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MUSCULOSKELETAL ONCOLOGY

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CONTENTS

MUSCULOSKELETAL ONCOLOGY INTRODUCTION

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The field of musculoskeletal oncology is wide and includes the study and treatment of a rare group of connective-tissue tumors. Although these tumors are uncommon, they significantly affect the life and the limb function of the patient. Bone tumor surgery is constantly evolving with improved surgical techniques, implementation of local adjuvants, biomaterials, implants and devices, in the aim to safeguard the life and obtain good oncologic results together as well as attempting to preserve as much healthy tissue as possible and to guarantee an acceptable functionality and mechanical stability. Primary bone tumors are much rarer than metastatic ones. After the spine, the pelvis and the proximal femur are the skeletal regions most commonly affected by metastases in cancer patients. Most of primary bone tumors are, fortunately, benign. Since it is very probable that all orthopedic surgeons sooner or later have to deal with these categories of bone tumors, this monograph thoroughly describes some specific issues on benign bone tumors and metastases as well as presenting a review of the most recent relative literature.

The aging of the general population, the development of diagnostic techniques and treatment protocols, have led to an increase in the life expectancy of cancer patients, so that more and more often, the orthopedic surgeon may have to manage and treat patients with bone metastases. Defining the decision-making approach and evidence-based treatment recommendations for bone metastases is a stated priority of all orthopedic research scientific societies. From the first studies by Capanna and Campanacci at the beginning of the past decade, the Italian Orthopedic School was proud of having set the criteria for the classification of metastatic patients. This careful and accurate work recently culminated in the drafting of the SIOT Guidelines in 2008. The Authors of this volume present in this special issue their long-established experience on some particular topics of the surgical treatment of bone metastases: the use of local adjuvants, the role of intramedullary nailing in pathological fractures of the femur, the mini-invasive technique of percutaneous cementoplasty for acetabular osteolysis.

The rest of the monograph deals with one of the most common benign bone tumors in the pediatric age, such as simple bone cysts, and the most common tumor in the hand, the enchondroma. The Authors report their clinical experience and a systematic review of the literarure on recent treatment approaches of simple bone cysts, with special particular attention to the potential role of platelet grow factors in the healing of the lesion, and about surgical options for hand enchondromas, underlining the importance in maintaining satisfactory functional

Key words: bone tumor, surgery, local adjuvants, biomaterials, implants

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results in spite of the high risk of recurrence of these tumors if they are not adequately treated.

Thus, the main purpose of this issue is to thoroughly focus on some aspects of oncological surgery in consideration of the extreme heterogeneity of this orthopedic field in terms of age of patients, anatomical sites, different prognosis and complex management of bone tumors.

LOCAL ADJUVANTS IN SURGICAL MANAGEMENT OF BONE METASTASES

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Curettage is one of the most common methods for surgical treatment of bone metastasis, benign bone tumors and low grade chondrosarcoma. Local adjuvant most commonly used for improving the effect of curettage in local cancer surgery may exert their effects either chemically or physically. In Orthopedic Oncology the most common are phenol, liquid nitrogen, laser and cement. This article reviews the main characteristics of the most common chemical and physical agents used in bone oncology, emphasizing the toxic effects of some of them, especially phenol and liquid nitrogen

Curettage is one of the most common method for surgical treatment of bone metastasis, benign bone tumors and low grade chondrosarcoma. Local adjuvants most commonly used for improving the effect of curettage in local cancer surgery may exert their effects either chemically either physically. At the beginning of the 1970's the first local adjuvant used in orthopedic oncology surgery was liquid nitrogen cryotherapy, developed by Marcove at the Memorial Sloan-Kettering in New York, and PMMA cementation, described for the first time by Persson and Wouters. Over time other local adjuvants, both chemical and physical, have been used such as speed burr, painting or irrigating with phenol, irrigation with hydrogen peroxide or with aqueous zinc chloride, thermal cautery with a carbon dioxide laser, defect-filling agents that elute methotrexate or doxorubicin.

The use of these substances is to improve the results obtained by curettage through the elimination of any remaining neoplastic cells. The choice of the adjuvant is generally based on the surgeon's personal experience.

It is important to highlight that the use of local adjuvants cannot substitute a proper curettage nor can it correct a poorly performed one, that must be performed aggressively, using s high-speed drill and eliminating the residual material by burr drilling. This is basic for oncological results and only in this way the utilization of local adjuvant will lead to a significant reduction in the percentage of local recurrences.

The aim of this study is to do a review of the literature analyzing the more commonly used local adjuvants.

Liquid Nitrogen

Cryosurgery is the therapeutic use of liquid nitrogen stored at -197 to induce tissue necrosis with ablative intent(1-3). This method determines good local control because its cytotoxic effect ranges from 7 to 12-mm, and good function because it does not affect articular cartilage, preserving the adjacent articulations and avoiding the need of massive reconstruction. The risks are: possible necrosis of the adjacent soft tissue, neuroapraxia of the near

Key words: local adjuvant, bone metastases, cement, liquid nitrogen, phenol

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nerve structure and fracture (5-25%) (4-6). The risk of fracture is due to trabecular necrosis with the interruption of osteoid matrix and extensive bone marrow necrosis with minimal inflammation and subsequent liquefaction with progressive fibrosis. The ossification of the cryonecrotized bone tissue, which behaves like an acellular graft, is slow. Therefore, cryosurgery can be defined as a biological intra-compartmental resection allowing a wide excision *in situ* but without the morbidity of massive resection and disarticulation.

The tissue necrosis is due to thermal shock, intracellular dehydration and toxic electrical imbalance, the formation of ice crystals (which causes direct cell death), the disruption of the cell membrane and microvascular alterations. Cellular necrosis occurs at temperatures varying between -21° and -60°, beyond which the percentage of necrosis does not increase. The tissue's response to cryotherapy depends on cell typology, density, tissue vascularization, the presence of cryoprotective molecules, the number of freeze-thaw cycles and the absolute temperature reached in the process and duration of freezing (7).

Marcove's procedure consists of an adequate protection of the soft tissue and nerve vascular structure; the use of a tourniquet when treating the lower leg; an aggressive curettage of the tumor with a large bone window and pouring the cryogenic agent through a funnel, monitoring the temperature of soft tissues with thermocouples; freeze-thaw cycles because after the first cycle, the conductivity of the cold temperatures increases irrigating the cavity with saline solution; intra-articular monitoring with thermocouples; reconstruction of bone to provide immediate mechanical stability (7). If a physis is still open, only one cycle should be administered.

Cryoprobes are an evolution within the field of cryosurgery; the low temperatures are achieved through local conduction and not through instillation, using Argon at -190° as a freezing agent and Helium at 35° as a thawing agent and a saline solution, or, in alternative, a viscous jelly (Surgilube) is used both as a thermal conductor and for thermo-modeling. The advantages of this method are reaching freezing point more rapidly than with liquid nitrogen, and having a more effective control of the temperature obtained, while limitations include the number, diameter and cost of each cryoprobe, the volume of pressurized Argon and the time needed to repeatedly administer the freeze-thaw cycle.

The cryoprobes are used to treat smaller lesions, while in our opinion major bone cavities are treated more rapidly and more cheaply with liquid nitrogen following Marcove's technique (8).

Acrylic cement (PMMA)

The adjuvant action of the PMMA is due to the exothermic polymerization of the compound and a possible toxic effect of the monomer itself that induces perilesional tissue necrosis (11-12). The cytotoxic effect of the cement is within the range of 1.5-2 mm of the spongy bone and 0.5 of the cortical bone (13-16).

The advantages of this technique are that the skeletal segment is preserved, local control is efficacious, there is a rapid recovery of weight-bearing because the cement can be used as a filler to reinforce the osteosynthesis, local recurrences are easily seen when other therapies are available (13).

The disadvantages are that experimental studies have shown that methyl methacrylate monomer does not have a significant cytotoxic effect, and that the thermal necrosis of the bone is induced within a temperature range of 48°-60° and that it is variable and time-dependent. While the maximum temperature of the bone/cement interface reached in an experimental model was 46°; the increase in temperature depends on the cement's size, the speed of heat dissipation depends on the bone vascularization (this is why the effect is greater if the blood flow is interrupted by applying a tourniquet) (14-16).

The cement should have a low-viscosity which has to be cooled to slow down the speed of polymerization and then introduced into the whole diaphysis in the case of permeating bone lesions. After the cementation of the canal, the locked intramedullary nail must be inserted in a static fashion, while in localized lesions, the cement has to fill the space left by curettage and the osteosynthesis device must to be set on it (17).

Cement added with antiblastics

In this method anticancer drugs (such as methotrexate, cisplatin and doxorubicin) are mixed

with PMMA to use a slow release effect from within the cement (18). In a recent Italian study, Rosa et al. (19) demonstrated that with this technique anticancer drugs are released in an active form from the cement over time. They tend to form granules and each drug conserves its own cytotoxic characteristics with a different effect on the cell vitality of the related culture. Even if the study has not clarified yet whether the drug is released only by the cell culture/drug-loaded cement interface, it has positively confirmed present data in medical literature which show that the heat induced by polymerization does not affect the pharmacodynamic features of these drugs (20).

Phenol

Phenol, also called phenolic acid, is a bacteriostatic compound in a concentration of 0.1-1%, bactericide above 1%, cytotoxic and non selective in concentrations higher than 3% and a local anesthetic in concentration higher than 5% (21). Its action is caused by the denaturation of cellular proteins which induce cell permeability and destruction of the cells. Its cytotoxic effect ranges from 1-1.5 mm.

The use of phenol is selectively indicated for cartilage tumors, in a variable concentration (range 5 – 90 %) at room temperature and is either poured directly into the tumor cavity or applied to the cavity surface with a tampon. It is important to wash the cavity before phenol instillation in order to remove any tissue debris or clots, taking care not to damage and/or irrigate the periskeletal soft tissue. This procedure must be repeated three times. An analysis of the literature has shown that phenol must be left *in situ* for a variable time (60 seconds - 5 minutes); it must then be removed using a saline solution wash (22). The saline solution has replaced both the 70% alcohol irrigation, as it is highly toxic and phenol is easily soluble in water in concentrations of 5%, and irrigation with the hydrogen carbonate solution (23).

Phenol can be used in association with PMMA as shown in literature by Trieb et al. (24) who report that recurrences are not related to the treatment of cancer with or without adjuvant phenol therapy, but rather to a well done curettage; while Capanna et al. (25) describe a recurrence rate of 41% in cancers treated without phenol compared to 7% of those treated with phenol out of 165 different benign tumors with recurrence potential.

