21

Bone Metastasis of Rectal Carcinoma

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1. Introduction

Bone metastases are the most common cause of osteolytic lesions of bones in adults. Cancers most likely to metastasize to bone include breast, lung, kidney and prostate, while metastases are rare in colorectal cancer (although they cannot be dismissed). In this last case, metastases usually appear in advanced stages of the disease. Most of the metastatic lesions in women derive from breast cancer, and in the case of men, they derive from prostate cancer. Primary sarcomas of the bone do not usually metastasize to bone.

Metastatic lesions are usually multiple, and they tend to appear on the axial skeleton and the proximal segments of the limbs. Their location, in decreasing order, is the following: dorso-lumbar spine, sacrum, pelvis, ribs, sternum, proximal third of the femur, proximal third of the humerus and cranium.

Metastases affect the cancellous bone more, but they have a larger repercussion if they affect a cortical bone, because if load-bearing bones are involved, pathological fractures may appear. Colorectal carcinoma may generate metastasis on the cancellous and cortical bone.

According to the statistics, three out of every four patients who die of cancer present a bone metastasis, and an estimated 90% of cancer patients die of metastasis. Therefore, this is one of the final causes of the high mortality rates associated to cancer, and there is a limited amount of therapeutic and clinical resources to deal with it.

The most common locations for these metastases are: spinal column, pelvis, ribs and pectoral and pelvic girdles. Acral metastases are rare and for this reason they will be analyzed separately.

2. Physiopatology

Bone destruction secondary to metastasis is not caused by the tumor cells, but by the activation of the osteoclasts. The tumor cells secrete an osteoclast activating factor, and the osteoclasts induce the loss of cortical bone and trabecular bone. This process is divided in four stages (Mundy&Yoneda,1995):

1. The tumor cells adhere to the basement membrane (laminin, E-cadherin, integrins).
2. The tumor cells produce proteolytic enzymes that damage the basement membrane.
3. The tumor cells migrate via the basement membrane under the specific control of chemotactic factors.

4. The tumor cells can stimulate the activity of the osteoclasts.

Clohisy et al. have described four mechanisms that stimulate osteoclast-mediated bone destruction (Clohisy et al. ,2000):

1. Stimulation of the union between the osteoclasts and the bone.
2. Stimulation of the osteoclast-mediated bone resorption.
3. Extension of the survival time of osteoclasts.
4. Acceleration of the production of osteoclasts by precursor cells.

3. Clinical presentation

a. *Constitutional symptoms*: Some patients report anorexia, nausea, vomiting, asthenia, malaise, and weight loss.
b. *Symptoms derived from the primary location*: Colorectal carcinoma usually presents itself accompanied by an alteration of the intestinal rhythm and by the expulsion of blood originated in the rectum. In advanced stages of the disease, the patient presents constipation, and a transabdominal mass can be perceived by palpation. A rectal examination needs to be performed, because tumors of the lower part of the rectum can be easily found.
c. *Symptoms derived from the metastatic disease*: Regardless of the symptoms that metastases may produce on other regions, bone metastases can lead to:
    a. PAIN in the affected area, or referred pain, which may be of insidious, and either progressive or sudden onset, and it may be slight and intermittent or continuous and activity-related. Night pain is a typical symptom, and it does not always disappear with oral analgesics, unlike the pain that derives from degenerative processes, such as osteoarthritis, which increases with loads and articular mobility. When pain affects a long bone, it is easily located by the patient, but when it affects the pelvis or the spinal column, the pain makes it difficult to properly locate the lesion. When it affects the femur or the tibia (load-bearing bones), the patients report pain on walking, although the pain usually appears when the bone destruction levels are over 50% and they indicate an imminent fracture.
    b. SWELLING: It may be a sign of lesion aggressiveness when the tumor invades the cortical bone and affects soft tissue. This presentation is characteristic from colorectal carcinoma, renal carcinoma and melanoma.
    c. FUNCTIONAL DEFICIT: it appears as a consequence of pain. It may be a result of a medullary or radicular involvement in the case of spinal metastases.
    d. IMMINENT FRACTURE: It is a fracture that can appear as a result of a physiological load. Anamnesis and plain X-ray are necessary for the diagnosis, and the cortical involvement, the location and characteristics of the lesion (lytic, sclerotic or mixed) and the existence of fracture lines must be assessed. Permeative and lytic lesions of the proximal third of the femur are prone to fractures. Pain after radiation is also a sign of an imminent fracture. In cases in which an imminent fracture is expected on an active patient, a prophylactic fixation is recommended, especially in load-bearing bones.

