing sarcoma, and the malign lymphoma is difficult and requires further investigation. Sometimes, the diagnosis is established after the imagistic identification of a cerebral metastasis, the symptomatology of the cerebral lesion being the only one present or the noisiest one. In our casuistry, 4 out of 10 patients with little cells classical osteogenic sarcoma have had, when they presented to the physician, cerebral metastases with primary asymptomatic tumor, from a total number of 50 osteogenic sarcomas.

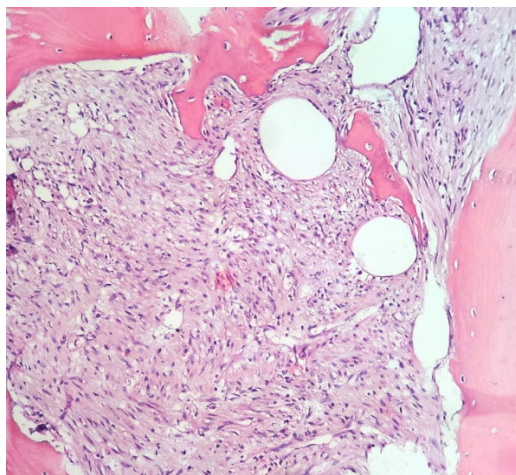
Juxtacortical osteogenic sarcoma develops in relation with the periosteum and in direct contact with the connective tissue, this being the reason why it is also called periosteal sarcoma. It is less frequently met and has a better prognosis.

The periosteal sarcoma represents approximately 2% of the total cases of osteosarcoma. The tumor is more aggressive than the parosteal form. Radiologically, this tumor's characteristic is a defective area, which does not exceed the medullar cavity and it is frequently localized proximally on the tibia and distally on the femur. Most frequently, these tumors have the aspect of a "sun eruption" or they decollate the periosteum, generating the image of Codman triangle. From the histological point of view, this tumor has an intermediary degree of differentiation, the cells composing it being mostly disposed in a cartilaginous matrix with calcified sides. The osteoid tissue appears in a small quantity.

Endosteal osteogenic sarcoma is a version of osteogenic sarcoma that develops at the level of the endosteal bone. It is a tumor with a low degree of malignity, with a slow evolution and late metastases. It represents almost 1% of the osteosarcomas and it appears between 30 and 40 years old. Radiologically, the osteolytic lesion does not have an aggressive character, due to the different degrees of septal ossification, sometimes presenting a circumferential sclerosis. It can sometimes be confused with fibrous dysplasia. The CT and MRI examinations certify the aggressive character by the presence of the cortical erosive lesions.

Telangiectatic osteogenic sarcoma is a very serious malign lesion, characterized by the presence of some ossification traces, with cystic and necrotic modifications in the development period. The bone affected by the osteolitical processes frequently present pathological fractures.

This form represents approximately 3% of the osteosarcoma forms, and appears in persons younger than 18 years old. 4 out of 10 patients with telangiectatic sarcoma present to the physician with a bone fracture at a pathological level. Radiologically, the osteolitical lesions appear eccentrically, with a tendency of extending to the metaphyseal area, uniformly or discontinuous, proximally on the tibia and distally on the femur. The telangiectatic osteosarcoma can present the aspect of a lesion that looks like the aneurism bone cyst. The contour of the lesion can present multiple sinusoids, in which blood can be discovered at the densiometric level. The histopathological examination shows numerous hematic cavities, reduced osteoid tissue, and mitoses in the septums. Giant cells can sometimes be traced, that is why the myeloplaxes malign stage of the tumor must be differentiated. Histologically, elements that can guide the diagnosis to the aneurism bone cyst can be present, but the presence of the sarcomatous cells with a high degree of differentiation in the septums, establishes the diagnosis of telangiectatic osteosarcoma (*fig. 4*).



*Fig. 4. Telangiectatic osteosarcoma: cavitory spaces full of blood, delimited by septa at the level of which sarcomatous cells with marked atypia and low osteoid production are found (Collection Dr. A. Enculescu)*

Paget sarcoma appears in the adult. Until present, no cases have been described in literature involving children and adolescents and neither in our experience; for a period of 35 years, we have not met this affection in the child's osteoarticular pathology.