Electric Current

This adjuvant technique consists in the application of radio frequency electric current directly to the tissue. It is easier to manage than others and causes a vaporization, carbonization due to tissue desiccation and coagulative necrosis, dependent on width, power and time . Electro-scalpel cauterization has a general cytotoxic effect within a 1 mm range. This technique is more effective if it is performed with an Argon beam. Electric current in the form of ionized argon gas has an ionizing power inferior to that of oxygen and also can enhance the effectiveness of the procedure by physically removing blood and other lesion tissues, thus enhancing visibility during surgery. An analysis of the literature shows an average efficacy reaches a depth of 2.4 mm, while the application time is 10 seconds for each bone portion to be treated, with power regulated at 100 W (26-27).

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INTRAMEDULLARY NAILING FOR THE TREATMENT OF PATHOLOGICAL FEMORAL FRACTURES DUE TO METASTATIC LESIONS

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Impending and actual pathologic fractures of the femur due to bone metastases seriously affect the quality of life of cancer patients. Local tumor control and early restoration of full weight bearing for the remaining of the patient's life are mandatory goals in surgical treatment of femoral metastases. Different surgical options are indicated, depending on several clinical, prognostic and mechanical factors. Locked intramedullary nailing is currently used in the treatment of femoral metastases when the trochanteric region or shaft are mainly involved in patients with multiple metastases. The aim of this study is to assess the outcomes of a consecutive series of 80 patients treated with intramedullary nailing for femoral fractures due to metastatic lesions. Fifty-six were partial and 24 were complete fractures. All patients were treated with a long titanium alloy Proximal or Lateral Anterograde Femoral Nail (PFN or LAFN, Synthes) inserted in locked static mode. In 12 patients (15%), acrylic cement for bone cavity filling was used after nail insertion; percutaneous cementoplasty was simultaneously performed in 11 cases (13.75%) of severe ipsilateral acetabular osteolysis. There were no wound or deep infection, no hardware or implant failure requiring component substitution or revision. Forty-eight patients (60%) died at six months follow-up and 90% at two years due to the primary disease. Non-fatal deep venous thrombosis without pulmonary embolism was observed as an early complication in 23 patients (28.75%). In 3 months, 68 patients (85%) returned to ambulate with or without crutches. Results confirmed that intramedullary reconstructive-locked nailing is the treatment of choice in advanced-stage cancer patients affected by diaphyseal and metaphyseal pathological fractures of the femur: it offers good and durable stability, gives pain relief and allows early postoperative mobilization and weight bearing, thus improving the quality of life of cancer patients.

Femur is the long bone most commonly affected by bone metastases (1-2); one-third of metastatic lesions to the skeleton occurs in the proximal femur, after spinal and pelvic localizations (3-4). As its major function is load-bearing, pathological fractures of the femur seriously deteriorate the quality of life of cancer patients (5-10). Although most femoral metastases are favorably treated radiation therapy (4), surgery is indicated to prevent or stabilize impending or pathologic fractures at this site, except in bedridden patients with a life expectancy of less than two months. Surgical goals in femoral metastases are to achieve local tumor control and early restoration of full weight bearing

Key words: metastases, femur, locked intramedullary nailing

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with a solid, definitive and durable system of fixation (5-12). Several retrospective series validate the use of different surgical options, depending on number of lesions, anatomic location in the femur, degree of cortical destruction, primary tumor and its response to chemo-radiotherapy, disease progression and estimate survival rate (1,3,5,7,9,13-14). Bone resection and prosthetic reconstruction are recommended for: pathologic fractures in the head, neck or distal femur involving the articular surface; destructive lesion with extensive bone loss; solitary femoral metastasis of renal cell, breast or thyroid carcinoma related to a prolonged patients' life expectancy (2,6-8,13,15-16). Osteosynthesis without resection is indicated in multiple lesions or in femoral shaft localization with no hip or knee extension, using a screw-plate fixation or the intramedullary nailing (9-12,14,17). Once the surgical procedure is chosen, pre- or post-operative radiotherapy, concomitant tumor curettage and adjuvant polimethylmethacrylate (PMMA) cement for filling bone cavity can complete the overall treatment strategy (2,6-7,11,13). Trends in osteosynthesis for femoral metastases shifted over the last three decades towards the use of locking intramedullary devices in comparison with plate fixation (4,18-19): open curettage and plate or double-plate fixation, filling the defect with PMMA cement, is indicated to metastatic lesions involving less than half of the epiphyseal or metaphyseal area. This procedure is more useful in the distal metadiaphysis than in the proximal femur, but it has an unacceptably high mechanical failure rate when metastatic progression occurs (6,12,15,18). Additionally, it is easier to stabilize the entire length of the femur with a nail than with plating techniques to prevent any fractures from further tumor enlargement or noncontiguous site in the same bone (6-8,15,19).

Intramedullary nailing is assessed to be a safe and effective treatment option for long bone metastases as it provides a minimally invasive stabilization and the procedure is commonly reproducible similarly to the nail insertion in traumatic fractures care (2,9,17,20). The Authors previously reported the outcomes of nailing for the treatment of femoral metastases (21-23). The aim of the study is to describe a large series of femoral pathologic fractures in patients with advanced-stage cancer treated with the intramedullary nailing, assessing indications, clinical and functional outcomes related to this procedure.

PATIENTS AND METHODS

Eighty consecutive cancer patients surgically treated for femoral pathologic fractures at the Authors' institution from September 2000 to January 2012 were included in this retrospective study. The series included 42 male and 38 female patients with a mean age of 61.2 years (range, 39–81 years). According to Capanna and Capanacci's classification of patients with metastases in the appendicular skeleton (6-7), 56 patients belonged to Class 3 (impending fracture) while 24 were defined as Class 2 (actual complete fracture); demographic data and primary malignancies are illustrated in Table I. Fractures from primary bone tumors, non-unions and lesions with uncertain diagnosis were excluded; neither head and neck fractures nor solitary renal cell and thyroid metastases were included in the series since resection and prosthetic reconstruction are recommended in these circumstances. Preoperative planning included: total body CT scan, alternatively bone scan or PET-CT in all cases for cancer staging; biplanar X-ray of the affected femur and hip, while gadolinium-enhanced MRI was performed only in case of impending fracture. Indication for surgery was assessed for all impending fractures with a score greater than 8 according to Mirels' score (1) and depended in all cases on patients' general conditions according to the Karnofsky general status scale (24). All patients were treated with a titanium alloy long Proximal or Lateral Anterograde Femoral Nail (PFN or LAFN respectively, Synthes, USA) inserted in a locked static mode after a closed or open reduction of the fracture (Fig. 1.A, B). The diameter of PFN was 10 mm while LAFN changed from 10 to 12 mm. One or two distal screws, in PFN and LAFN respectively, was always inserted in a static mode. Osteolyses greater than 50% of the diameter of the bone in its maximal dimension were treated with PMMA cement for filling of bone cavity after PFN insertion to improve mechanical stability of the system (15); it was not necessary with LAFN stabilization since a big proximal diameter of the nail was selected to entirely fill the transverse diameter of the femoral lesion.

A bone biopsy was always performed to confirm diagnosis: the same hole of nail insertion was used in most of the sub- and trochanteric localizations, while a new hole for tissue sampling was necessary on the femur shaft in diaphyseal or more distal lesions. Tumor debulking or curettage was performed after open reduction when tumor extended widely in the soft tissues around the fracture. Ipsilateral acetabular osteolysis was treated simultaneously in the operating room with fluoroscopically- guided percutaneous cementoplasty (25).

Antibiotic therapy with third generation cephalosporin was administered from 2h preoperatively to third day postoperatively. Low dose heparin was administered from the day of admittance to 30 days postoperatively. Adjuvant chemo- and/or radiotherapies were performed in all patients as the individual occasions required. Pain relief, surgical and postoperative complications, walking capability and survival rate were considered in the evaluation after surgery. Clinical and radiographic follow-up was at average 10 months (range from 1 to 24 months).

RESULTS

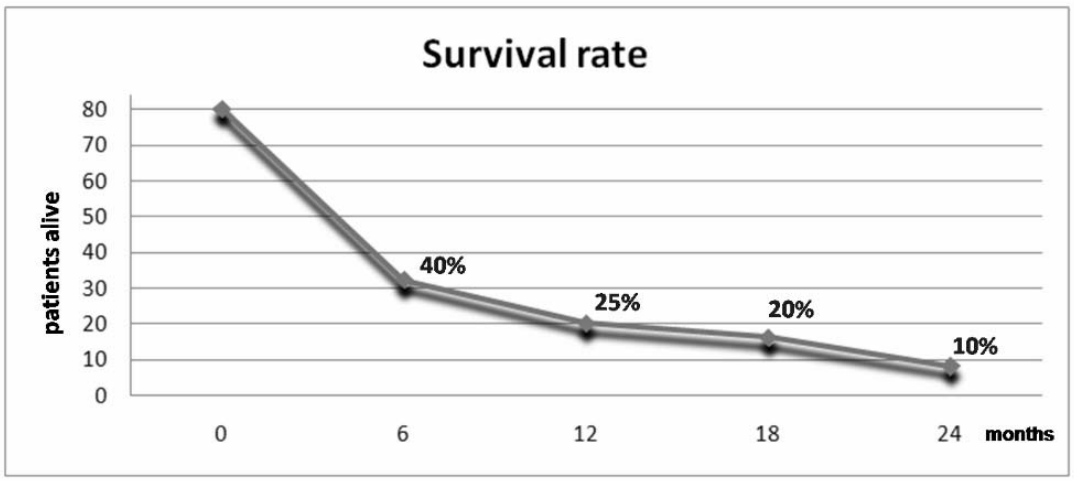
Fifty-four patients were treated with LAFN (67.5%); PFN was used in the remaining 26 cases (32.5%). The pathologic fracture was the first presentation of the primary cancer in 25 patients (31.25%). Fractures were localized in the inter-/ sub-trochanteric region in 52 patients (65%) and at femur shaft in 28 patients (35%). In 43 (76.78%) of 56 impending fractures, MRI analysis revealed concomitant multiple spot lesions proximally to the main shaft localization: 21 were observed in the neck, 13 were subtrochanteric, in 9 cases both neck and subtrochanteric region were involved besides the diaphyseal fracture. Most of these lesions were not evident at X-ray imaging (Fig. 2.A-C). Spot lesions were found also distally to shaft fractures in 4 cases.