4. Diagnostic assessment

In the context of colorectal carcinoma, bone metastases normally appear when the disease is already in an advanced stage (with metastases on other areas), and when the diagnosis has

already been established. For this reason, a histological diagnosis is not usually necessary, and the treatment can be planned. However, we must also take into account the fact that in 1-2% of the cases, the osteolytic lesion is unrelated to the primary tumor, which means that a biopsy is advisable. Myelomas can represent an exception, because they can be diagnosed with an electrophoresis test. Nevertheless, there are also cases in which the diagnosis of the primary tumor has not been yet established, and the orthopedic surgeon is asked to assess and treat an imminent or pathological fracture, or to perform the biopsy of a bone lesion for its final diagnosis, before the surgical stabilization.

In the case of an osteolytic lesion without diagnosis of the primary tumor, the differential diagnosis must be performed with benign conditions (Paget's disease, hyperparathyroidism, myeloma, lymphoma, chondrosarcoma, malignant fibrous histiocytoma, sarcomas) and an approach that includes:

4.1 Complete physical examination

including the thyroid gland, breasts, lungs and digestive system.

4.2 Laboratory analysis

1. COMPLETE BLOOD COUNT: Anemia, leukopenia or thrombocytopenia may be a sign of medullary involvement.
2. ESR: High levels may indicate a myeloma or an active process.
3. ELECTROPHORESIS OF SERUM PROTEINS: They can show a monoclonal gammopathy and they can confirm a possible myeloma diagnosis.
4. BIOCHEMICAL ANALYSIS: It can rule out hyperparathyroidism.
5. ALKALINE PHOSPHATASE: It shows high levels in cases of advanced metastatic disease. Very high levels show an unfavorable prognostic factor.
6. CARCINOEMBRYONIC ANTIGEN: Its levels are high in digestive or hepatocellular carcinomas.
7. PROSTATE-SPECIFIC ANTIGEN: It can detect a prostate carcinoma.
8. HEPATIC ENZYMES AND SERUM ELECTROLYTES: They can show bone and liver involvement.

4.3 Imaging tests

1. ANTEROPOSTERIOR AND LATERAL X-RAYS OF THE LESION: In order to assess an imminent fracture and to analyze the information they provide.
2. THORACIC X-RAY: In order to see the existence of carcinoma or lung metastases.
3. THORACIC AND ABDOMINAL CT SCAN: In order to assess the existence of possible visceral metastases.
4. Tc^{99m} BONE SCINTIGRAPHY: In order to assess bone lesions.

Data from the clinical record, an exhaustive physical examination, blood tests and imaging tests identify more than 85% of all the primary tumors that appear as a bone metastasis. The following tests could also be performed, albeit only when required:

-NMR: It is seldom recommended in cases of isolated bone lesions (fig. 1) , but it may be useful in cases of a single metastasis in which a resection can be performed, in order to rule out *skip metastases* or metastases inside the bone and on the vertebrae, due to its excellent properties for the exploration of the bone marrow.

Fig. 1. Metastatic lesion on T12

-POSITRON EMISSION TOMOGRAPHY (PET): This imaging technique is becoming more and more important in the field of orthopedic oncology. It uses [18F]2-fluoro-2-deoxy-D-glucose (FDG) as a tracer. This is a glucose analog which is taken to the cells by a group of proteins. This marker is absorbed by malignant tissue with an increased metabolic activity. PET scans have a very high sensitivity, and it is an important technique for the identification of primary lesions and other metastases. It can establish the difference between a local recurrence and a scar, and it is also useful in the assessment of response to treatment.