## TREATMENT

### Principles

The main principles of the quality medical assistance in osteosarcomas are the following: *precocious diagnosis, staging, chemotherapy, oncological resection and osteoplastic reconstruction, when the epiphysis is intact, or osteoarthroplasty, with modular endoprosthesis, when the epiphysis is invaded.*

The therapy of the osteogenic sarcoma must take into account the age of the patient, the severity of the histologic type of the tumor, staging, anatomical localization, answer to the preoperative chemotherapy treatment, socio-economical environment, and cultural degree of the family, technical possibilities and the possible divergences of view in the multidisciplinary team.

In children under 10 years old, the treatment, and the evaluations of the patient are differently done: for a 5-year-old child or younger, the therapeutic strategy is totally different from the one of the adult, and it can be different even in comparison to the one for a 10-year-old child. A child who has a survival rate of 5 years after the cytostatics and surgical treatment, cannot be considered cured; the same aspect can be taken into account when analysing adults, no matter the survival rate, when the death is due to the local recurrence, the metastases and their complications.

### The staging of the tumor

In order for the treatment to be efficient and the results to assure a survival rate of 70-80% on a long term or possibly the healing, immediately after the clinical, imagistic evaluation and the histologic examination, the diseases' evolution stage must be established. The classification which is mostly used, based on the histological stage, localization and the presence of metastases, is the

Enneking classification (*table 1*), although it presents a disadvantage of not being applied to little cells osteosarcomas.

*Table 1. Enneking Staging*

<i>State</i>	<i>Degree</i>	<i>Localization</i>	<i>Metastases</i>
<i>I A</i>	Low	Intra compartmental	NO
<i>I B</i>	Low	Extra compartmental	NO
<i>II A</i>	High	Intra compartmental	NO
<i>II B</i>	High	Extra compartmental	NO
<i>III</i>	Low or High	Intra compartmental or Extra compartmental	YES

Unfortunately, most of the osteosarcoma patients present to the physician in Enneking stage II B.

The American Joint Committee on Cancer has established an alternative method for the staging of the malignant bone tumors. This evaluates the size of the tumor (lower, equal to 8 cm, or higher than 8 cm), the implication of the lymphatic ganglions and the presence of distance metastases [5].

#### Pre- and Postoperative Chemotherapy

After establishing the histopathological diagnosis, the first physician who will take care of the disease is the oncologist. By principle, the therapeutic conduct must be coordinated by the paediatrician oncologist. In order to approach the therapy correctly, a group of physicians made up of the paediatrician oncologist, orthopaedic surgeon, the radiologist, the pathologist, and the psychologist will treat the patient.

The chemotherapeutical treatment has the role of reducing the dimensions of the primary tumor and decreasing the edema. In the Enneking I A, I B and II A

tumors, the occult micrometastases and the local micro extensions are destructed, being undetectable imagistically or intraoperatively in the macroscopic evaluation. The preoperative effect of these cytostatics improves the survival prognosis.

The chemotherapeutic treatment aims for a combination of many drugs in order to avoid chemoresistance and to reduce the dimensions of the tumor as much as possible. This way, the surgery is easier, due to the appearance of a pseudocapsule, which delineates the tumor and allows the surgeon to make a cleavage at the limit of the surrounding tissues. The most efficient chemotherapeutical drugs are the following: high dosages of Methotrexat, Bleomycin, Cyclophosphamide and Dactinomycine. The therapy is differentiated according to the histological type of the osteosarcoma. At present, the special research centers worldwide are oriented towards the study of some new therapeutic agents, which are less toxic and more efficient. The en bloc oncological resection surgery is done at approximately 3 weeks after the last preoperative chemotherapy session. Contrary to expectations, the delay in the surgical resection after this date to another 2 weeks does not seem to affect the survival rate.

In 2 weeks time, postoperative or after the cure of the wound, the postoperative chemotherapy starts and lasts for approximately a year.