The use of PMMA after nail insertion for filling of bone cavity was performed in 15% of PFN stabilizations (12 cases): 9 cases of diaphyseal and 3 of metaphyseal localization. Ipsilateral acetabuloplasty was performed in 11 patients (13.75%) (Fig. 3 A-C). The mean operative time was 102 minutes (range 70-140); the average blood loss was about 270 cc (range 200-350). The average length of hospitalization was 10 days. Forty-eight patients (60%) died within 6 months after operation for the progression of the primary disease. Patient survival rate at one year was 25% and 10% at two years (Table II). There were no wound or deep infection nor hardware or implant failure requiring component substitution or revision. Twenty-three patients (28.75%) suffered from non-fatal deep venous thrombosis as early post-surgical complication, with no pulmonary embolism. Patients were mobilized from bed during the early

Table I. *Patient demographics regarding clinical presentation and treatment*

Data	Patients (n = TOT)
Age	Mean age 61.2 yrs (range, 39-81yrs)
Gender (male/female)	42/38
Type of cancer	
Breast	23
Prostate	12
Lung	8
Colon	6
Thyroid	4
Kidney	2
Myeloma	16
Lymphoma	4
Bladder	3
Liver	2
Pathologic fracture	
Impending	56
Actual	24
Location	
Inter/Sub-trochanteric	22
Shaft	58
Femoral metastases	
Solitary	37
Multiple	43
Staging (metastases)	
Other skeletal	35
Visceral	48
Nailing device	
PFN	26
AFN	54
PMMA	
Adjuvant to nailing	12
Acetabuloplasty	11
Adiuvant treatments	
Radiotherapy	69
Chemotherapy	34

Table II *Data on patient survival rate during follow-up.*



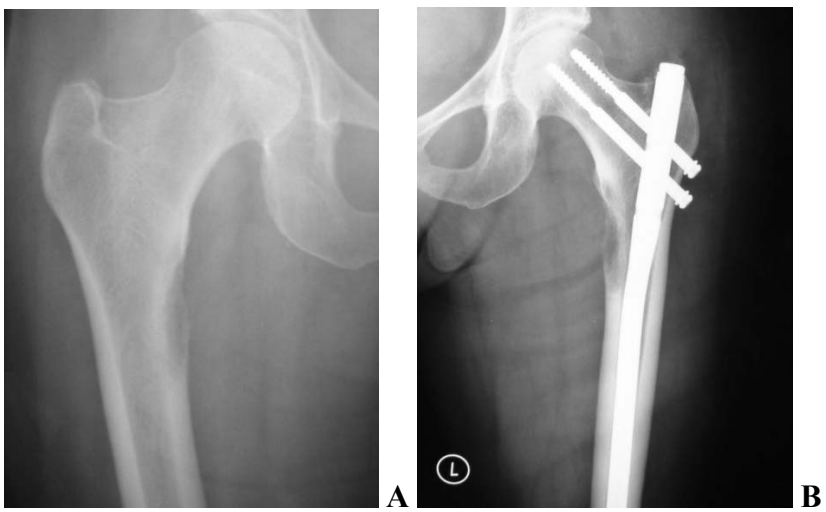


Fig.1. ***A and B)*** *Pre- and postoperative anteroposterior radiographs of an impending fracture of the medial cortex of the left proximal femur treated with AFN system.*

post-operative period (from 48 h after surgery). In 3 months, 68 patients (85%) were able to walk with or without crutches.

DISCUSSION

Femur is the long bone most commonly affected by metastases, especially from the so-called bone seeking tumors: breast, prostate and kidney followed by lung, colon and thyroid. Fractures from myeloma and lymphoma can be managed similarly to bone lesions from carcinomas since their biological behavior and mechanical implications are similar to those of metastatic disease (6-8,15). Approximately 10% of patients with metastatic disease will sustain a pathologic fracture, and 65% of all fractures requiring surgery occurs in the femur (12). Considering the extensive bone loss, the impaired bone-healing after pathologic fractures, the postoperative radiation given to most patients, the fixation construct must support a delayed union or nonunion ensuring prompt full weight bearing postoperatively, in order to maintain function and satisfactory quality of the patient's remaining life (6,8,11,15). The neck and sub-trochanteric region are the most frequently areas involved by pathologic fractures, followed

Fig. 2. ***A)*** *Preoperative X-ray showing osteolysis of lateral cortex of femur in a 64 years-old female patient with breast carcinoma.* ***B)*** *Sagittal MRI showing the wide involvement of subtrochanteric region.* ***C)*** *Postoperative X-Ray showing the femur treated with the AFN system.*

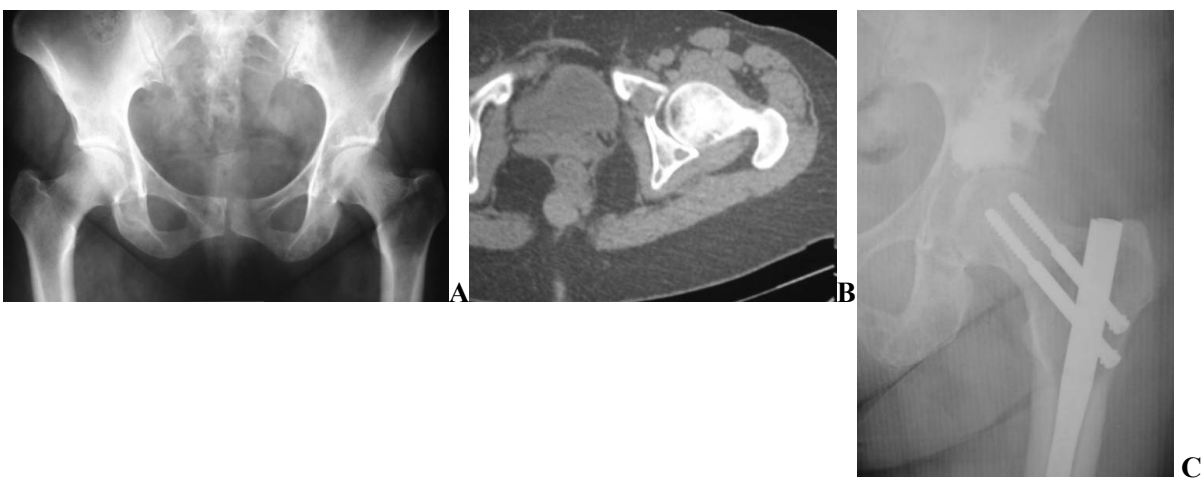


Fig. 3. ***A and B)*** *Preoperative X-ray and CT showing subtrochanteric osteolysis of the left femur and a concomitant acetabular lesion.* ***C)*** *Postoperative X-ray showing AFN system and percutaneous acetabular cementoplasty.*

by femur shaft (15). Intramedullary nailing of long bones has become an accepted modality of treatment for impending and pathologic fractures, eventually in association to curettage of metastasis and local adjuvants such as acrylic cement for filling of bone cavity. Current indications for locked intramedullary nailing in femoral metastases are impending or actual pathologic fracture of the inter- and sub-trochanteric areas, the diaphysis, or the distal femur without knee joint involvement, especially when primary

malignancy responds to radiation therapy and life expectancy is less than 6 months (6-8,15,23).

A proper surgical planning requires MRI or alternatively CT of the entire length of the femur and acetabulum besides biplanar X-ray, in order to exclude the risk of additional spot lesions which could cause, if located proximally or distally to the pathologic fracture, further fractures on weight-bearing of the affected extremity and eventually implant failure. Using MRI it is possible to demonstrate multiple lesions simultaneously localized in the neck, intertrochanteric area or distally in the shaft, not ever detectable at initial X-ray; the identification of further osteolyses precludes the indication of plate fixation or resection and reconstruction of the proximal femur suggesting a less invasive stabilization with locked nailing as the proper treatment. Even when imaging reveals only the impending or actual fracture without any further lesion in the neck at presentation, it is not unlikely that later metastases may develop in this site, confirming the risk of delayed fracture if the cervical region is not stabilized at the beginning (15,22); thus standard nails with locking into the lesser trochanter is nowadays replaced by reconstruction locked nail with interlocking screws replaced into the femoral head and neck from which possible future lesions could raise, as well as transversely through the distal femur, providing resistance to torsional stresses as well as to angular displacement through the full length of the femur (3,26). Lateral Anterograde Femoral Nail presents some mechanical advantages over other nails for the osteosynthesis of pathologic fractures: its distal diameter is available in different sizes, so it can be used specifically for the characteristic of the patient (gender, weight, femoral diameter); it presents two static plus one dynamic distal holes, so the stresses are concentrated over two screws; the presence of two proximal full screws with recon mode offers a high rotational stability in the proximal femur.

Although intramedullary nailing is nowadays a commonplace for the treatment of long bone metastases, concerns still arise regarding the risks of pulmonary compromise and mortality owing to fat and tumor emboli that are generated during nailing. Specific techniques, such as venting and unreamed nailing, potentially might reduce emboli formation (27). Cole et al. (28) compared reamed versus unreamed femoral nails for treating pathologic fractures and reported no influence on outcome. In our opinion, even if unreamed locked nail like PFN potentially avoids tumor or emboli dissemination, the mechanical advantage of reaming, inserting a nail with a greater diameter, such as LAFN, should be taken into account; in any case, bone metastasis is itself the manifestation of a systemic disease and therefore it is only a theoretic problem. In our series no patient had pulmonary complications; in any case, a nail 12 mm in diameter inserted without reaming may be considered a good compromise between the risk of reaming and the advantage of big diameter. Moreover, especially in the proximal femur, the use of a LAFN with a big proximal diameter obviates filling the bone cavity with PMMA after nail insertion.

Van Doorn et al. (17) published a multicentre retrospective analysis of 110 impending and actual pathologic femoral fractures stabilized with a cephalocondylic intramedullary device (Gamma™ nail, Stryker Orthopaedics, USA) without curettage or use of PMMA, reporting a complication rate of 5%, with two cases of implant breakage. Wedin and Bauer (11) evaluated 142 surgically treated proximal femoral metastases: they reported a nailing failure rate of 13.6%. Sarahrudi et al. (9) also performed a retrospective analysis of 142 pathologic fractures of the femur, reporting that the nailing failure rate was only 3.2%, considerably lower compared with the Swedish study. As more patients with skeletal metastases live longer, recent literature reports an increasing risk for implant failure ranging from 3.1% up to 42% for the few patients with cancer who survive more than one year after fixation for femoral pathologic fracture (10,13,20). The improvement of estimated cancer patient survival also brings nowadays to consider resection and endoprosthetic reconstruction as a preferable method of treatment for proximal femoral metastases in patients with good general fitness and life expectancy: in spite of the high risk of dislocations and infections, it assures greater local tumor control and it has not a significant higher complication and/or failure rate compared with osteosynthesis, especially when the latter procedure is associated to curettage and adjuvant cement (2,6,11-12). On the other hand, the finding of multiple lesions besides the level of fracture, the low

incidence of intra- and postoperative complications and the possibility of early mobilization strongly support the use of intramedullary nailing for pathologic fractures located in the inter- and sub-trochanteric regions in advanced-stage cancer patients.

