Treatment of Metastasis in the Appendicular Skeleton

Tratamento das metástases no esqueleto apendicular

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Abstract

Bone metastases may evolve with events (pain, fractures and compression) that the orthopedic surgeon will encounter regardless of his subspecialty. Accumulated surgical knowledge is predictive for the prevention of impending fractures, as well as of pathological fractures. We will present a guide to properly evaluate and conduct a patient with bone implant for surgeons who are not specialists in this area.

Keywords
- bone neoplasms
- metastases
- fractures, pathologic/surgery
- carcinoma

Resumo

As metástases ósseas podem evoluir com eventos (dor, fraturas e compressão) com os quais o cirurgião ortopédico irá se depararar independentemente da sua subespecialidade. Os conhecimentos cirúrgicos acumulados são predicativos para a prevenção de fraturas iminentes, assim como de fraturas patológicas. Apresentaremos um guia para avaliar e conduzir de forma adequada um paciente com implante ósseo para cirurgiões que não sejam especialistas na área.

Palavras-chave
- neoplasias ósseas
- metástases
- fraturas patológicas/cirurgia
- carcinoma

Introduction

There is an increase in overall survival not only of patients but also of the human being. The causes of mortality in developed countries have already changed, and cancer has become the main cause in these countries. In addition, patients live longer and with a better quality of life.[1]

In the medical career, the orthopedic surgeon will probably evaluate patients with bone metastases, having enough orthopedic capacity and knowledge to be able to guide appropriate treatments for the impediment of fractures as well as of pathological fractures of the extremities. In cases of greater complexity, patients should be referred to the specialist in the area. In the present article, we will focus on guidelines for an appropriate treatment in cases of risk or pathological fracture of the limbs.[2]

The prevalence of bone metastases reaches 280,000 affected patients per year, and the costs of properly handling these patients are high, ~ 13 billion dollars.[3,4]

Complaints of musculoskeletal pain, especially low back pain, are the second cause of consultations in patients > 40 years old, and metastatic disease may present with diffuse and persistent symptoms.

Pain is the most prevalent initial symptom in the appendicular skeleton.

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The purpose of the present article is to review and to expose ways of presentation, diagnosis, and treatment of metastasis in long bones.

Clinical presentation

Patients may present as follows: 1) previous history of neoplasia; 2) in treatment; 3) with bone pain and pathological fracture without a known history of neoplasia; these patients are called "primary unknown". In these patients, there is a need for caution in the decision-making process, as it may be a primary neoplasm or metastatic adenocarcinoma, which occurs in $\sim$ between 15 and 20% of the cases.[4,5]

Pain is the cardinal symptom and is described as a warning sign. The most typical pains are nocturnal pains, stinging pains and *pang pain*, pains that do not improve with common analgesics and reoccur in the same place. The famous *"moving pain"* is not typical, and the most severe pains are those that denote disabling pain, such as pain on supporting oneself and those that determine lameness. These are more severe, as they may be a sign of fragility or an imminent pathological fracture. Therefore, the concern should be over the persistence of pain or discomfort for >2 weeks, and it should be investigated with imaging exams (radiography/computed tomography [CT] and magnetic resonance imaging [MRI]) of the painful or referred site.

Occurrences are more frequent in the upper body and in the proximal part of the limbs: the spine; the pelvic region; the shoulder; and the distal femur.

Metastases below the knee and elbow, acrometastases, are rare and are more often associated with lung, renal and thyroid neoplasms.

On physical examination, it is recommended to examine the limbs, observing the mobility, pain limitations, dysmetria, edemas, masses, collateral circulation, and measurement of the circumference of the limbs. It is essential to perform the examination of the thyroid, lymph node chains, pulmonary, cardiac, abdominal auscultation, breast examination, both in females and males, in addition to digital rectal and gynecological examination.[4] Since these are not part of the orthopedist's practice, it is necessary to have communication with related areas for a complete clinical evaluation.

Imaging exams

In radiology, the secondary implant in the bone depends on the localization. It is easier to understand it by looking at the cross-section of the bone: we observe whether the lesion compromises the cortex or the bone marrow and, translating to radiography, cortical lesions are easier to diagnose than medullary ones, because spinal cord lesions will be visible on radiography when at least between 30 and 50% of the bone is replaced by neoplastic tissue; on the other hand, in the bone cortex, the evidence of lytic injury ranges from 10 to 20%. This difference determines a longer time for diagnosis by radiography; therefore, tissue localized in the cortex is more easily diagnosed than in the bone marrow.