In case the tumor necrosis is more than 90% in the moment of the surgery, the postoperative chemotherapeutical diet will be identical to the preoperative one. If the necrosis is under 90%, the therapeutic diet will contain higher doses and the period of the postoperative treatment will be longer, or the cytostatic agents will be changed. There are no clear evidences yet to attest the improvement of the results [6].

The osteosarcoma radiotherapy does not have favourable effects.

### Surgical treatment

The surgical methods implied amputation or en bloc oncological resection with reconstruction. The surgical treatment in children and adolescents presents certain particularities. The therapeutic objectives try to:



save the life of the patient;

save the affected limb;

keep the motor function of the limb;

equalize the limbs.

In our casuistry, due to the presentation to the physician, which is usually late, the endoprosthesis has only been possible to 21.3% of the patients treated during 1995-2009.

### Amputation

Until the 1970s, the amputation of the affected limbs has been the intervention of choice in Romania [7]. At present, it is done in cases of osteosarcomas which invade the neuromuscular axis, or when the biopsy indicates an extensive contamination of the neighbouring tissues (muscles, subcutaneous cellular tissue and even skin). There are cases in which the choice between amputation and the operation of limb saving is very difficult for the physician, taking into account the postoperative functionality of the limb, the emotional effect, the potential complications and, especially, the oncological result. There are situations when the saving of the limb is followed, at a variable period of time, by amputation, at the patient's request, as a result of the difficulties regarding the functional deficiency [8].

There are situations in which the amputation, as a primary indication, can end up with a weak blunt or one that is not functional at all.

Disjoints do not offer good results from the functional point of view and they are not recommended. Among the exception indications, the very little tumors are counted. However, it cannot preserve the whole articulation, but the supradjacent growth cartilage resection would result in a very short blunt in maturity stage. An example is the proximal tibia osteosarcoma in a very small child, a case in which the intervention will target the knee disarticulation, followed by the maturation of the bones, through an inspection of the blunt in order to install a more functional prosthesis.

The amputation techniques in oncological pathology vary according to the localization of the tumor and the purpose of the intervention (radical or palliative), however, certain principles must be respected. The resection limit preoperatively planned is classically given by the angiography, its limits being of 1-2 cm from the superior limit of the “red tumor” (the tumor’s contour in the late venous phase). Some authors mention the resection limit established intraoperatively; 5 cm for the bone and 5-10 mm for the soft tissues [9]. Presently, MRI can establish this limit very well, without the risk of arterial catheter complications and other injections of the contrast substance.

The tegument incision for the amputation at the level of the thoracic and pelvic limbs is made up of two concave arcs oriented upward, which meet in two sharp angles situated medially and laterally, close to the amputation plan at the level of the bone. The two round flaps must have a summed length, which is approximately equal to the diameter of the limb at the osteotomy level, but with unequal lengths, so that the scar is far from the area of the blunt. In the case of the amputations at the level of the belts, the incisions are specific for each technique.

The tegument incisions continue at the level of the subcutaneous cellular tissue, fascia, and muscles, eventually turning into hemostasis. The main vascular nervous axis/axes is/are isolated above the level of the amputation; each element is isolated, a double ligature is done and a sectioning is realized. The incision of the soft tissues is done to a certain distance from the tumor, in order to avoid the contamination with tumoral cells.

After the circular freeing from the periosteum, the bone is sectioned perpendicular on its axis. It is very important to obtain some free resection margins, which have not been affected by the tumor; they are assured by the extemporaneous histopathological exam and by the retaking of the resection if necessary. A sample has to be taken from the medullar channel too.

The edges of the sectioned bone are flattened and afterwards the muscles, the fascia, the subcutaneous tissue and the tegument are successively closed, on a tube of aspiration drain. After the cure, usually at 6-8 weeks, the patient must be permanently given prostheses.

### Rotationplasty

The rotationplasty is a non-anatomical procedure of function recovery of an inferior limb that presents a tumor in the neighbourhood of the knee. The procedure presupposes the dissection of the neurovascular axis, the resection of a segment of the limb that contains the knee, followed by the fixation of the bones of the leg, rotated to 180° from the femoral blunt, so that the talocrural joint keeps the place of the resected knee. The flexor and extensor muscles of the knee are reattached to the bones of the leg in functional positions. The patient will wear a special prosthesis after curing.