In this series, there were no local tumor progression leading to nail or screws breakage, neither nailing failures requiring component change or revision nor postoperative superficial or deep infections; the short follow-up and the poor patients' survival rate due to the high mortality (60%) at 6 months may be the explanation of these results. Pain in the site of nail and/or screws insertion was never reported, yet it might be due to the assumption of high dose of analgesic drugs and radiotherapy administered postoperatively.

Considering that only 20% of patients with bone plurimetastatic disease survive at 3 years (29), the Authors consider locked intramedullary nailing as an optimal long-term load-sharing device for a stable fixation of inter-/sub-trochanteric and shaft pathologic fractures of the femur; it allows early and painless postoperative mobilization and weight bearing, thus improving the quality of life of plurimetastatic patients. The current study supports the favorable outcomes of locked intramedullary nailing as the gold standard for surgical treatment of femoral metastases, provided the most suitable surgical strategy and technique are correctly selected on the basis of the cancer patient's medical condition and exact criteria related to staging, prognosis and mechanical consequences of bone metastases.

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THE TREATMENT OF ACETABULAR OSTEOLYSIS WITH A MINI-INVASIVE TECHNIQUE OF PERCUTANEOUS ACETABULOPLASTY: OUR EXPERIENCE AND REVIEW OF THE LITERATURE

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Percutaneous acetabuloplasty is a palliative mini-invasive technique that produces effective results in the management of acetabular osteolysis in patients with multiple metastases and with a low life expectancy. Acetabuloplasty appears to be an effective palliative treatment tool for improving the pain and disability related to acetabular metastatic lesions. With adequate imaging and technique, it carries a low risk of complications, making it an attractive treatment option for patients with systemic malignancies who are often poor candidates for open reconstructive procedures. It can be an effective aid to chemo- and radiotherapy in the management of acetabular bone metastases due to carcinoma.

Osteolytic metastases around the acetabulum are frequent in cancer patients (ilium is affected in 45% of cases), and may cause intense and drug resistant pain of the hip. The osteolytic lesions often lead to pathological fractures, forcing the patients to bed rest, with a considerable increase of co-morbidity (1-5)

CT or MR imaging are used to evaluate lesion extent, including cortical destruction of the articular surface as well as proximity of neurovascular structures (6)

Curettage and bone cement reinforced with pins according to Harrington's technique is indicated in patients affected by primary tumor with good prognosis or with single metastasis, but surgical treatment is difficult when the metastasis is extensive and is rarely suitable for treating cancer patients with multifocal lesions. Besides reconstructive surgery is not well tolerated in this patient population and carries a substantial risk of complications (7-14).

Several procedures have been used to alleviate symptoms arising from acetabular metastases.

External beam radiation therapy has been shown to decrease the rate of tumor growth. However, radiotherapy alone is usually unable to control the pain and/or to restore the integrity of the acetabular area, so as to allow a return to early weight-bearing (15-17).

Percutaneous ablation techniques, such as radiofrequency ablation (RFA) and cryoablation, have been shown to produce significant pain reduction but do not address the increased risk of pathological fractures in this weight bearing region (18-20).

Percutaneous acetabuloplasty is an image guided intervention in which acrylic cement is injected

Key words: mechanical stabilization, acetabular osteolysis, percutaneous acetabuloplasty, osteolytic metastases, radiotherapy

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directly into the lesion in order to provide pain relief and potential structural support (4, 21-26).

The aim of the study was to report the surgical technique of percutaneous acetabuloplasty and the clinical outcomes of 60 patients (a total of 65 acetabula - 5 bilateral cases) afflicted by multiple metastasis due to carcinoma with a painful metastasis located to the acetabulum.

MATERIALS AND METHODS

Acrylic cement has been used to fill secondary benign or malignant osteolytic lesions of the long bones after curettage. Vertebroplasty and kyphoplasty are able to obtain reduction or the elimination of pain by injection of acrylic cement into the pathological or osteoporotic fractures of the spine(27-32). Similar techniques have been reported in the management of metastatic lesions around the acetabulum.

Indications for percutaneous acetabuloplasty have been addressed in a previous paper (4) (Table I).

The procedure is performed under general, spinal or local anaesthesia. Patients are positioned on a fracture table either supine or in lateral decubitus, and antero-lateral and postero-lateral portals are used to fill the whole cavity with cement. After having prepared a sterile field, two Kirschner wires are inserted into the acetabulum under image intensifier control. Using the two Kirschner wires as an initial guide, two appropriately sized introducer cannulas are slid over these Kirschner wires for cement injection (e.g. 10 Gauge), and inserted into the osteolytic cavity. The Kirschner wires are removed, and the cannula may be oriented with its beveled stylet for subsequent cement injection in the desired location. If required, prior to injecting the cement, a percutaneous bone biopsy can be performed using another cannula in conjunction with the introducer cannula (Stryker Bone Biopsy Kit, Stryker Corp Kalamazoo, MI, USA). This way a small cylindrical sample of tissue can be obtained. The positioning of the cannula and the injection of the cement are constantly monitored in antero-posterior and oblique projections. While the cement is being injected, no leakage should occur outside the bone. Should this occur, the cement injection should be interrupted, and the cannula may have to be withdrawn so the cement that has already been injected can harden, and to avoid any further leakage. At a later stage, more cement can be injected, if necessary. Some authors suggest injecting contrast medium before using the cement, to see how this will spread inside the osteolytic lesion(21-26, 33-35). If the cement leaks into the hip joint, besides stopping the injection, the leg is brought to the full range of motion in order to spread the leaked cement over the surface of the joint before it hardens(4).

If the patients receive general or spinal anesthesia, they are positioned in lateral or supine decubitus. If local anesthesia is used (10 ml of 7.5 mg of ropivacaine mixed with 10 ml of 1% mepivacaine), the patient is supine. The average length of time of the procedure is about 30 minutes. The average hospital stay is 3 days.

Standard pre-operative blood tests and a CT scan of the hips with frontal and sagittal reconstructions are performed. Surgical cement of adequate viscosity, opacified with tungsten powder as described for vertebroplasty, is injected under front fluoroscopy. In most cases the patient was permitted to stand up the next day (4)

RESULTS

We observed 60 patients with mechanical stabilization of the osteolytic lesion due to carcinoma, treated with percutaneous acetabuloplasty, according to indications reported by Maccauro et al (4).

Table II reports the histology. We did not have pathological fractures and we did not have clinical symptoms related to cement leakage. Sixteen patients reported transiently increased pain of the hip and pyrexia in the immediate postoperative 48 hours. In four patients, the cement was injected in a blood vessel, but there were no clinical manifestations of this. The images were reviewed by a trained interventional intern radiologist who, in the absence of clinical symptoms, did not require any further imaging. An overall improvement of the quality of life of the patients was evident, and patients were able to return to their activities of daily life. The ECOG index showed an improvement of the patients' general condition up to 6 months after the index procedure, with the average score improving from 3.44 preoperatively, to 2.00 at 1 month, 1.24 at 3 months, and 1.84 at 6 months. Worsening of the patients' general condition was observed one year after surgery, with an average score of 3.76 and 20 patients deceased by that time. The HHS index showed an improvement in the ability to carry out standard daily activities autonomously, with a preoperative score of 34.60% rising to a postoperative score of 72.75% one month after surgery, which further improved (81.79%) 3 months after the treatment. At 1 year follow-up a worsening of their general condition was observed,

with reduced autonomy and the average HHS score dropping to 59.16%, yet still higher than the score recorded preoperatively. A similar trend was observed for pain, measured by the VAS score. Pain improved from an average preoperative score of 8.60 to 2.84 at 1 month, to 2.12 at 3 months, to 2.45 at 6 months, and to 5.06 at 1 year. Local function, evaluated with the WOMAC questionnaire, showed a considerable improvement over the first 6 months after treatment, from an average preoperative score of 78.80% to 39.17% at 6 months. One year after the injection, the local function dropped to an average score of 55.31%. In short, complete pain relief was achieved in 59% of patients (n = 30). Pain reduction was achieved in 20 of 50 patients (40%). The mean duration of pain relief was 7.3 months (median: 6 months). Pain recurred in six patients between 2 weeks to 3 months. Twenty patients died, and 30 patients were still alive at the time of the one year follow up. The one-year survival rate was 40% (observation period: 1–30 months) (4).

Acetabuloplasty can aid radiotherapy, both by improving pain and by providing a mechanical support at a stage during which radiotherapy alone would not be able to prevent pathological fractures.

DISCUSSION

The incidence of complications of skeletal metastases seems to be steadily increasing. This may be because patients with cancer are living longer because of improvements in the treatment of primary lesions and disseminated cancer (1-5)

Radiotherapy is indicated for bone pain caused either directly or indirectly by malignant lesions. Malignant lesions may produce pain from direct action on the nervous system. However, different modalities of pain production may act in the presence of skeletal metastases (mild, moderate, mechanical). Radiotherapy does not improve the mechanical properties of the affected acetabular region, and transient osteoporosis is usually observed, with the risk of pathological fractures (15, 17).

Surgical procedures include curettage of the lesion followed by PMMA packing and pin fixation (Harrington's technique), total hip replacement, and rarely hemipelvectomy. Special preoperative considerations are needed because these patients often have extensive metabolic, hematological and nutritional deficiencies.

Surgical reconstruction in metastatic disease of the acetabulum should fulfill three aims: resection of the tumor, filling of the bone defect, and stabilization of the skeletal segment. Usually, the lesion is curetted, followed by filling with cement and reinforcement with Steinman pins, or the use of a hip or pelvic prosthesis (4).

The Harrington's technique is recommended for the treatment of painful metastatic lesions of the acetabulum; it can provide immediate and long-term pain relief and increase resistance to subsequent fracture (7, 14)

In Harrington's original series of 25 cases using retrograde pins there was one intra-operative hemorrhage, leading to death post-operatively and two further peri-operative deaths (7). There were no deep infections, no loss of fixation, and one complete femoral nerve palsy. In the series of Vena et al. of 21 cases, there were three peri-operative deaths, two dislocations and two nerve palsies (36). Allan et al.'s patients were not subdivided by treatment and included 14 treated with a bulk allograft and a re-inforcement ring (1). The overall complications consisted of three pulmonary emboli (one fatal), two dislocations and three intra-operative bleeds of more than 1500 ml (maximum 8500 ml). In the series by Marco et al (15 from a larger series of 55 cases using a number of different techniques), it was again not possible to differentiate the adverse events resulting from cases using other techniques (10).

Parikh and Kreder used multiple antegrade pins combined with an acetabular reconstruction ring which they supplemented with screws and on occasion with reconstruction plating of the posterior column. This series of ten cases produced one dislocation but no other major complications (12).

