

***“VICTOR BABEŞ”
UNIVERSITY OF MEDICINE AND PHARMACY OF TIMIŞOARA
FACULTY OF MEDICINE
DEPARTMENT XV – ORTHOPAEDICS-TRAUMATOLOGY***

DANIEL LAURENŢIU POP



PhD THESIS

**RECONSTRUCTIVE SURGICAL TECHNIQUES USED IN THE
PRESERVATION OF THE UPPER LIMB IN MALIGNANT
MUSCULOSKELETAL TUMOUR PATHOLOGY OF THE
THORACIC LIMB**

SUMMARY

Scientific Advisor

PROF. DINU VERMEŞAN, PhD, MD

**Timișoara
2020**

INTRODUCTION:

Tumour pathology in general, but also that which affects the bone system is constantly growing, on the one hand due to the increase in life expectancy, and on the other hand due to the increasing exposure of the body to various aggressive agents in the context of new technology and industry.

The development of genetics and the permanent discoveries that are made in this field bring us closer to understanding the triggering mechanisms of tumour transformation and also open new therapeutic possibilities by mastering gene manipulation.

At the same time, therapeutic, surgical and adjuvant methods are constantly evolving. If in the past the only surgery accepted as having radical results was amputation, now we are discussing customised modular prostheses and extensible prostheses needed in the treatment of children with growth cartilage damage.

Recently, limb rescue surgeries have thus become a viable alternative to amputation surgeries used for the local control of aggressive musculoskeletal malignant tumours.

Non-randomised studies have shown that limb rescue interventions do not negatively influence survival.

With the development of chemotherapy protocols, surgical techniques, and imaging staging methods, patients can be treated by resection and affected limb rescue or reconstruction.

Epidemiological studies on benign musculoskeletal pseudotumour and tumour formations do not exist in the literature because they are diagnosed by chance, and represent 0.8-1% of all tumour formations, with a ratio of 1/1.5-women/men in the first four decades of life, followed by a decrease in incidence with age. In terms of malignant musculoskeletal tumour pathology, studies describe about 90 histopathological subtypes of malignant tumours of the musculoskeletal system as a result of which a group of extremely heterogeneous diseases is formed.

Primary malignant tumours are considered to have an incidence of 5 new cases per 100,000 inhabitants per year globally, most of the bone malignant tumour pathology being represented by osteosarcoma; 80% of these are located in the metaphyses of long bones, such as the femur (proximal and distal), tibia (proximal) and humerus (proximal).

There are insufficient data on the epidemiology of pseudotumour and benign bone lesions. More reliable epidemiological data are available for primary malignant lesions. The incidence is usually assessed including soft

tissue sarcomas. The overall reported incidence is about 5 new cases/100,000 inhabitants/year.

If scintigraphy, radiography, arteriography and ultrasound were used as imaging methods in the past, now they have been replaced by modern imaging techniques such as Nuclear Magnetic Resonance (NMR), Computer Tomography (CT) and PET SCAN.

Due to state-of-the-art imaging investigations along with chemotherapy and conservative surgical treatment, the patient's survival time has increased.

As there are approximately 90 different histopathological types of bone malignant tumours, they are difficult to differentiate and diagnose with certainty by the histopathologist without a clinical and imaging context. Their highly invasive nature, their local as well as recurrent proliferation rate, the increased incidence in young patients, and the unfavourable prognosis are well known.

In an attempt to establish a definite diagnosis, it was noted that there is a need for close collaboration between the orthopaedist, radiologist, anatomopathologist and oncologist to monitor the patient for a better therapeutic result and a more rapid reintegration into society. To achieve this, the orthopaedist needs to follow a well-established protocol.

In order to establish a definite diagnosis in aggressive malignant tumours, it is necessary for the orthopaedist to establish the appropriate type of biopsy, considering the complexity of the anatomical structures in that region, the multitude of malignant tumour formations, and the avoidance of dissemination.

The staging system proposed by Enneking et al. and adopted by the Musculoskeletal Tumor Society (MTS) is based on three factors: degree of tissue differentiation, location in a compartment of one or more formations, and whether there are metastases.

Currently, the treatment used to treat malignant tumours of the thoracic limb are: neoadjuvant chemotherapy, block resection or amputation, and postoperative chemotherapy.

Chemotherapy treatment is based on post-resection tumour margins that may be well defined or diffuse, and the patient's response to therapy. Multiple agent chemotherapy by combination with reconstructive surgical techniques to save the limb has increased the 5-year survival rate by over 70% in recent years. Although serious progress has been made in recent decades in the management of patients with malignant musculoskeletal pathology, opinions differ between the authors regarding optimal treatment and results. Patients with this pathology represent only a small percentage

of all patients with traumatic and orthopaedic disorders. Despite this, the socio-economic impact is the largest due to comorbidities associated with both the peak at which these tumours are met and the mortality rate. In the national medical system, malignant musculoskeletal tumour pathology in the thoracic limb is insufficiently addressed, this having a negative impact on the development of diagnosis and treatment.