The indications of rotationplasty are the following: bone tumor in the neighbourhood of the knee, in a growing patient who wishes to continue a sports activity, a failed reconstruction of the distal femur intervention and the fracture on a pathological bone. The intervention is counter indicated if the sciatic nerve cannot be conserved with all its branches.

Through the rotationplasty, better results can be obtained than in the amputation above the knee, taking into account the capacity of the patient to flex the leg from the middle with his own muscles and not with an artificial joint. Nevertheless, some of the patients can reject this intervention, considering the postoperative aspect extremely disgraceful.

### En bloc oncologic resection with osteoplastic reconstruction or modular endoprosthesis

In our casuistry regarding the malign bone tumor, the intervention of saving the limb by the en bloc resection followed by reconstruction was possible in 19 out of 94 cases (about 20%); out of these, in 16 cases an osteoarthroplastic reconstruction was done through endoprosthesis and, in the rest of 3 cases osteoplastic reconstruction with allograph was done. During 1995-2009, 47 cases of osteosarcoma were operated, out of which, amputation was done in 37 patients and en bloc oncological resection was done in 10 patients, followed by reconstructions. The osteosarcomas have the largest share, 50%, from the total malign bone tumors operated (*table 2*).

*Table 2. The statistics of our clinic during 1995-2009, regarding the cases of malign tumors diagnosed and operated. The cases that were lost were eliminated from the statistics.*

<i>Histological type</i>	<i>Number of diagnosed cases</i>	<i>Number of endoprosthesis cases</i>	<i>Number of amputated cases</i>
Osteosarcoma	47	10	37
Ewing Sarcoma	24	5	19
Chondrosarcoma	14	3	11
4 <sup>th</sup> degree tumor with myeloplaxes	9	1	0
Total	94	19	75

The joint resection is necessary when the tumor has overcome the growth cartilage and has invaded the epiphysis. The conservation of the neighbouring epiphysis and the growing cartilage is the option that can be followed when the tumor is localized in the metaphysis-diaphysis and the growth cartilage is intact, this being the best alternative when the child is little. In the presence of an intact growth cartilage, which presents a subjacent area of less than 2 cm, the recourse to extemporaneous decollation or slow and progressive decollation, followed by osteoplastic reconstruction is done. In these cases, the growth cartilage is broken. If the area is bigger than 2 cm, the growth cartilage is saved and the osteoplastic reconstruction is practiced. When the saving of the growth cartilage is obtained in little children, the chance of equalization is higher, multiple surgeries are avoided, surgeries which can lead to rigidities and ankiloses, a reason for a late amputation. Nevertheless, the growth rhythm is diminished but enough for the prolongation or epiphysiodesis interventions, which could allow the equalisation [10,11].

If the tumor has expanded at the epiphysis level, the modular endoprosthesis is the optimal solution. The younger the child the more it is desired that the prosthesis is expanded.

The pathological bone fracture has a relative indication regarding the reconstructive interventions. It does not represent a major disadvantage if the movement is moderated and the resection can assure the en bloc lifting both of the fracture centre and the peripheral hematoma. This leads to a more important sacrifice of the soft tissues [12].

The long-term survival rates, after the surgical and chemotherapeutical treatment, vary from one author to the other and oscillate between 60% and 80%, reaching even 91% at five years old, for the patients with parosteal sarcoma and to 83% at ten years old, for the periosteal sarcoma. The local recurrence rate is situated between 4% and 6% both in the patients whose limbs were saved by reconstruction and in the cases to which amputation was indicated [13].

The oncological resection followed by endoprosthesis that cannot be excised without sacrificing an epiphysis is indicated in patients with malign bone tumors. This intervention is contraindicated if, by any reason, the tumor cannot be excised en bloc (for example, if it invades the neurovascular axis). The other contraindications are the bacterial infections, the lesions of the post-radiotherapy soft tissues (this is not the case for osteosarcoma) and the general contraindications of the major surgeries.