It is more common for metastases to start in the medullary bone. Lesions are typically permeative lytic or in moth noise (erroneously, but popularly called "pouched-out erosion"), with the possibility of having both in the same bone. Periosteal reactions may also be absent due to aggressive activity, since the more severe they are, less local reaction and typical unilamellar reactions they cause, multilamellar and Coodman triangle are not present, and tissue production related to the source gland is also present. Blast lesions occur in prostate metastasis and in subtypes of breast metastasis. They are calcifications with a "dense tissue" description fitting better than labeling the lesions as "blastic". The lytic lesions, which correspond to the majority of cases, do not induce specific tissue nor, quite often, the reactional type. In short, the affected tissue may have little reactional response, and the neoplasm determines greater destruction.

Good quality radiographs in two positions (anteroposterior [AP] and posterior [P]), followed by TC and MRI analysis (which has better accuracy), can provide the staging and the actual extent of the neoplasm and its involvement in vessels and nerves. Multislice scans provide greater clarity analysis of fractures and bone destruction, with a greater amount of information and better choice of implant. Tc99 bone scintigraphy is commonly used to find other sites affected by metastases, and, in suspected multiple myeloma, a radiological inventory of the skeleton has greater accuracy than scintigraphy in the identification of lesions.[6]

If the presentation is of unknown primary neoplasia, it is recommended to perform full oncological staging, radiography of the affected site, axial CT) of the chest and total abdomen, in addition to bone scintigraphy. These tests identify 85% of the primary tumors, a rate that is reproducible and in line with a Brazilian study series by Garcia-Filho et al.[6] Complemented with endoscopy and colonoscopy, thyroid ultrasonography, and mammography for women, diagnosis rates can reach $>90\%$.[7]

Positron emission computed tomography (PET-CT) can replace this larger number of tests, which may shorten the investigation time, but the cost is higher than those of other exams and a smaller number of centers perform it, since PET-CT is restricted to indication by regulatory norms and not primarily by medical indication.[7] The marker with the best metabolism in prostatic lesions is Prostate-Specific Membrane Antigen/ PET (PSMA-PET), otherwise, Fluorodeoxyglucose-Positron Emission Tomography (^{18}F.FDG-PET) is sufficient.

Laboratory tests

Laboratory tests may not be altered and should be performed, seeking differentiation from hematological diseases such as multiple myeloma and lymphoma: blood count; metabolic panel; urine with sediment; erythrocyte sedimentation volume (ESR); ultra-sensitive c-reactive protein (CRP); parathyroid Hormone (PTH); electrophoresis of the protein of the form, and urinary protein. If present, alterations may indicate a neoplasm. But they are not pathognosomes.[7]

Pathological anatomy

Biopsy is recommended when the primary lesion is not known or if this is a single lesion. This analysis is necessary to differentiate bone sarcoma from single metastatic lesions. The use of 1.5-mm-diameter trephines, guided or not by computed axial tomography (CAT), is a method of choice, and open biopsy can be performed in selected cases or in negative cases of percutaneous biopsy. If it presents with pathological fracture and there is a fixation plan, biopsy with freezing is a good tactic because it provides minimal differentiation between metastatic adenocarcinomas and primary neoplasia. In the confirmation of adenocarcinoma, surgery can be continued and, if it is inconclusive, the wait for the final result of pathological anatomy is the recommended approach.

It is recommended that the biopsy be performed in a medical center where there is capacity for definitive treatment of the patient, because inadequate biopsies may determine morbidities that determine greater resection of normal tissues and bone, function and/or local recurrences. Poorly planned CT-guided biopsies also change the course of treatment.[8]

Treatments

Treatment will depend on the diagnosis, and this includes both the origin of the primary tumor as well as the extent of neoplastic disease in organs and bones. In asymptomatic patients, radiological evaluation using some mechanical criteria, defined as: No risk of fracture - we can perform periodic observation using imaging methods at each return appointment, and the response or not after therapies will define the future treatment.

Symptomatic patients who do no present risk of pathological fracture may be candidates for external radiotherapy. Today, modern techniques have decreased local complications and decreased lymphoedemas in the extremities. The use of fractioned 30 Gy favors adequate local control, but it may not have the expected response and may compromise a future surgical treatment (mainly lesions that do not respond to radiotherapy). After treatment with radiotherapy, surgical infection rates will be higher, so smaller lesions are preferred for this method,[9] but the largest lesions should preferably be operated. Those with multiple lesions without risk of fracture may be candidates for pharmacological and radiotherapy treatments.