A patient management plan is needed to establish a definite diagnosis, appropriate chemotherapeutic and surgical treatment, as well as timely monitoring of the patient.

In order to have optimal results, a short hospitalisation time and a reintegration of the patient into society, a well-established protocol is needed.

The reintegration of the patient with a malignant musculoskeletal tumour pathology depends on a large number of factors such as belonging or not to a social group, the patient's treatment, the treatment result, and the psychological characteristics of each individual.

Currently, studies in the literature are case presentations or level III and IV evidence studies, due to the fact that the pathology of musculoskeletal tumour formations in the thoracic limb are rare, and the only level I evidence paper is the one published by Puri et al., who research the necessary frequency of visits to the doctor postoperatively of the sarcoma patient to detect a possible recurrence as soon as possible. Thus, malignant musculoskeletal tumour pathology in the thoracic limb is insufficiently addressed, this having a negative impact on the development of diagnosis and treatment.

Special part:

1. PURPOSE:

The objective of this scientific paper is to find a management plan for patients with benign or malignant musculoskeletal tumour pathology in the thoracic limb given that much of the pathology is found in the active population and in an attempt to optimise chemotherapy and surgical treatment in the hope that the integrity and functionality of the affected member is maintained so as to allow a more rapid integration into society, and avoid unnecessary care expenses.

Based on modern imaging techniques such as computed tomography, nuclear magnetic resonance, PET-SCAN, the affected anatomical region and the extent of tumour formations in neighbouring structures can be determined with certainty.

Imaging techniques can lead more accurately to the type of biopsy established by the orthopaedist in order to obtain a specimen that is as relevant as possible for the histopathological examination that will allow a definite diagnosis.

With a well-established diagnosis and a multidisciplinary team consisting of an orthopaedist, a radiologist, a pathologist and an oncologist, we will be able to develop a management plan for patients with musculoskeletal tumour formations in the thoracic limb, and establish an optimal neoadjuvant and postoperative chemotherapy protocol for different cases of malignant tumour formations.

2. MATERIAL AND METHODS:

In patients with malignant musculoskeletal tumour formations, a series of tests will be performed to detect the primary tumour, if it is not musculoskeletal. This set of tests will detect the primary tumour, if it exists elsewhere, and if the musculoskeletal tumour formation is a metastasis. In this manner, we can differentiate primary malignant tumours from the metastases of other neoplasms with a different starting point than the musculoskeletal one.

A detailed anamnesis will be performed for each patient, as well as imaging investigations to establish the affected region, the affected structures in the region, the possible vascularisation of the formation, a

biopsy from that area, a set of tests to exclude other diseases and possibly the diagnosis of new ones.

This retrospective study included patients over a period of 10 years (15.09.2009-15.09.2019), and collected data from 74 patients. We included all the patients surveyed from the two Orthopaedic departments as well as patients from the Plastic and Reconstructive Surgery department of the Timiș Emergency Clinical Hospital with a diagnosis of musculoskeletal tumours in the thoracic limb. Radiography was used as the first diagnostic imaging method, then MRI and CT, and in some cases also PET-SCANS, which were used for a more detailed diagnosis and preoperative planning.

Simple radiology was performed as a standard method of investigation in all patients. MRI was used as an additional diagnostic imaging method for 52 of the patients. Computed tomography was used to obtain 3D reconstructions for 23 of the patients. Thus, a distribution was made according to the anatomical location of the musculoskeletal tumour formations in the thoracic limb. It was noted that the anatomical topographic areas with the highest incidence is the hand with a percentage of 32%, followed by the shoulder with a percentage of 27%, and arm with 25%. The forearm and elbow are the areas with a lower incidence: 11% for the forearm, and 5% for the elbow, respectively.

The distribution of musculoskeletal tumours studied following the histopathological result. The best represented tumour group is that of bone metastasis with a percentage of 27%, followed by osteosarcomas with a percentage of 25%. Leiomyosarcoma, Ewing's sarcoma, synovial sarcoma and rhabdomyosarcoma were the least common. In terms of metastases, the most common tumour causes were prostate adenocarcinoma, lung neoplasm and breast neoplasm.