The oncological resection has as objectives the en bloc removal of the tumor and obtaining the resection margins which are free from the tumoral cells. The cutaneous incision must allow a wide approach of the affected bone and the joint, and, in the same time, it should contain the scar of the biopsy, which has the shape of “an island”. If wrongly positioned, multiple biopsies can compromise the en bloc excision attempt, the trajectories of the biopsy incision being considered contaminated with tumoral cells.

The tumor is circumferentially released, dissecting only the healthy tissue. The nervous and vascular structures are released, while checking if they have been invaded by the tumor. The diaphysis of the affected bone is emptied at the level

chosen for the resection, based on the preoperative imagistic investigations; after that, a sectioning is done. At the opposite pole of the tumor, the attitude depends on the presence or absence of the joint invasion. For example, in the case of a distal femur tumor resection, which in MRI seemed to invade the knee, the resection block is released at the inferior pole through a horizontal section of the tibial plateau and vertically through the patella, without opening the joint. If the knee is not flooded, disarticulation is done.

Tissue samples at the level of the resection limit are sent for the extemporaneous histopathological examination. If in these samples, tumoral cells appear, the resection is resumed.

In order to replace the resected bone and the joint, numerous tumoral or reconstruction prostheses are available on the market, having technical characteristics and various implanting modules. We will use *Howmedica Modular Resection System* (Stryker Howmedica Osteonics, a surgery technique elaborated by Prof. R. Kotz, Prof. M. Campanacci, Dr. R. Capanna), to illustrate their general characteristics. This system can be used for the replacement of the proximal femur, the distal femur, the femur itself and/or the proximal tibia. This is a modular prosthesis, like most of the prostheses for oncological interventions, offering the possibility of assembling, from pieces of different sizes, with a proper implant specific to the morphology of the patient and the resection level. The main modules of the prosthesis are the osteoarticular substitution components, joint substitution, and diaphysis anchoring.

The osteoarticular substitution components replace the bone segment that has contained the tumor. At one of the heads, it has one of the halves of the artificial joint and at the other a conical combination (Morse Cone), to which the diaphyseal fixation component is attached by impaction, directly or through a prolongation element.

The proximal femoral and tibia components are equipped with filleted holes for the fixation of the retention plates, used to reattach the adductor muscles, the patella ligament respectively.

The non-articular surfaces present a porous finishing, its purpose being the adherence to the neighbouring tissues.

The joint substitution components replace the joint extremity of the healthy bone.

The fixation in the bone is done with the help of a central rod characterized by a porous finishing, which allows the integration of the implant in the bone, and it is supplemented with a screw. The two joint components, femoral and tibial, articulate with the help of a metallic spindle and a polyethylene sleeve, allowing the flexion-extension movement in only one plan. The establishment of this fitting replaces the ligaments of the knee from the functional point of view, the ligaments being sacrificed during the resection procedure.

The diaphyseal anchoring components fixate in the bone with the help of a rod placed in the medullar channel, which was anteriorly prepared by reaming. The fixation can be done by pressing, if the piece has the right porous finishing or with cement. The fixation in this kind of system is supplemented through a metal placed at the exterior of the bone, through which screws can be introduced.

It is necessary that the articular surface of the patella is replaced by using a component compatible with the resection prosthesis.

The en bloc oncological resection, especially in the telangiectatic osteosarcomas, sometimes imposes the excessive removal of the muscles, ligaments, tendons, and tegument. This way, difficulties in covering the endoprosthesis and in closing the wound may appear, a reason to refer to plastic surgeries that will allow the maintaining of a muscular and joint balance, as well as the reinforcement of the junction between the diaphysis and the endoprosthesis stem (*table 3*).