The possibilities of treatments in specialized cancer centers favor the reduction of complications. However, the local reality is determinant for orthopedic treatment; therefore, knowledge of trauma surgery is decisive to treat most metastatic lesions of the extremities, especially when it comes to fracture avoidance. This condition has fewer clinical and local complications, such as bleeding, hospital stay, and infections, as well as better function and survival.[10]

Mirel's criteria should be used because they have a high predictive value of fractures. They are (see ►**Table 1**).

If the sum of the evaluated variables (location; size; pain; and tissue) is < 8, the chance of fracture is $< 15\%$, and if it is > 8, the chance of fracture is $> 30\%$.

Table 1 Mirel's point scale for prophylactic fixation of pathological fracture impediments[11]

Score	1	2	3
Location	Upper limb	Lower limb	Peri trochanteric
Pain	Mild	Moderate	Strong
Size	$<1/3$	$<2/3$	$>2/3$
Feature	Blastic	Mixed	Lytic

Computed tomography can be used, since it gives us a rigorous evaluation of the size of the lesion, and it is possible to better determine the tissue matrix.[11]

After the surgical treatment criterion is established, the next step is planning. In the case of patients who are eligible to prophylactic fixation of pathological fractures, it is necessary to decide based on survival criteria, level of pharmacological therapeutic response and/or radiotherapy, in addition to their functional condition. The surgeon should question the surgical risk/benefit: will the reconstruction technique allow immediate functional recovery, and be prophylactic for possible metastasis progress, in addition to allowing other treatment modalities, such as radiotherapy.[12]

►**Figure 1** is an example of inadvertent evaluation of the pathological fracture, after which the patient spent several months unable to walk.

Performance evaluation includes surgical risk, Goldman classification, and anesthetic evaluation. Oncological evaluation to determine life expectancy is difficult, and its accuracy is low. Several factors, such as blood count, number of metastases, Karnofsky index, or Eastern Cooperative Oncology Group Score are used.[12]

Surgery should provide an immediate functional recovery reconstruction, and the use of intramedullary rods and

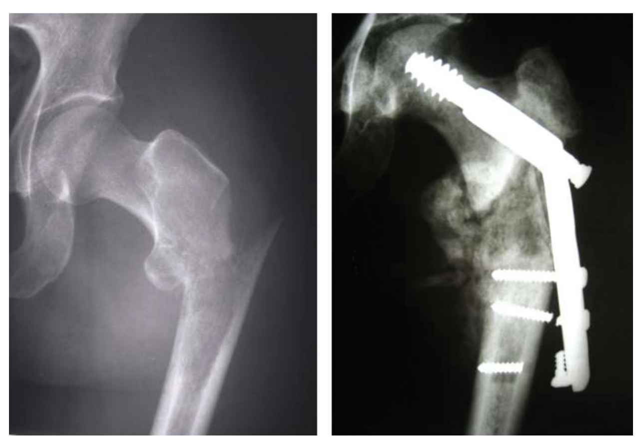

Fig. 1 45-year-old patient, fall from own height at home, shows a perceptual litic lesion in the region near the fracture. The incorrect interpretation of the image led to surgical treatment as a conventional fracture, submitted to fixation with plate and sliding pin without cement, which evolved with loosening because there was no consolidation due to metastatic disease. The patient could not walk for months, being treated with chemotherapy. Finally, the tumor was resected and replaced by unconventional endoprosthesis, allowing early ambulation.

metaphyseal or diaphyseal plaques by minimally invasive techniques are recommended in association or not with bone cement. Open curettage of the tumor with the aim of filling the area of the failure with bone cement has the disadvantages of removal in pieces, local contamination, longer surgical delay, bleeding with increased risk of infection, and the need for radiotherapy in the postoperative period, but allows rapid functional recovery.[12,13]

In the case of the use of bone cement in association with intramedullary nail, the cement should be used in a way that it is of low viscosity, with low pressurization, canal washing with iced serum (vasoconstriction of the endoconsteum), and adequate hydration of the patient before introducing bone cement. The rods or plates should be long in order to protect all the affected bone.[13,14] A study by Narazaki et al.[15] shows that survival in patients treated with intramedullary nail without bone cement had a better survival than those treated with endoprostheses, because they were less bitten surgeries.