The types of surgeries used were: osteosynthesis with a locked rod, performed in patients with tumour formations at the level of the humeral diaphysis using poly-methyl-methacrylate (PMMA) spacer augmentation in patients with bone defect (this type of surgery was used in 22% of patients); plate and screw osteosynthesis, as well as the use of bone grafts where needed was used in a percentage of 16%. For one of the patients with malignant musculoskeletal tumour pathology that included the elbow joint, a total modular arthroplasty of the type Implant Cast Mutars was selected, practically replacing the joint. Amputations were used in 6% of the cases only for those patients for whom the capabilities of reconstructive orthopaedic surgery were exceeded and for whom no alternatives were found.

Surgical treatment of bone and soft tissue tumours of the upper limb is a large-scale topic that requires an approach strategy that is initiated

correctly and in accordance with the priorities of this topic, so that conducting a study on the incidence and surgical treatment of bone and soft tissue tumour pathology is a necessary point to achieve in the development of this PhD thesis. This thesis provides data on treatment strategies and demographics of operated tumours, but also raises questions about some treatments that are already under study and that in the future can treat this pathology even in some advanced stages to allow the patient's rapid reintegration into society.

We found that, in addition to a safe resection of tumour formations, another reference stage in surgical therapeutic conduct is the type of implant that can provide the best stability.

All studies and financial resources for treatment are directed to other malignant tumour formations in the human body, due to the fact that the incidence of musculoskeletal malignant tumours out of all malignant tumours is only 1%.

Even if the percentage seems small, most of it is represented by the active population.

In this study, we aim to find a management plan for patients with musculoskeletal tumours, given that much of the pathology is found in the population mentioned above.

Noting this aspect, we decided to research and establish a management that contains an early diagnosis, and a conservative surgical treatment aided by neoadjuvant, adjuvant or postoperative chemotherapy in an attempt to preserve the integrity and functionality of the affected thoracic limb so that the patient is integrated as fast as possible into society thus avoiding unnecessary care expenses for a long period of time.

CONCLUSIONS, PERSONAL CONTRIBUTIONS AND FUTURE DIRECTIONS

From the point of view of the distribution of benign tumours compared to malignant ones, a ratio of 1:1.6 was noted. This ratio seems to be unusual due to the fact that the most likely cause would be the underdiagnosis of benign tumours.

The most common tumours were bone metastases, osteosarcomas, and chondrosarcomas.

Amputation was required in 4 cases, 3.5%.

Of the 20 cases with pathological bone fracture, two were in the humerus, two in the radius and one in the ulna, four were in the pelvic bones,

six were in the spine, and five in the ribs. The most commonly used surgical treatment was osteosynthesis with a locked rod.

Bone grafting was used in five cases (two primary tumours and three metastases). The average follow-up period was 3.5 years.

Treatment using bone grafting showed an average improvement in functional scores one year after surgery.

Bone remodelling markers play an important role in diagnosing bone metastases as well as in the response to treatment, evolution and prognosis.

Markers that can express bone resorption are the first indicators of skeletal malignancy. They can be found in excessive amounts (50-150%).

The markers that show bone formation and that represent high levels most often in bone metastases are TAP (total alkaline phosphatase) and BAP (specific bone alkaline phosphatase).

Compared to sBAP, the urinary level of NTX-I is a stronger indicator of a negative prognosis. Also, the high urinary level of NTX-I entails the need for a more aggressive treatment in order to combat the increased risk of bone pathological events.

A good indicator in the case of bisphosphonate treatment applied to patients with bone pathological events is given by the level of OC (serum osteocalin), which sometimes drops even below normal values after treatment.

On the incidence of musculoskeletal tumours in the thoracic limb, we have created a clear picture, which is, obviously, unclear in some aspects with regard to the accessibility of people living in rural areas to specialised medical services and the addressability of these people, many of whom go to the doctor at that time when the tumour staging shows advanced malignancy processes.

This shows that amputation remains a treatment used only in extremely advanced cases, which are found in a very small population among the patients studied.

The use of bone grafts in surgical treatment in malignant musculoskeletal pathology is a noteworthy option that can be considered in cases that require it. It proves to be beneficial among our patients.

Scintigraphic screening or PET-SCANS in patients with malignant musculoskeletal pathology will help us diagnose bone metastases early even in the treatment of imminent pathological bone fractures.

The new drug treatment lines used in bone metastases as well as bisphosphonates and monoclonal antibodies that attack the tumour at molecular level and prevent it from spreading, while reducing the pain felt by the patient and the risk of a pathological bone fracture.

New modalities of radiotherapy increasingly represent the elective treatment in cases of bone metastases regarding palliation. The options for expanding surgical treatment are innumerable: osteosynthesis that is performed more easily, and then the joint prosthesis benefiting from state-of-the-art implants and having lower and lower wear rates.