4.4 Biopsy

Puncture biopsy is an excellent way to confirm a diagnosis of bone metastasis. CT-guided fine-needle aspiration and thick- or trephine-needle biopsies are very precise techniques, and they are easy to use. The orthopedic surgeon must choose the exact location, taking into account the location of the lesion, viable access routes and, whenever possible, the final incision line of the operation, in case of resection surgery, excising all the area of the biopsy, because it might be contaminated.

When finding certain locations (usually on the pelvis), a CT scan may be necessary in order to identify the best point and route of access that will reach the metastatic area and to avoid regions with reactive sclerotic bone, because these parts may not have tumor cells.

If there is more than one metastasis, the most accessible one will be chosen.
The anatomopathological analysis requires several tissue samples. For this reason, the pathologist should attend the biopsy in order to confirm that enough tissue has been extracted.
With regard to colorectal carcinoma, if it presents itself with a bone metastasis and the lesion is biopsied, the biopsy may not always provide a diagnosis for the primary tumor, because a tissue compatible with adenocarcinoma does not always tell the difference between primary tumors of the digestive system, prostate, breast and lung.

5. Imaging tests for the metastasic bone lesion

5.1 Plain radiography

Plain radiographies are useful in the characterization of known lesions or in lesions at risk of imminent fracture, but they are not helpful in the detection of a metastatic bone disease, because this condition is undetectable if the bone mineral loss is below 30-50% (fig. 2)