*Table 3. Surgical difficulties and their solutions in the oncological resection and the prosthesis at the level of the le.*

<i>Problem</i>	<i>Solution</i>
Lack of tissue covering of the prosthesis	Pedicated flaps or myocutaneous flaps freely transferred
Patellar imbalance – the resection of vastus lateralis	Transfer of the femoral biceps insertion on the patella
Patellar imbalance – the resection of vastus intermedius	Transfer of the Sartorius muscle into patella
The oncologic resection compromises the expander of the knee	The restoration of the extensor apparatus with fascia lata
Strengthening of the junction between the shaft and the prosthesis	Autograft bone around the junction
Preventing the desinsertion of the patella ligament from the tibial osteoarticular component	Anterior transposition of the fibula or the origin of the gastrocnemius muscle

The patients with pulmonary metastases detectable in CT scan or MRI have a survival rate of less than 30% at 10 years, but only if the metastases are surgically removed.

If the patient presents metastases, lymphadenopathies, high volume of the tumor, alkaline phosphatase and high LDH, as well as a weak answer to chemotherapy preoperatively, the prognosis is reserved. The risk of the growth of existent metastases and the appearance of new ones is high in these patients [14,15].

The current chemotherapeutical protocols and the resection with reconstruction are followed by local relapse in 30-40% of the cases, after 3 years from the treatment [16,17].



It is advisable that the psychological counselling is assured to the patients who are in the advanced state of the disease and who present the risk of relapse, a situation which implies the fact that the survival rate is below 20% at 5 years. Many of these patients die after 2.5-3 years from the surgery. The patients in inoperable stages, who present an osteogenic sarcoma diagnosis, which was confirmed histopathologically, die after 6 months – 1 year.

#### Limb-length discrepancy after the reconstructions

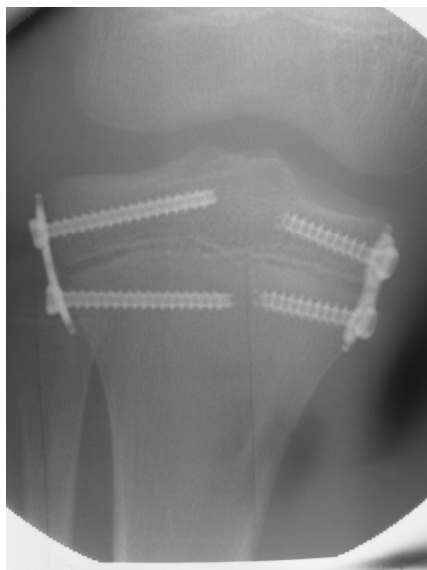
Frequently, after the osteoarthroplastic reconstruction, but also after the osteoplastic one, the inequality of the length of the limbs appears in children. The shortening of the operated pelvic limb represents a particularity in the treatment of these tumors and it varies according to the age of the child, the dimensions of the resection and the reconstruction area – hip, knee, or ankle. In order to assure the equality in the length of the limbs, the evaluation of the growth rhythm in boys and girls must be assessed, according to Anderson-Green scheme, the growth formula according to the age ( $L=5V+80$ ), the scheme of the periodical growth (*table 4*) or the formula described by D. Paley  $G=L(M-1)$ , where G represents the growth potential of the free limb, L represents the actual length of the unaffected limb and M, the multiplication factor, dependant on the age and sex.

*Table 4. Scheme of periodic growth*

<i>At birth</i>	<i>0-1 years old</i>	<i>1-2 years old</i>	<i>2-10 years old</i>	<i>10-14 years old</i>	<i>14-18 years old (22 in boys)</i>
50-52 cm	25 cm	12 cm	5 cm /year	12-15 cm	1 cm /year

The estimation of the potential length discrepancy at the end of the growth process, obtained according to these schemes, orients us as close to the reality as possible. The deviation is of +/- 1 cm, a difference which is insignificant in statics and dynamics, especially if the 1 cm difference is on the right in right-handed subjects and on the left in left-handed subjects. The appreciation according to D.

Paley is the most frequently used and it is also the most exact one. In a 2-5 cm shortage, the inequality can be controlled in children up to 14 years old, through controlateral epiphysiodesis with boards in 8, I or H (*fig.5*). The guided growth control through controlateral transitory epiphysiodesis in 8 boards has been practiced in our clinic since 2008.