A combined retrograde and antegrade placement of pins was used by Nilsson et al. in 33 hips. There were three cases of severe hemorrhage, two of which were fatal. There were two dislocations, one deep infection and two peri-prosthetic fractures distal to the femoral component (11). Kunisada and Choong managed 25 of 40 patients in this way with one intra-operative death and one dislocation (9).

Acetabuloplasty is reliable for the management of acetabular osteolysis in patients who cannot be candidates for major surgery. In patients in whom

radiotherapy was not effective, it can be performed by orthopedic surgeons and interventional radiologists. In selected patients, local anesthesia may be used. The contemporary presence of an impending or complete femoral fracture should be an indication for acetabular cementoplasty during the same anesthesia.

Bone cement is able to restore some of the compromised mechanical proprieties after filling bone cavities. Periacetabular defects may increase the vulnerability of the pelvis to fracture, depending on size and cortical involvement. Acetabular cement filling may lower the risk of periacetabular fractures, as little as 10% cement by volume could result in significant compressive strength increases, thus reducing the risk of fracture (4).

In 1995, Cotten suggested to extend the vertebroplasty technique to the acetabulum for the management of secondary osteolytic lesions. They showed that these techniques were as effective as palliative methods for controlling pain and reinforcing bone (21-22).

Acetabuloplasty is achieved by performing a percutaneous injection of low viscosity acrylic cement into the osteolytic cavity of acetabulum. Acetabuloplasty aims to immediately restore the mechanical properties of the affected skeletal segment, it imparts increased resistance to compressive stresses to the treated acetabulum preventing the continuous microtrauma responsible for the increased risk of fractures, thus allowing immediate weight-bearing and preventing pathological fractures. It also reduces or eliminates pain. Furthermore, the exothermic reaction developed during the polymerization of the cement exerts a local cytotoxic action on the tumor. Acetabuloplasty is indicated in patients suffering from acetabular metastatic disease of the weight-bearing area, with drug-resistant pain of the hip, gait limitation and inability to tolerate major surgery, either due to the local or systemic extension of the disease, or particularly poor clinical conditions. Hip fractures are not a contraindication, and the opportunity to use a bipolar endoprosthesis combined with the injection of acetabular cement

Table I.

INDICATIONS FOR ACETABULOPLASTY:

-Weight-bearing acetabular osteolysis

-Hip pain resistant to drugs

-Patients with multiple metastases

-Short life expectancy

-Inability to tolerate major surgery

-Histotype differing from that of the kidney and the thyroid gland

-Radiotherapy failure

CONTRAINDICATIONS TO ACETABULOPLASTY:

a. Absolute contraindications to acetabuloplasty

-Acetabular fracture

-Pelvic discontinuity

b. Relative contraindications to acetabuloplasty

-Radiographic signs of medial wall interruption

-Local infection

-Bleeding disorders

Table II.

Histology of primary tumor	-Weight-bearing acetabular osteolysis
Breast (30 patients)	
Lung (16 patients)	
Prostate (6 patients)	
Kidney (1 case)	
Bladder (4 cases	
Unknown origin (3 cases)	

offers mechanical support for the acetabulum. Thus the patient avoids the risk of hemorrhage, and other problems linked to the preparation of the acetabulum. The same considerations can be made for combined lesions of the femoral shaft and the acetabulum, and for patients with bilateral disease (4, 23-26).

Cotten et al. suggest two radiographic and CT findings as possible contraindications for acetabuloplasty: articular cortical destruction of the acetabular roof greater than 5 mm in diameter and soft-tissue involvement greater than three times the area of bone destruction (21-22).

Complications may include, but are not limited to, bleeding, infection, nerve or tissue damage, leakage of cement into the soft tissue and hip joints, and, rarely, hypotension during the injection of cement (4).

Knowledge of where the the sciatic nerve passes is critical for the safe performance of acetabuloplasty. The sciatic nerve passes through the inferior part of the greater sciatic foramen and is the most lateral structure emerging below the pyriformis. It runs inferolaterally under the gluteus maximus, midway between the greater trochanter and ischial tuberosity. As the nerve passes distally, it is intimately related to the posterior portion of the acetabulum. Authors with the greatest experience in acetabuloplasty to date report the use of a supine or lateral decubitus position. All of our patients were in prone or prone oblique position, minimizing risks to the pelvic vasculature; however, this exposes the sciatic nerve to potential injury. When using this approach, knowledge of the anatomy of the sciatic nerve is important for safe needle insertion. In general, the cement should be injected carefully to limit extravasation beyond the acetabulum, where the heat of polymerization may damage the sciatic nerve (21-26, 33-35) .

Another percutaneous treatment option is RF ablation, which has been shown to significantly reduce pain from lytic metastatic lesions, including those in the acetabulum. However, ablation techniques do not address the increased risk of pathologic fracture in weight bearing regions such as the acetabulum. Cement placement has the theoretical advantage of structural stabilization, which is the primary reason for choosing acetabuloplasty over the other percutaneous approaches.

RFA may be combined with percutaneous acetabuloplasty and is thought to improve cement filling and decrease cement extrusion by creating an ablation cavity for the cement injection (18-20).

Lane et al. report 53 combined RFA and cementoplasty procedures, of which 14 were in the acetabulum (18). Toyota et al. found a significant improvement in patient pain in 17 adult patients with 23 painful bone metastases who underwent.

Schaefer described a patient with a stage IV malignant melanoma and a pathological fracture of the left tibial plateau who underwent radiofrequency heat ablation and percutaneous cementoplasty for defect filling and stabilization (19).

The exothermic reaction arising from the cement's polymerization is basically the same as that obtained by radiofrequency. Therefore, no increase of cytotoxic effect on the tumor should be obtained(18-20).

CONCLUSION

Curettage and bone cement reinforced with pins

according to Harrington's technique is indicated in patients affected by primary tumor with good prognosis or with a single metastasis, but surgical treatment is difficult when the metastasis is extensive and is rarely considered suitable to treat cancer patients with multifocal lesions.

Percutaneous acetabuloplasty is a palliative mini-invasive technique that produces effective results in the management of acetabular osteolysis in patients with multiple metastases and with a low life expectancy. Acetabuloplasty appears to be an effective palliative treatment for improving the pain and disability related to acetabular metastatic lesions. With adequate imaging and technique, it carries a low risk of complications, making it an attractive treatment option for patients with systemic malignancies who are often poor candidates for open reconstructive procedures. It can be an effective aid to chemo- and radiotherapy in the management of acetabular metastases.

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BONE SUBSTITUTES AND GROWTH FACTORS IN THE TREATMENT OF SIMPLE BONE CYSTS: REVIEW OF THE LITERATURE AND CLINICAL EXPERIENCE

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The solitary bone cyst is a tumor like lesion typical of the immature skeleton whose etiology and pathogenesis is unclear. Treatment depends on symptoms if they are present, the presence of a fracture, the size, the location and the presence of cysts in an active phase. The literature shows many treatment options, often conflicting with each others. The purpose of this study is to perform a review of the literature focusing on the possible role of platelet gel to heal the lesion. The injection of substances such as methylprednisolone, autologous bone marrow, demineralized bone matrix and calcium sulfate are the most used, but due to the high failure rate, often we use more aggressive surgical techniques such as curettage, resection, associated with bone graft and, possibly, the intramedullary nailing. We report two cases of lesions resistant to injected steroids and treated with curettage and bone marrow, platelet gel and bone substitutes. In bone cysts resistant to minimally invasive treatment, curettage associated with platelet gel and bone substitutes represent a valid therapeutic option.

The solitary bone cyst is a tumor-like lesion typical of the immature skeleton, characterized by the presence of an intramedullary cavity full of liquid. It is formed close to the metaphysis, juxtaposed or near the physis and it tends to grow thus weakening the bone (1-2).

It represents 3% of all bone tumors, and it was been first described by Virchow in 1876 (3).

The lesion generally appears between the 3rd and 14th year of age, with approximately a 2-2.5:1 male/female ratio (1-2).

In 80% of the cases it is located in the proximal part of humerus and femur but it is also found in other locations like heel and iliac bone (1).

Pathogenesis

Different pathogenetic mechanisms have been proposed.

According to Mirra, they are intraosseous synovial cysts (4); Jaffe et al. have observed dysplastic areas in the lesion that develop in response to trauma (5); Cohen thinks that the cysts are formed in response to vein occlusion in the medullary spaces (6), while the origin near the growth plate supports the hypothesis that they represent more a growth disorder than a true neoplastic process (2).

Histology

At the histological examination, we observe a little layer of fibrous tissue with giant inflammatory, multinucleated and synovial scattered cells; with frequent focal deposits of hemosiderin (2,7). The liquid contains a high concentration of oxygen

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free radicals, prostaglandins, and hydroxyproline-binding proteins, alkaline phosphatase and lactate that may cause bone resorption and play a role in cyst formation and growth (7-9). The pressure inside is very high, so if liquid is injected into the cyst, it may exude into the venous system of the limb (7). This has led some authors to argue that restoring the normal channels of output or lowering the pore pressure with multiple perforations can get an involution of the cyst (10-11).

Clinical Examination

Most lesions are asymptomatic and discovered following the performance of instrumental tests conducted for other reasons; cysts are rarely symptomatic.

However, patients may often present pain, edema and deformity consequent to pathologic fractures due to low-energy trauma, which usually are composed or moderately decomposed (68% of cases) (1-2, 12).

Radiologically the lesion appears as an area of intramedullary transparency like a map, the cortex is often thin and the profile of the bone expanded; periosteal reactive changes are rarely observed unless there is a pathologic fracture. Sometimes a piece of fractured cortex may fall into the cyst, the signal from the fallen fragment will be picked up; the lesion may border on the physis or even cross it, it usually occurs in children and indicates an active cyst. In older children the lesion tends to locate itself into a more metadiaphyseal or diaphyseal zone and has been defined as the inactive cyst. It tends to regress or heal once skeletal maturity is reached (2,7). The differential diagnosis is usually made to exclude fibrous dysplasia or aneurysmal bone cysts (2,7).

Treatment

In the course of their natural history cysts progress from an active to an inactive phase and may heal spontaneously after completion of growth (2, 13). The quiescent forms often resolve spontaneously with skeletal maturity, but this happens in 7-15% of the symptomatic forms only (2, 14-15). Moreover, often the diagnosis is not possible to determine with certainty if the cyst is in an active phase of involution or quiescence. That is why the choice of treatment can be complicated even because, as literature shows, the treatment of an active cyst may not be successful and the treatment of an quiescent cyst can be successful but unnecessary. However, although there are certain guidelines on the subject, it is believed that if a cyst is incidentally discovered and it is asymptomatic, it is reasonable to observe it over time; should it prove to be active it would then be appropriate to treat it. However, if, the cyst remains asymptomatic and the patient is able to carry out his activities without restrictions, the observation period can be continued because the cyst may resolve spontaneously. An exception is when the lesion is in the subtrochanteric femoral region and, generally, in areas subject to high stress during load, like the femur (2). When the cyst is large, active or associated with fracture, treatment should be commenced immediately. After a pathological fracture, few cysts can obliterate completely, but they may have sufficient stability; in this case surgical treatment may not be necessary. However; if they still show signs of activity after the fracture has healed, treatment is indicated (2).