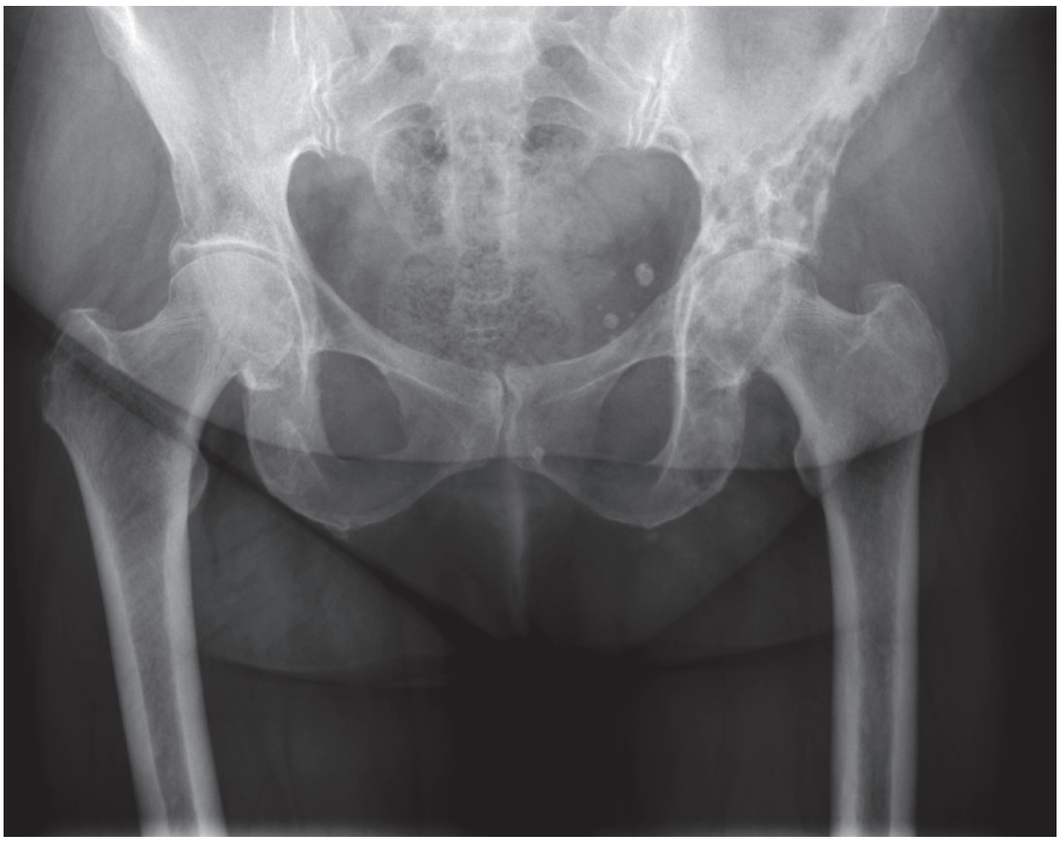

Fig. 2. Metastasic periacetabular lesion

A bone X-ray series, in the case of a metastasis, includes anteroposterior and lateral radiographies of the dorso-lumbar spine (fig. 3) and the pelvis, as well as lateral radiographies of the skull and the cervical spine and anteroposterior radiographies of the thorax, the humerus and the femur. However, in view of their low sensitivity, bone series have largely been replaced by scintigraphy.

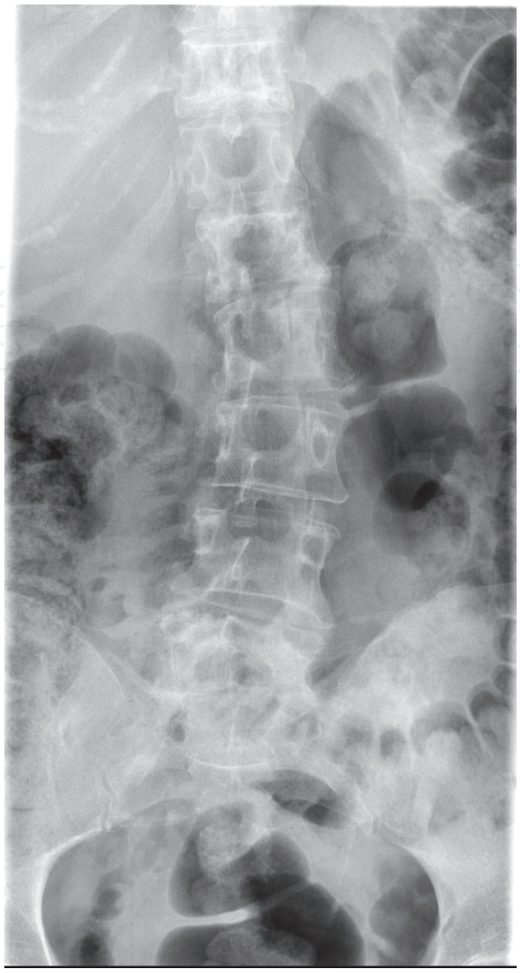

Fig. 3. Lytic vertebral lesions, mainly on L1

The radiological aspects of the bone lesion will depend on the bone response. In the case of malignant digestive tumors, metastases are usually either lytic or mixed. Reactive bones represent an attempt at reparation, which usually takes place. Osteolysis is mediated by osteoclastic resorption, and it may be geographical, moth-eaten or pervious, and the margins may be well- or ill-defined. They can occasionally present themselves with a periosteal reaction and a soft-tissue mass. Metastases that invade the cortical bone or that show a pervious or moth-eaten pattern are more aggressive than metastasis with a geographic pattern.

Another useful aspect of plain radiographies is the assessment of response to treatment. Osteolytic metastases create a sclerotic edge of reactive bone, followed by an increase in sclerosis, moving from the edges towards the center. In then becomes even and finally reduces its size. Comparisons with earlier radiographies make it possible to tell the difference between progression and a positive response to treatment.

The detection or prediction of fracture risk is another objective of this technique. It requires a detailed assessment of the size, reach and character of the bone destruction. Osteolytic lesions are associated to a higher risk than mixed and osteoblastic lesions, just as lesions that invade more than half of the diameter of the cortical bone, lesions located on the

trochanteric region or lesions that affect a load-bearing bone. All these findings, together with clinical data, define the need for a prophylactic osteosynthesis.