In ►**Figure 2**, initially, the trial was of a patient with metastatic pulmonary and bone hepatocarcinoma, with fixing using intramedullary nail bone cement. The disease was controlled in the lung with new antineoplasic drugs, and the patient needed a replacement with endoprosthesis because there was progression of the disease in the hip region. In addition to the replacement, auxiliary external radiotherapy was performed.

In case of pathological fractures with an area that is not possible to be minimally filled with cement, such as where there is impairment of the regions of tendinous insertions, as in trochanters, and if the minimum reconstruction will be of dubious stability, conventional or unconventional prostheses should be used, and prostheses without cement should be avoided because bone plasticity for fixation under impaction may be altered due to cancer treatments, which determine an osteopenic fragile bone, or by adjuvants such as biphosphates, which give a greater hardness to the bone, making them prone to fractures during the impaction procedure. Osteopenia promoted as paraneoplastic syndrome will also not allow adequate fixation. In addition, another recommendation for not using the prosthesis without cement is that the use of radiotherapy in an adjuvant way in the postoperative period prevents the fixation of the prosthesis, preventing the growth of the bone around it and, consequently, its fixation.[13,14]

Endoprostheses promote, with resection of the metastatic lesion, a greater local control than intramedullary stems and plaques; however the nonfixation of tissues around the endoprosthesis both for the upper limb as well as for the proximal femur causes great functional loss. Reverse endoprosthesis can increase the maintenance of shoulder function, since it does not extend beyond the deltoid muscle insertion; if this happens, it is necessary to use a constricted reverse endoprosthesis that is not as available as proibais humeral endoprosthesis.

In the proximal femur, numerous attempts to restore hip abduction were fruitless, but a postdoctoral thesis at the Universidade de São Paulo, state of São Paulo, Brazil, in which the musculotendinous transfer of the iliotibial tract is allowing the restoration of abduction and the consequent disappearance of the Trendelenburg sign is in the publication phase.[16]

In ►**Figure 3**, due to the initial presentation being of unknown primary neoplasia at the oncological staging, it is seen to be a renal and single neoplasm, performing a wide resection and replacing by endoprosthesis and musculotendinous transference of the iliotibial tract, had evolution with heterotopic ossification but without compromising hip function.

The use of drains is necessary due to the magnitude of the surgery and to the effects of cardiac medications, especially,

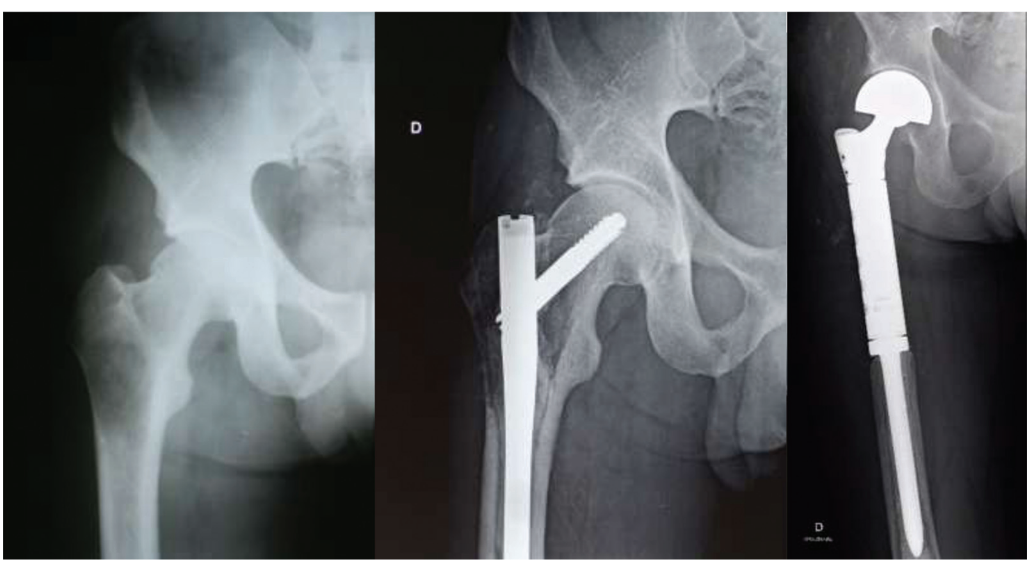

Fig. 2 Patient, 39 years old, liver transplant due to hepatitis, develops hepatocarcinoma before transplantation, which was diagnosed in the pathologic piece, post-transplant, and presented with proximal nonfemur bone metastasis and pulmonary metastasis, with criteria for preventing the fracture but with reserved prognosis, submitted to surgery for impediment with medullary nail, but had response in pulmonary lesions and progress in bone lesions, being submitted to resection and replacement by endoprosthesis, complemented with radiotherapy due to previous contamination in the placement of the intramedullary nail in the femur. The patient survived for 3 years and 4 months after a reversal to endoprostheses.