Aim of the study

An analysis of the literature suggests that different therapeutic methods have been proposed for bone cysts with different results but, nevertheless, none of them proved to be effective for all forms of bone cysts.

The purpose of this study is to review the literature concerning the different therapeutic methods for bone cysts, focusing on the role that growth factors may play in the healing of these lesions.

MATERIALS AND METHODS

We analyzed two patients with unicameral bone cysts treated with synthetic platelet gel after the failure of conventional treatment.

Clinical Case 1 (Fig. 1)

One 6-year-old male patient developed a non traumatic metaphyseal fracture of the proximal humerus on an asymptomatic bone cyst (Fig. 1A). An operation for reduction and fixation with 2 Kirschner wires of 2.5mm was performed. At day 45 radiographs revealed that the fracture appeared healed while the cystic lesion of about 2 x 1cm remained (Fig. 1B). The patient underwent surgery for fixation removal and infiltration with 20 mg of Depomedrol (methylprednisolone acetate) (Fig. 1C).

At the subsequent outpatient visits including follow-up subsequent radiographs and 3 cortisone injections, following an initial clinical improvement of the cystic cavities in the bone marrow, there was a recurrence of active cysts (Fig.1D-F). For this reason, a year after the last surgery, the patient underwent surgery to drain the cyst, perform curettage and stemming of the cyst with bone grafts and synthetic platelet gel, prepared with special instruments using the peripheral blood taken from the patient (Figure 1G).

Clinical Case 2 (Fig. 2)

Eight year old patient with a large cystic lesion, proximal metaphyseal flare of humerus and shortening of the segment compared to the contralateral (Fig. 2A). The patient underwent two infiltration of the cyst with 40 mg of Depo Medrol (methylprednisolone acetate) after three months (Fig. 2B). At the radiographic controls the cyst did not appear healed so the patient underwent 3 autologous bone marrow infiltrations taken from the iliac crest (Fig. 2C-D). Although a slight improvement was observed with an initial filling of the cystic cavity, we decided to perform curettage and synthetic bone stemming (30 cc) with platelet gel, suitably prepared with special instruments using the peripheral blood taken from the patient, to avoid repeated anesthesias and exposure to radiation (Fig. 2E). In subsequent inspections, the cystic cavity appeared completely filled: however, the deformity in the proximal humeral metaphyseal flare remains.

RESULTS

Clinical Cases

In both cases the follow-up visits carried out up to 2 years later, showed that the cystic cavities were completely filled by newly formed bone tissue (Fig. 1H, 2E).

Literature Review

A PubMed search found a lot of studies about the treatment of unicameral bone cysts.

The therapeutic methods proposed over the years, and still valid, range from the more simple injection of corticosteroids to open surgical techniques, as evidence of how far we still are from completely understanding the disease in terms of etiology and pathogenesis.

Injection Techniques

They include the aspiration of the fluid within the cyst, rinsing it with a saline solution and injecting different substances using fluoroscopic guidance.

The rationale for injections with methylprednisolone is the presence of high levels of prostaglandins in the cystic fluid, just like in an inflammatory process. This treatment has produced conflicting results. Scaglietti reported healing of the cyst with less morbidity than resection or curettage with bone grafts (16); other papers have not reported a significant efficacy, but the need for multiple injections and anesthesias. A literature review reveals recurrence rates from 15% to 88% after an average of 3 injections (2, 17-19).

The bone cyst is a cavity where the wall isolates the lesion from the intramedullary veins. High speed saline injections associated with alternating aspiration and injections of the cyst fluid and reaming of the medullary canal opening of vascular channels that connect the bone cyst to the intramedullary venous system, proposed by Gebhart, is based on the need to create a communication channel between the cyst and the endosteal circulation which led to the healing 11 of 12 patients, with an emphasis on the injected agent's (20) action over mechanics.

The injection of autologous bone marrow is effective but needs multiple injection (21-22); Lokiec (23) showed a cure rate of 100% in a preliminary study in which multiple drilling was also performed: however, this rate was not confirmed by Yandow who, without performing the drilling, showed a substantial recovery in 67% of the patients, a partial recovery in 17% and a non-response to therapy in 17% of the cases. Thus the single injection of bone marrow seems to be associated with a higher success rate and earlier recovery; greater efficacy was observed in older patients but there was an increased incidence of fractures compared to other studies (22).

Following percutaneous injections of demineralized bone matrix, Killian reports the obliteration of a 9 out of 11 (82%) cysts at 2-year follow-up after only one administration (24). Bone grafting is used to enhance healing in osteotomies, arthrodesis and multifragmentary fractures as well as to replace bone loss following neoplasia or cysts (25).

The percutaneous injection of bone marrow and demineralized bone matrix showed failure rates of 11% for bone marrow and 11% (26) to 22% (27) for demineralized bone matrix.

Fig.1. *Clinical case n.1.* ***A)*** *Pathologic fracture due to a humeral bone cyst.* ***B)*** *Control 45 days after surgery.* ***C)*** *X-ray control after removal of fixation and methylpredinisolone acetate infiltration.* ***D)*** *X-ray control 2 months after surgery.* ***E)*** *X-ray control 7 months after surgery.* ***F)*** *X-ray control at 1 year postoperatively.* ***G)*** *X-ray control after stemming surgery.* ***H)*** *X-ray control 2 years after stemming.*

The administration of demineralized bone matrix and calcium sulfate, after rinsing with the saline solution and drilling, obliterates the cystic spaces and allows a rapid stimulation of bone growth. Wilkins used this technique to treat 11 patients and none required further treatment, recurrence occurred in one case that still remained asymptomatic (28).

The percutaneous decompression associated with the transplantation of calcium sulfate gave a partial or complete response in 80% of the cases after the first injection and reached 100% after 3 injections (29).

All methods involving the injection of substances into the cystic cavity are based on the perforation provoked by continuous flushing and pressure on the cystic contents, possibly creating contact between the medullary canal and the cavity; thus underlining the importance of the mechanical disruption of the wall rather than the actual therapeutic role of the substances injected.

Surgical Techniques

Resection or curettage associated with bone graft was a technique created in order to provide a definite treatment for unicameral bone cysts: but even this treatment has shown recurrence rates, sometimes higher, ranging from 22% to 64%, that associated with donor site morbidity, have reduced the use of this procedure, favoring less invasive techniques also in consideration of the self-limiting and benign nature of the lesion (2, 14, 30-33).

The aim was to open a window in the cortex, access the cavity, remove the fluid inside, perform the curettage of the fibrous membrane of the cyst wall and implant the bone graft (2). There is no need to use local adjuvants such as phenol or liquid nitrogen (2). To reduce the pathology of the graft donor site, various methods have been proposed, such as subtotal resection without bone graft used by McKay in 21 patients with satisfactory healing in 19 cases and a recurrence rate of 9% (34), the use of allografts, which has proven effective in various studies (12, 35) or bone substitutes such as calcium sulfate have been used successfully with low recurrence rates (11%) (36).

Flexible intramedullary nailing is based on the same principle of the injection: that is, stop the wall, leaving an opening at the same time. This method,

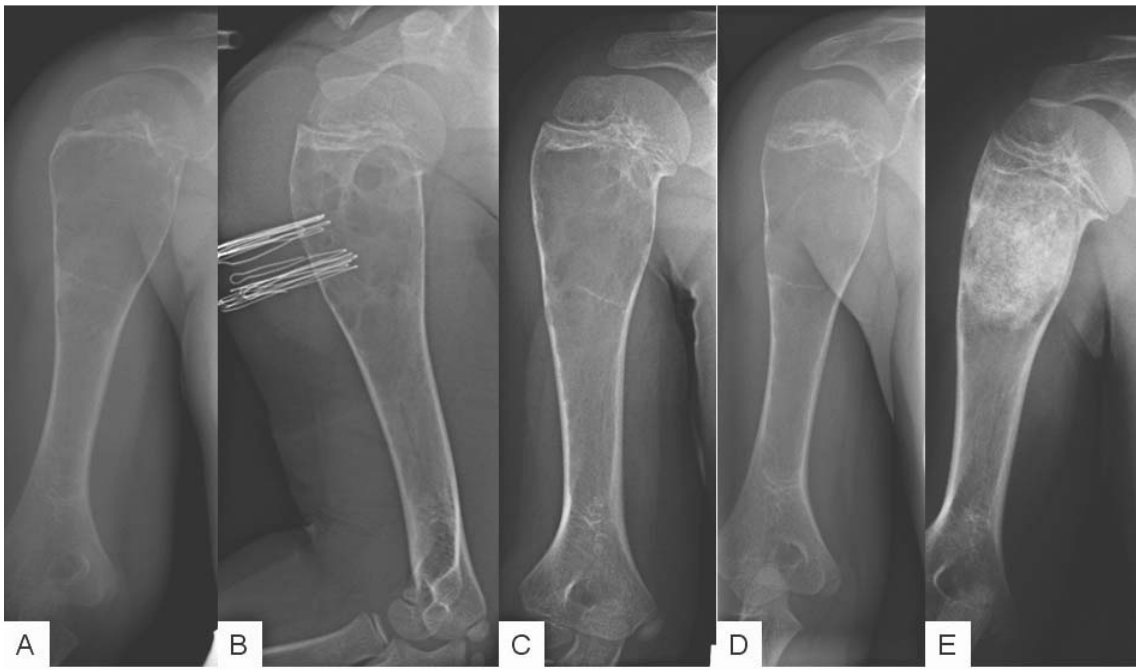

Fig.2. *Clinical case n.2.* ***A)*** *Patient with humeral bone cyst.* ***B)*** *X-ray control after 2 injections.* ***C)*** *X-ray control 2 months after infiltration.* ***D)*** *X-ray control 7 months after the infiltration.* ***E)*** *X-ray control after stemming.*

however, presents failure rates varying from 0% (37) to 6% (38) and is associated with the need to substitute the nail as it shortens during growth in 28% (38) of the cases presented. De Sanctis has shown a complete recovery in 65.9% and in 34.1% healing with a residual radiolucent lesion without recurrence. Hence, he has concluded that this method can solve the disease over time and, in experienced hands, is the best method for treating bone cysts in long bones in children 37. Roposch reported 14 cases out of 16 of complete healing with residual radiolucent lesions, thus a positive response to treatment for all cysts but there was a need to change the nail in 9 cases, hence also for this author, the treatment method was considered excellent (38).