5.2 Bone scintigraphy

Tc-99m bone scintigraphy offers certain advantages (Galasko, 1995)

- High sensitivity.
- It provides information for the staging of the lesion.
- It assesses the entire skeleton simultaneously.
- It assesses the response to treatment.

The isotope is absorbed by areas with increased blood flow and increased exchange of reactive bone. It shows enhanced areas in osteolytic and osteoblastic lesions, due to the bone renewal that takes place at the periphery of the lesion.

A group of randomly dispersed lesions with scintigraphic enhancement on the axial skeleton may be a sign of metastatic disease. However, isolated lesions may be difficult to interpret. There are certain considerations that we must take into account with regard to the interpretation of potential false positive and false negative results:

- Fractures and surgical operations can be enhanced up to 1-3 years after they have taken place (fig. 4)
- Enhancement of the ribs is difficult to interpret: If the enhancement follows the longitudinal axis of the rib, it can be a sign of metastasis.
- The scintigraphy should be assessed in combination with NMR and CT scans in order to reduce the rate of false positive and false negative results.
- Highly anaplastic carcinomas or diffuse metastatic disease may lead to false negatives, due to an increased enhancement in the entire skeleton.
- Other related processes that increase enhancement, such as radiation-induced osteonecrosis or steroid abuse, must be also taken into account.

Scintigraphy is also useful in the assessment of recovery: At first, an increase in enhancement can be observed as a consequence of an increased local blood flow, followed by a gradual decrease in enhancement.

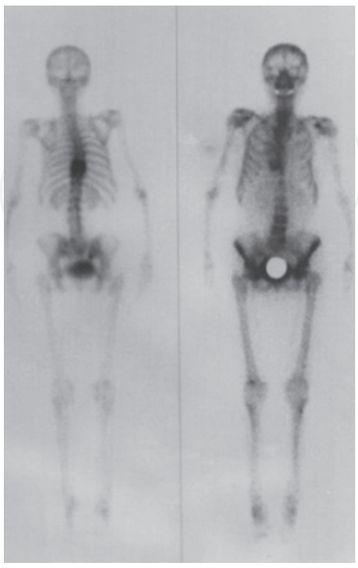

Fig. 4. Enhancement of vertebral column because of vertebral fracture

5.3 CT

It is a useful tool that complements radiographies and provides more information on the presence of hematomas, cortical involvement or the possibility of an imminent fracture. It is useful in the assessment of the vertebral column and the pelvis (fig. 5).