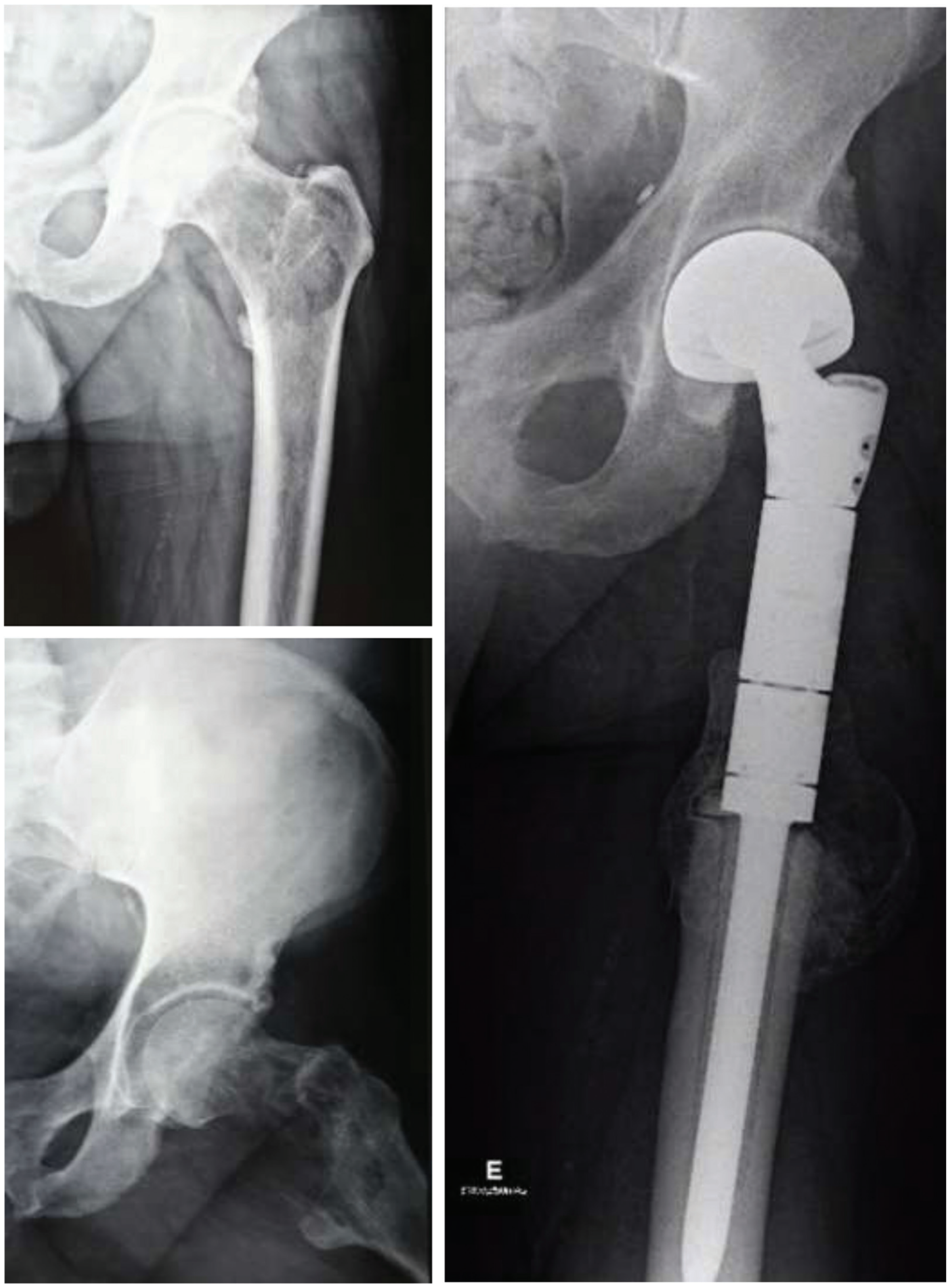

Fig. 3 Male patient, 59 years old, presents with pain in the proximal region of the thigh. The initial treatments were for trochanteric bursitis. Evolving with disability, he is hospitalized, and a perceptual litic lesion in the intertrochanteric region of the proximal femur is diagnosed. At staging, it is seen that it is a single lesion originated from renal neoplasia, which was submitted to resection and replacement by endoprosthesis, with local control without the need for radiotherapy. The patient is alive after 3 years due to new treatment modalities for renal cancer; he developed heterotopic ossification around the prosthesis, with autonomy for daily routine.