The drilling tool powered with or without K-wire presents failure rates after the first treatment ranging from 27% (8) to 52% (39). Chigira reported 10 cases in which there was recovery after the drilling. The use of only one rig leaving a Kirschner wire proved to be a valid therapeutic method in the prevention of local recurrence (40), although in some cases, the removal of the wire was then followed by recurrence of the cyst (40). Shinozaki treated 23 simple bone cysts with multiple perforations using a motorized instrument; recurrence of the cyst occurred in 15 cases after the initial operation. Twelve patients were re-operated; there was a good follow-up bone formation without signs of recurrence in 15 cases, while a residual cyst was found in 8 cases without treatment (39).

The percutaneous drilling may normalize the local circulation and unblock venous obstructions (11).

Furthermore, several studies have shown the efficacy of platelet gel in the treatment of bone defects and this technique can also be used to treat bone cysts (41-42).

The experience reported is based on a combination of the mechanical curettage of substitute bone and platelet gel in lesions that were not responsive to corticosteroids followed by bone marrow injections. These cases are carefully selected, however, because we believe that percutaneous techniques are preferable to open ones but in active lesions, particularly large ones, it is difficult to believe that a percutaneous action can guarantee success, at least in terms of making the cysts inactive.

DISCUSSION

From the analysis of the literature comparing the various treatment methods, conflicting results emerge. From the study by Sung et al., we see that the failure rate after initial treatment with steroids was 84%, 64% with curettage and 50% with the use of a combination of steroid-demineralized bone matrix and bone marrow aspirate (SDB). Failure occurred earlier with steroids and the failure rate after re-treatment with steroids was 76%, 63% with curettage and 71% with SDB. In addition, 18% of the patients initially treated with steroids had a subsequent pathologic fracture compared with 2.6% of patients treated with curettage and 12% with SDB. So the authors concluded that SDB is more effective as an initial treatment in association with steroids and offers lower morbidity compared to curettage; therefore it should be considered as the first line of treatment for simple bone cysts of the humerus and femur in patients under 20 years old, and curettage has a better chance of success as a second line of treatment (14). Chang et al. have compared treatment with aspiration and injection of bone marrow to aspiration and steroid injections. Of the 79 patients analyzed, 14 received a total of 27 injections of bone marrow and 65 a total of 99 injections of steroids; repeat injections were required in 57% of the patients who had received bone marrow and in 49% of those who had received steroids, thus concluding that the advantages of using bone marrow compared to steroids (34) could not be shown.

The only randomized controlled trials for the treatment of bone cysts show that injections of steroids have a cure rate of 42%, higher than that of bone marrow injections which was 23% (43).

Oppenheim, comparing curettage with bone grafts associated with steroid injections, reported higher rates of recurrence and complications in the group that underwent surgery (17). Farber did not find mean differences between the two groups (30) and Glaser, on the other hand, in treating cystic lesions of the heel, concluded that surgical treatment is associated with greater success (44).

Canavese et al., comparing three methods of treatment, shows that at 2-year follow-up, patients who have undergone curettage and percutaneous intra-medullary decompression have had a cure rate of 70% compared to patients who have been administered bone marrow injections (21%) and injections of methylprednisolone (41%), suggesting that the mechanical destruction of the membrane and the decompression of the cysts can be helpful in activating the osteogenic potential of bone healing and thus the lesion, and that this technique may be preferred to the simple intralesional injection (45).

Di Bella et al. compared the healing rate of patients treated with multiple injections of corticosteroids and a single injection of demineralized bone matrix combined with bone marrow. The second method showed a higher healing rate (58% versus 21%), a higher failure rate after a single injection of steroids (63%) compared to a single injection of demineralized bone matrix and aspirated bone marrow (24%) (31). Hou demonstrated that minimally invasive methods such as curettage, cauterization with ethanol, breaking the cystic membrane, the inclusion of calcium sulfate and the placement of cannulated screws to allow drainage, have a more favorable outcome than the injection of steroids and bone marrow transplantation and open curettage with calcium sulfate and internal fixation (46). The treatment we propose is placed on the same path of the methods of debridement and decompression of the cysts, but also considers the combination of mechanical debridement and decompression of the cysts with the effect of the combination of osteoconductive tricalcium phosphate based bone substitutes and platelet gel. The main advantage is the accuracy of the surgical decompression and the residual cavity filling with known volumes of platelet gel and, therefore, of growth factors with an osteoconductive effect. The limitations of this method, which must be reserved for very selected cases not responding to percutaneous treatment, is that the surgical scar is larger than that obtained in percutaneous decompression, surgery will be slightly longer due to the time necessary for preparing the platelet gel and, of course, the increased costs caused by the combination of platelet gel and bone substitutes. However, it must be remembered that these methods, although very invasive, do not expose the pediatric patient, to numerous percutaneous treatments, often performed under general anesthesia, with repeated exposure to radiation, but with all the necessary precautions.

CONCLUSIONS

In conclusion, Donaldson (47) argues that at present the only evidence-based treatment is represented by injections of steroids, however, this method is burdened with a large number of failures: therefore, different and more aggressive methods must be considered. Curettage, either open or percutaneous, may be a solution after the failure of percutaneous methods: in most cases the percutaneous method can be considered; however, in large bone cysts or in non responsive bone cysts, the mechanical action of a suitable open curettage, combined with the osteoconductive action of the platelet gel and bone substitutes, is a valid treatment option in well selected cases. The limits of this method are a larger surgical wound, increased cost and surgical time because of the preparation of platelet gel. However it must be remembered that these methods, though more invasive, do not expose the pediatric patient to numerous percutaneous applications, often under general anesthesia, nor to repeated radiation exposure.

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DIFFERENT TREATMENT MODALITIES OF HAND ENCHONDROMAS: A REVIEW OF THE LITERATURE

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Enchondroma is the most common benign cartilage tumor of bone and the most common bone tumor in the hand. Fracture is a common complication of this pathology. Intralesional curettage surgery is the treatment of choice for hand enchondromas and various modalities of bone reconstruction have been proposed. The aim of this study was to analyze the literature in English concerning surgery in hand chondroma, taking into account modality of treatment, results and possible complications.

Enchondroma is the most common benign cartilage tumor of bone and the most common osseous tumor in the hand (1).

The small bones of the hand are the most frequent anatomic site for enchondromas with approximately 40% of the cases occurring at these sites. These lesions are most frequently located in the proximal phalanx, followed by the middle phalanx, metacarpals, distal phalanx, and, rarely, in the carpal bone (2).

Fracture of the affected bone is a frequent complication of this benign tumor. Surgery is considered the only treatment needed for treating the tumor, for excluding histologically the rare malignant cases, and for fracture and preventing possible deformity.

Different surgical techniques have been used in the management of enchondroma:

- curettage;
- curettage + homologous bone graft;
- curettage + autologous bone graft;
- curettage + cancellous bone grafting;
- curettage + complementary actions.

The aim of this study was to analyze the literature in English concerning surgery in hand chondroma, taking into account modality of treatment, results and possible complications.

REVIEW OF THE LITERATURE

Curettage without bone filling

The first choice in treating hand chondromas is curettage without filling the bone cavity, as reported firstly by Tordai et al. in 1990 (3) , and then confirmed by Hasselgren et al. in 1991 (4) and Goto et al. in 2002 (5). More recently this technique has been demonstrated to be useful because the curettage of small bones does not usually require bone filling.(6).

In fact if a fracture site is surrounded by a hematoma, which will be invaded by multipotent mesenchymal stem cells that differentiate into osteoblasts with this biological process resulting in new bone formation and fracture healing, the same process will be expected in a bone cavity filled with blood following curettage of enchondroma.

Key words: hand enchondroma, benign bone tumor

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Consequently, new bone formation and remodeling will occur in the bone defect following curettage even without bone grafting.

The possible advantages of this technique are to eliminate pain and discomfort at the bone donor site and to reduce operation time, costs and risk of infection.

There were no postoperative pathological fractures after curettage. No infections or other complications were observed because the lesions were small and the conditions of surrounding bone and soft tissue were good. These are important factors for achieving satisfactory new bone formation and remodeling without resorting to bone grafting (3-6).

Curettage with bone filling

Many authors recommend that after curettage of benign bone tumors, the defect should be filled with bone grafts or substitutes. The rationale to fill the defect seems to be the final increased bone strength, minimizing the bone defect volume and reducing the local recurrence risk.

Autogenous bone grafting from the iliac crest (7-9) has the advantage of there being no immunological reaction but a good bone induction. However it may not be able to provide enough bone graft if there is a large defect that needs to be filled and there may be complications at the donor site, such as chronic pain, infection and undesirable scars.

Table I. *Numbers and recurrence rates in several large studies*

Study	Surgical method	Follow-up time (in years)	Number of patients	Recurrences	Recurrence rate	Recurrence at 1 year
Gaulke et al. (28)	Curettage + autogenous bone graft	9	21	3	14.2%	1.59%
Baer et al. (13)	curettage + hydroxyapatite	> 5	16	0	0%	-
Bauer et al. (10)	curettage + allograft bone	2.9	12	0	0%	-
Kuur et al. (27)	various	4.7	20	0	0%	-
Hasselgren et al. (4)	curettage	6.0	28	0	0%	-
Tordai et al. (3)	curettage	6.5	44	1	2.3%	-
Gaasbeek et al. (18)	cancellous bone graft	4.5	17	0	0%	-
Machens (30)	>90% cancellous bone graft	6.0	73	1	1.4%	-
Takigawa (7)	>90% cancellous bone graft	5.9	110	5	4.5%	-

In order to avoid donor-site morbidity of the iliac crest some authors (10-11), have proposed using allograft chips. These grafts are osteoconductive, acting as a scaffold upon which new bone can form but they have the theoretical disadvantages of tissue banking: they may take longer to adapt to the region they are placed, they may be immunologically rejected by the receiver or act as a viral infection carrier. The efficiency of the procedures involved in bone allograft banking has improved significantly over the last three decades. The incidence of reported adverse reactions and events reflects positively on the safety of transplanted tissues. In fact, in response to infections associated with the implantation of allograft tissue, some tissue banks have developed methods to sterilize allograft tissue.

Cases of infection transmission by allografts occurred mainly with those that contained viable cells, had not been processed to remove cells, or were not disinfected or sterilized (12).

However, Bauer et al. reported that they had never observed these complications (10).

Furthermore, materials such as hydroxyapatite have also been used to fill the cavities (13-14)

Putting hydroxyapatite in the cavity has become a common procedure due to its osteoconductive effect. However some investigators have attributed the local pain observed in some cases to the irritation caused by hydroxyapatite interacting with human monocytes which leads to the release of inflammatory cytokines (15-16).