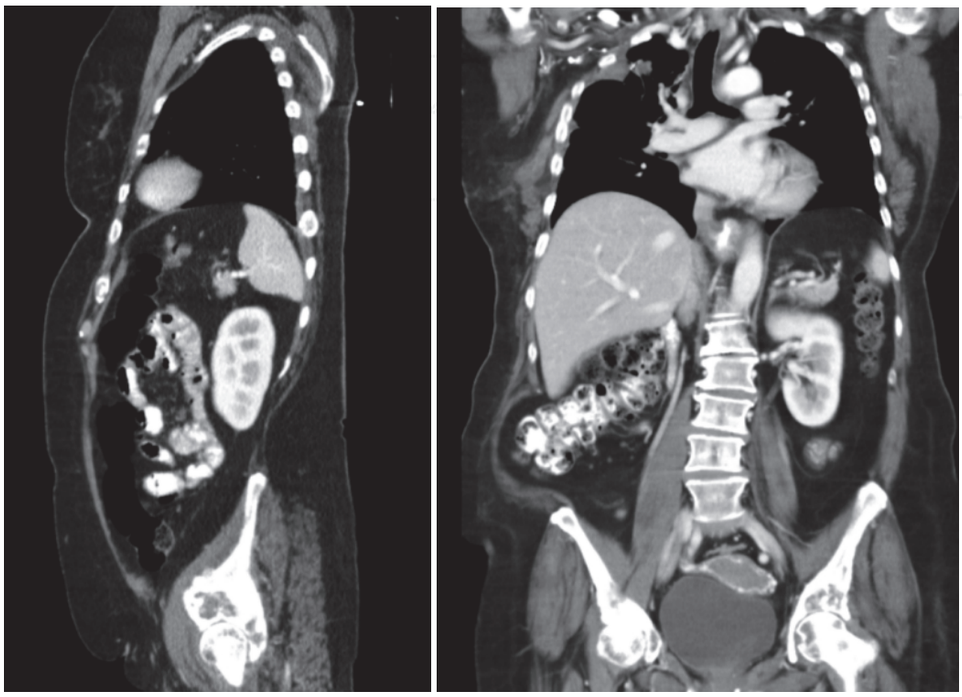

Fig. 5. Periacetabular metastatic lesions and femoral head metastatic lesions

This technique is also very useful for guided biopsies.

5.4 RMN

NMR presents high sensitivity for the detection of metastasis, and high specificity for the characterization of lesions. Metastatic lesions show low intensity in T1-weighted images, while they present high intensity in T2-weighted images. Fat suppression techniques are required in order to increase the visibility of T2-weighted images. The characteristics of the signal may vary according to the type of tissue, its cellularity, its water contents, and the presence of fibrosis, necrosis, hematoma or inflammation. This technique presents certain advantages:

- It assesses peritumoral soft tissue.
- If offers a more accurate assessment of neurovascular compression.
- It provides a better characterization of the bone marrow and the possibility of skip metastases.
- It assesses the risk of medullary compression (fig.6)

The differential diagnosis between a metastatic bone lesion and an osteoporotic spinal fracture is very interesting: old fractures present normal fat signal, but the intensity of acute fractures is similar. Multiple lesions, the presence of soft-tissue masses, the involvement of posterior elements, a convex shape and a sharp edge between normal marrow and affected marrow are signs of metastasis.