which increase postoperative bleeding and result in a higher risk of infection.[13,14]

Postoperative control

Early mobility and respiratory physiotherapy should be implemented in the first 24 hours. The management of clinical and oncological problems should be multidisciplinary. The postoperative use of antibiotics should be during 48 hours with reduced risk of infection. The risk of deep vein thrombosis should also be prevented; the use of CS or oral anticoagulants should be extended due to the surgical and inherent risk of paraneoplastic syndrome. The worst-case scenario occurs in areas where radiotherapy has been applied, or in the presence of chemotherapy or immunotherapy effects, which may be determinant in tissue

Table 2 Suggestion of orthopedic treatment for the impediment and treatment of pathological fracture, in order of higher frequency of occurence

Affected site	Preventing pathologic fracture*	Treating pathologic fracture
1. Proximal femur 2. Femur diaphysis 3. Distal femur	1. Cephalomedullary nail or partial prothesis 2. Cephalomedullary nail 3. Retrograde rod or plate/screw	1. **a:** head/neck: partial hip arthroplasty (PHA) long rod with cement. **b**: inter trochanter: endoprosthesis or long IM rod with PMMN 2. IM rod with PMMN/diafiseal endoprosthesis 3. Distal femur endoprosthesis or plate/screw with PMMN
1. Proximal humerus 2. Humeros diaphysis 3. Distal humerus	1. Long plate and/or long IM rod 2. IM rod 3. Plate/screw	1. Endoprostheses of proximal humerus or plate/screw with PMMN 2. IM rod with PMMN/diafiseal endoprosthesis 3. Partial elbow or total endoprosthesis. plate/screw with PMMN
1. Proximal tibia 2. Tibia diaphysis 3. Distal tibia	1. Plate/screw 2. IM nail 3. Plate/screw	1. Pate/screw with PMMN or proximal tibia endoprostheses 2. IM rod with PMMN/diafiseal endoprosthesis 3. Plate/screw with PMMN or arthrodesis with structural graft or amputation
1. Proximal ulna 2. Ulna diaphysis 3. Distal ulna	1. Olecranon plate 2. Plate/screw and or flexible rod 3. Plate/screw	1. Plate/screw with PMMN or elbow endoprostheses 2. Plate/screw with PMMN or flexible rod with PMMN 3. Plate/screw with PMMN or resection
1. Proximal radial 2. Radio diaphysis 3. Distal radial	1. Plate/screw or radial head arthroplasty 2. Plate/screw or flexible rod 3. Distal radial plate	1. Screw plate with PMMN or thread replacement 2. Screw plate and/or flexible rod with PMMN 3. Plate/screw with PMMN or resection with arthrodesis of the structural graft handle
1. Proximal fibula 2. Fibula diaphysis 3. Distal fibula	1. Nonsurgical 2. Nonsurgical 3. Plate/screw or dry	1. Nonsurgical 2. Nonsurgical 3. Plate/screw with PMMN or arthrodesis with structural graft

Abbreviations: IM, intramedullary; PMMN, polymethylmethacrylate.
**PMMN bone cement can be used at surgical discretion.*

necrosis; if it occurs, treatments with vacuum dressings are indicated.[13,14]

Final Considerations

The management of the metastatic patient is complex and requires a multidisciplinary team. Establishing such a team favors more appropriate treatments, but in different clinical circumstances, pathological fracture is possible, or in those diagnosed early with the imminence of the pathological fracture. A variety of preoperative care and examinations are necessary to improve treatment and, consequently, decrease complications. But, in many cases, it is possible to carry out orthopedic treatments in such a way that not necessarily an orthopedic oncologist or cancer hospital needs to perform it. ►**Table 2** provides a suggestion of surgical treatments listed in order of frequency and based on therapeutic possibilities that are available to all orthopedic surgeons.[17]

Conflict of Interests
The author has no conflict of interest to declare.

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