Packing of defects with methylmethacrylate cement, calcium phosphate bone cement or plaster of Paris tablets gives immediate stability, especially for lesions located near joints (17-19). The thermal shock of cement polymerization induces several millimeters of bone necrosis, which may kill residual tumor (20). Moreover cement gives a degree of mechanical strength that is sufficient for immediate weight bearing but it has no osteogenic potential. Bickels et al. used polymethylmetacrilate and k-wire within the tumor cavity without observing postoperative fractures or infection. However, they did report a reduced range of motion probably due to the effect that lesion expansion has on neighboring soft tissue or to the exposure of large lesions which creates greater potential scar tissue formation, which, in turn, could compromise postoperative range of motion (22).

DISCUSSION

Enchondromas are usually painless because of their slow growth, minimal peritumoral reaction and avascularity.

Enchondromas may be present with localized swelling and deformity, with or without pain; they may be discovered accidentally during an unrelated X ray examination but more often they are found after pathological fractures caused by structural weakening. Dysfunction of the extensor and flexor tendons of the fingers as a result of fracture have also been described (22).

Radiologically, a single enchondroma appears as a well-defined, geographical osteolytic lesion that is usually centrally located within the metadiaphysis. The cortex remains intact, although it may be thinner due to endosteal scalloping and expansion. This remodeling leads to fractures (1-2).

According to biomechanical studies (8), slow-growing tumors are characterized by a progressive thinning of cortical bone associated with bone swelling due to an increase in diameter of the segment affected. This situation leads to a condition of segmental iso-resistance, so the occurrence of a spontaneous fracture is more unlikely than the X-ray images lead us to believe.

Microscopically, benign cartilage is seen. High cellularity may be present in enchondromas of the hand, but any sort of mitotic figures may be seen. Histologically, an enchondroma originates from groups of chondrocytes in the growth plates and then forms extending columns of uncalcified cartilage under the growth plates. This growth may then be walled off and proliferate further to form an intraosseous chondroma (1).

Malignant transformation of a benign solitary enchondroma to chondrosarcoma is rare, however the borderline between enchondroma and chondrosarcoma is not clearly defined (23)

A low-grade chondrosarcoma can follow an aggressive course even when it is histologically indistinguishable from an enchondroma. Therefore, additional methods are needed to help identify the biological potential of these tumors. The degree of angiogenesis that is induced by the tumor may assist

the physician in this task.

Our ongoing studies are trying to identify, by cytometric DNA analysis, the expression of growth factors linked with grade, local recurrence and the metastatic potential of the tumor (24).

Cartilage in normal adult tissue is considered an avascular tissue, although the hypertrophic layer produces angiogenesis activators.

Angiogenesis is a fundamental step in both the neoplastic transformation and the regulation of tumor growth. The interaction of vessels with cartilaginous tissue is not a physiological step, except during skeletal development. Thus, the presence of vessels within cartilaginous tissue is associated with pathological conditions, such as osteoarthritis and tumors.

Recently the direct correlation among expression of VEGF, other growth factors, proliferation markers (such as TGFβ2, Ki-67, TNF, p53, FGF1) and the malignant course of cartilaginous tumors has been demonstrated (24)

Based on this some authors have suggested that radiological and clinical findings are the most decisive factors for the choice of treatment but should there be the suspicion of a malignant disease, a cytometric DNA analysis should be performed in order to reduce the risk of degeneration or metastasis (25-26).

The gold standard in the management of hand chondroma is intralesional curettage, which creates a bone defect.

Curettage alone plays an important role in preventing recurrence (27). According to the literature, the recurrence rate of enchondroma ranges between 0% and 13.3% without significant differences between the techniques used.

However there are no prospective data regarding the time of radiological appearance of recurrent enchondroma. Recurrence may occur even more than 10 years postoperatively. Clinical examinations alone are insufficient because cortical erosion may remain asymptomatic until a fracture occurs. In view of the slow growth of solitary enchondroma, re-evaluation intervals of 2 to 5 years should be adeguate (28).

Most surgeons who operate hand enchondromas perform curettage followed by augmentation of the bone defect using autologous bone grafting or bone graft substitutes however over the last decade, simple curettage without bone grafting or bone substitutes has been tried and good clinical results have been reported (29).

Leaving the bone cavity after curettage causes concern regarding instability and weakness. Bone grafting fills the cavity but cannot offer immediate stability until the bone begins to remodel. Plaster of Paris can offer some immediate stability, but there is evidence of marginal bone resorption even after 2 weeks. On the other hand the use of hydroxyapatite cement has the advantage of offering immediate stability that is not resorbed quickly like plaster but no studies have evaluated the long term success of the method.

Unfortunately. no method has been demonstrated to be fully satisfactory. Autologous bone graft is limited in supply and is often associated with significant donor site morbidity, while the use of allografts or xenografts may increase the potential risk of infection and/or cause an adverse immune response by the host tissue after implantation. In addition, while biomaterials have the advantage of unlimited availability and good osteoconductivity, their application is limited as they lack osteoinductivity.

There is no doubt that new bone formation and remodeling occur in the bone defect following curettage even without bone grafting. In fact the bone cavity will fill with blood and be invaded by mesenchymal cells that differentiate into osteoblasts, and subsequently form new bone to fill in the cavity.

In our experience and by analyzing literature we found that both the prognosis after curettage and insertion of autogenous bone graft or allograft and curettage alone have been reported to offer satisfactory results. Accurate curettage is the gold standard to healing and preventing recurrences but we strongly believe that functional stability and the structural integrity of the bone and adjacent joint must be maintained.

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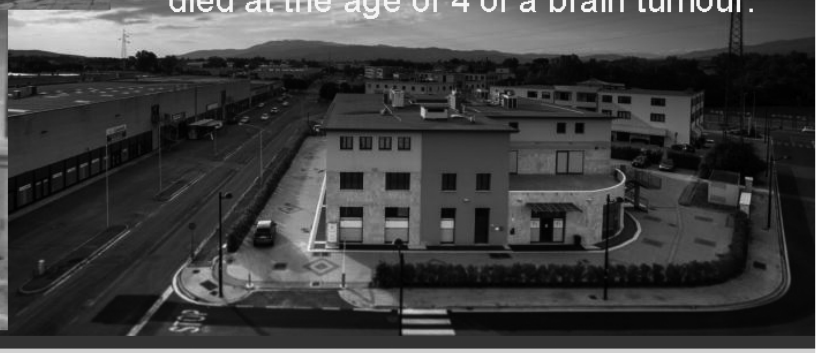
The Foundation was constituted on November 21, 2006 with the name of Nicola's Foundation ONLUS, in memory of Prof. Giuliano Cerulli's son Nicola, who died at the age of 4 of a brain tumour.



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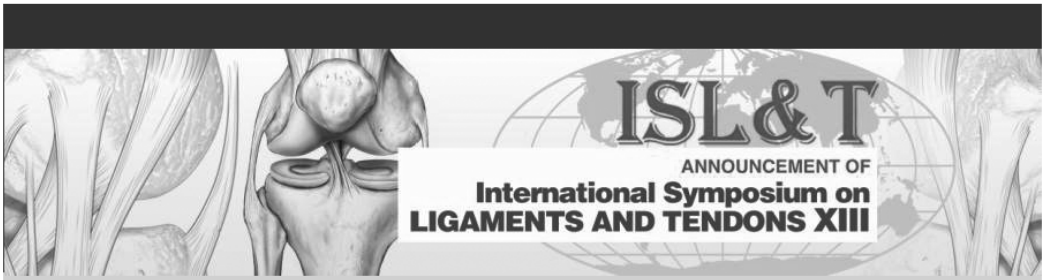

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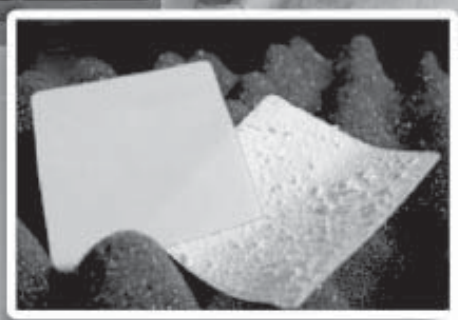

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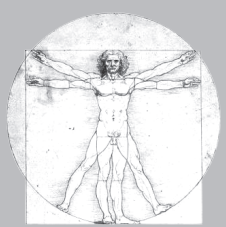

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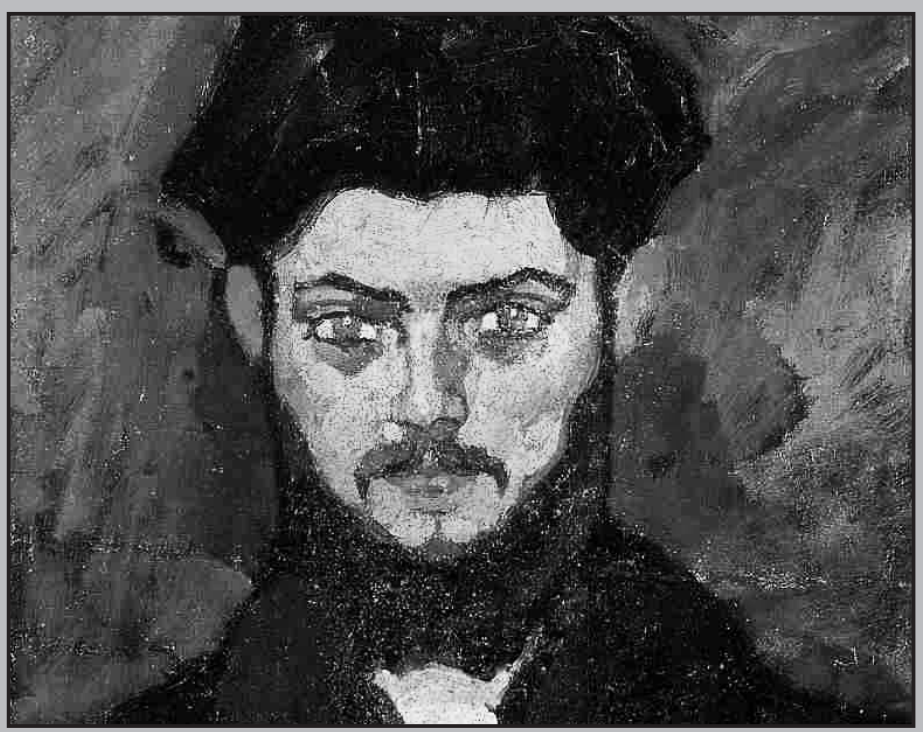

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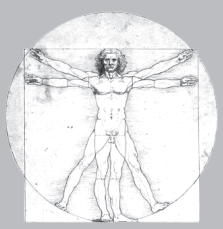

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