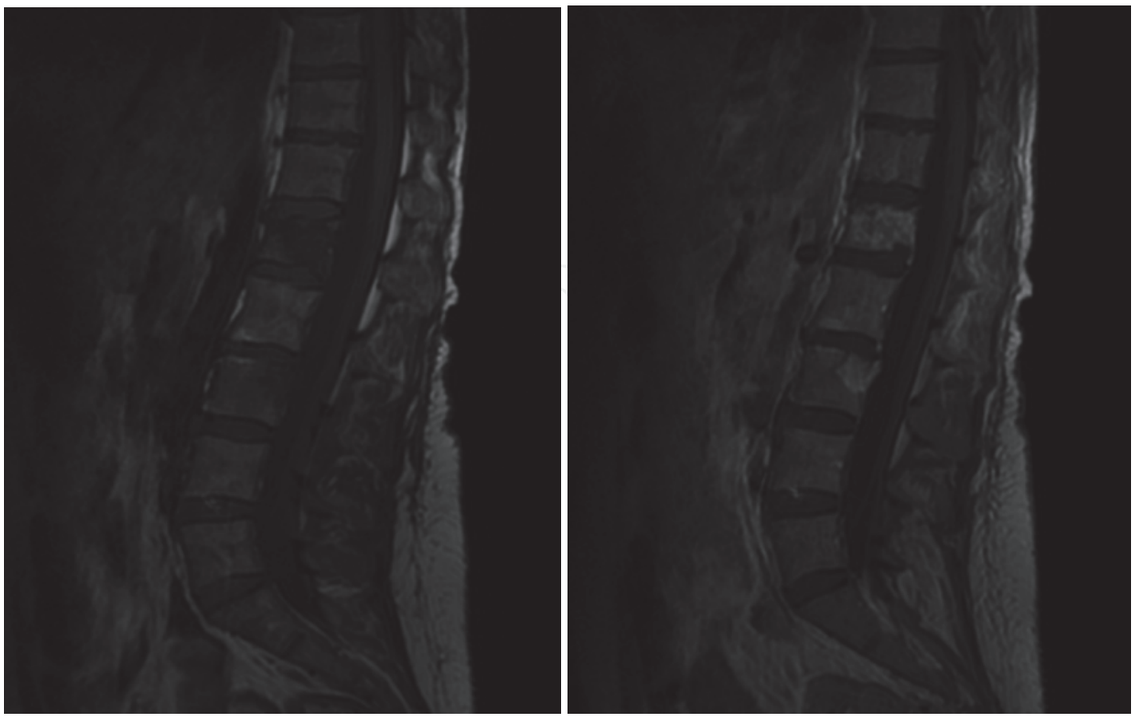

Fig. 6. Lumbar metastases

5.5 Angiography

It is a useful technique in the case of a preoperative embolization of highly vascularized lesions.

6. Treatment

The therapeutic approach for bone metastases, as in any neoplastic pathology, is a multidisciplinary one. A joint effort between oncologists, anatomopathologists, interventional radiologists, pain therapeutics and orthopedic surgeons is of paramount importance.

6.1 Supportive measures

6.1.1 Analgesic therapy

Around 70% of all patients with a bone metastasis report pain at some point along the course of the disease. The physiopathological pain may be due to medullary compression, distension of the periosteum or peripheral neurovascular involvement, as well as to pathological fractures, whenever they are present and mediated by substances such as histamine, substance P or other cytokines.

Other important factors are the characterization of the intensity of pain, its topography and nature and the factors that alleviate or worsen it, as well as a complete clinical record, an exhaustive clinical examination and adequate imaging tests.

Pain, fatigue and psychological angst have been proven to be the most common symptoms in cancer patients.

The therapeutic plan will begin with a simple posological scheme and with non-invasive or minimally invasive treatment. Patients with slight or moderate pain will be started on non-

opioid analgesics, such as paracetamol, acetylsalicylic acid or NSAIDs. If the pain does not disappear with maximum doses of these drugs, a mild opioid, such as codeine or hydrocodone. Patients who suffer moderate or intense pain in spite of the opioids should be treated with third-step analgesics, that is, narcotics and NSAIDs administered separately.
Although they are ideally administered orally, in cases of dysphagia, digestive disorders or lack of adherence to treatment, they can be applied via transdermal, rectal, endovenous, subcutaneous or intrathecal administration. If the patients do not respond to opioids, there are other strategies that include nerve block and neurostimulation and rehabilitation surgery.

6.1.2 Biphosphonates

Metastatic osteolysis is caused by the stimulation of osteoclast activity. For this reason, bisphosphonates can play an important role in this process, because they inhibit the osteoclast activity. They bind with the mineral bone matrix and they have a great physico-chemical impact on the hydroxylapatite crystals.
Some authors have suggested that they are not only useful in the treatment of pain and the prevention of osteolytic complications, but that they can also modify the natural course of evolution of cancer in some cases, due to the effect they have on some intermediate products, such as growth factors.
Ross et al. carried out a systematic review of all randomized essays on patients with bone metastasis. It is a meta-analysis based on 18 randomized studies in which different bisphosphonates have been compared with a placebo or between themselves. Most of these studies were performed on patients with breast carcinoma (Ross et al, 2004). The review showed a decrease in the incidence and an increase in the time until the appearance of bone complications, with a better evolution of pain and functional capacity, with regard to the control group who received a placebo. Treatment with oral bisphosphonates (clodronate, etidronate) caused a decrease in the number of spinal and non-spinal fractures, but it had no effect on the indications of radiotherapy or in hypercalcaemia.
The American Society of Clinical Oncology (ASCO) recommends treatment with bisphosphonates in patients with breast carcinoma and bone metastasis whenever there is radiological evidence of a lytic lesion, regardless of whether it causes pain or not.