*Fig. 5. Proximal transitory tibial epiphysiodesis of the free pelvic limb made for a 4 cm length discrepancy of the pelvic limbs*

In the case of the patients who have had the resection and the reconstruction 3-5 years ago, the problem of equalizing the limbs in 20% of them is approached, and, in the ones with a surviving rate of over 5 years to 60%.

In case an expansible modular endoprosthesis is applied, the equalisation of the pelvic limbs is done progressively by elongating the operated limb; this type of prosthesis allowing a periodic elongation through a mechanic or electromagnetic mechanism.

## REFERENCES

1. Corneliu Zaharia, Elemente de patologie a aparatului locomotor: ortopedie, traumatologie si chirurgie reparatorie, pag. 340-342:340, Ed. Paidea, Bucuresti, 1994.
2. Andrei Voinea, C. Zaharia, Elemente de chirurgie ortopedica, pag 344-347:346, Editura Militara, 1985.
3. Burnei G, Nayef TE, Hodorogea D, Georgescu I, Vlad C, Gavrilu S, Drăghic I.: Malignant bone tumors: therapeutical strategies related to localization. Rom J Intern Med. 2010;48(2):117-20.
4. Klein MJ, Siegal GP: Osteosarcoma: Anatomic and Histologic Variants, Am.J. Clin. Pathol. 2006; 125:555-581.
5. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Bone Cancer, 2009 version 1, p. 14 : [http://www.nccn.org/professionals/physician\\_gls/pdf/bone.pdf](http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf)
6. Messerschmidt PJ, Garcia RM, Abdul-Karim FW et al.: Osteosarcoma, J. Am. Acad. Orthop. Surg 2009; 17:515-527.
7. Pană, A Voinea, Nicolina Roven□a, Gh. Filipescu, N. Gorun, N. Vlăduceanu. Tumorile osului, Editura Academiei Republicii Socialiste România, București, 1984.
8. Burnei Gh., Neagoe P. - Amputația și protezarea la copil; pag. 791-807– Patologia aparatului locomotor, vol. I, Ed. Medicală, București, 2006, sub redacția Prof. Dr. Dinu Antonescu.
9. Tachdjian's Pediatric Orthopaedics, 4th Edition, 2008, Ed. Saunders – Elsevier, Malignant Bone Tumors; 2255 – 2352, p. 2312.
10. Burnei Gh., Gavrilu Șt., Vlad C., Georgescu Ileana, Dan Daniela, Hodorogea D., Hurmuz Lucia. Particularitățile rezecției-reconstrucție în tumorile osoase maligne la copil, – Al III-lea Congres Național ARTOP, București, 29 septembrie- 1 octombrie 2010 (Codex Aureus, Anul I, Nr. 1, Septembrie 2010, p. 49).

11. Burnei Gh., Burnei Cristian, Hodorogea Dan, Gavrilu Ștefan, Georgescu Ileana, Vlad Costel: Osteoarticular reconstructive surgery in malignant bone tumors: the importance of external fixators. *Journal of Medicine and Life*, vol. 1, no. 3, July – September 2008, p. 295-306.
12. D. Stănculescu, H. Orban. *Tumorile aparatului locomotor: concepții actuale*, pag. 92-101:99, Ed. Tehnică, 1997.
13. Bacci G, Ferrari S, Lari S et al: Osteosarcoma of the Limbs: Amputation or Limb Salvage in Partients Treated by Neoadjuvant Chemotherapy: *J. Bone Joint Surg. Br.* 2002; 84:88-92.
14. Bielack SS, Kempf-Bielack B, Delling G et al.: Prognostic Factors in High-Grade Osteosarcoma of the Extremities or Trunk, *j. Clin. Oncol.* 2002; 20:776-790.
15. Enneking WF, Spanier SS, Goodman MA: A System for the Surgical Staging of Musculo-Skeletal Sarcoma, *Clin. Orthop. Relat. Res.* 1980; 153:106-120.
16. Meyers PA, Garlick R: Osteosarcoma, *Pediatr clin. North Am.* 1997; 44:973-989.
17. Longhi A, Errani C, De Poalis M et al: Primary Bone Osteosarcoma in the Pediatric Age; *Cancer Treat. Rev.* 2006; 32:423-436.