6.1.3 Treatment of hypercalcaemia

Hypercalcaemia affects 10-40% of cancer patients at some point, and it causes anorexia, nausea, vomiting, polydipsia, polyuria, dehydration, constipation, confusion and coma.
It is the result of PTHrP production, which activates bone metabolism and induces an excess of osteoclast activity. Osteoclasts are then stimulated by local factors produced by tumor cells, such as interleukin 6. Moreover, calcium levels are also increased due to lower levels of renal calcium elimination, because PTHrP acts on the renal receptors of the parathyroid hormone and it increases calcium resorption on the renal tubule. Polyuria and reduction of intravascular volume appear as a consequence, and for this reason, the initial treatment with these patients is rehydration with intravenous saline serum in order to balance the intravascular volume and to improve glomerular filtration and renal secretion of calcium.
Calcitonin inhibits osteoclasts and it has a rapid effect, although for a brief period of time. For this reason, it is mainly used in emergency treatments.
Plicamycin normalizes calcium levels in up to 50% of the cases, but its serious adverse effects make it unadvisable to use it.

Bisphosphonates represent the cornerstone of hypercalcaemia treatment: The intravenous pamidronate balances serum calcium in 70-100% of the cases, and serum calcium, phosphate, magnesium, electrolytes and creatinine levels need to be measured.
In any case, the best possible treatment for hypercalcaemia is the remission of the cancer.

6.2 Non-surgical treatment

6.2.1 Treatment of metastatic bone disease secondary to colorectal carcinoma

The treatment of bone metastases derived from colorectal tumors is the same as the treatment for other metastases caused by other tumors. Surgical resection of the primary tumor, together with chemotherapy and radiotherapy for the rectal cancer is the treatment of choice, depending on the cases.

6.2.2 Radiotherapy

Radiotherapy is the most widely used palliative treatment for bone metastasis. It is the treatment of choice for painful lytic bone metastases without short-term risk of fracture, and it is combined with surgery when there is an imminent fracture or when the fracture has already taken place. It leads to the necrosis of tumor cells, which makes it possible for the bone tissue to regenerate afterwards. The result is pain relief and, later on, a re-calcification of the destroyed areas of the bone, which is important for the functional recovery of the patient and the prevention of pathological fractures.
Two different radiation methods are used: external radiation therapy and systemic or metabolic radiation therapy.

a) External radiation therapy

Radiation therapy causes pain relief in 80-90% of the patients, and in 55-60% of them, the effect lasts for at least a year. Tong et al. presented a study in which 50-70% of the patients who showed pain relief on the radiated area did not report pain on that same location for the rest of their life. Bone re-calcification can be observed in X-rays between one and three months after radiation in 60-80% of the patients. For this reason, a period for the protection and prevention of mechanical interventions that may endanger the integrity of the affected bone needs to be observed.
Radiotherapy is applied on the bone lesion with variable margins according to the location of the lesion and the type of tumor. The imaging techniques that were described before are needed in the treatment planning, in order to define the area of the bone lesion, as well as a possible soft-tissue involvement.
Several courses of action and treatment fractions have been applied. In the eighties, the results of a study that compared several fraction systems were published (15 fractioned doses of 275cGy, 15 fractioned doses of 300 cGy, 10 fractioned doses of 300 cGy, 5 fractioned doses of 400 cGy, and 5 fractioned doses of 500 cGy). No significant differences were found with regard to pain control, although the most fractioned schemes were the most effective in the long term: 15 fractioned doses of 275 cGy and 10 fractioned doses of 300 cGy.
Some European groups of scientists have carried out studies with radiation therapy administration in a single fraction, and they observed a symptomatic pain relief in 70% of the patients. When fractioned radiation therapy studies were compared with one-fraction radiation therapy, this last option required more re-treatments and a greater number of pathological fractures.

b) Sistemic radiation therapy

Systemic treatment with radiopharmaceuticals is the recommended approach for patients with symptomatic diffuse bone involvement, and as an adjuvant therapy for patients who receive localized radiation therapy and also present diffuse involvement.

Patients must present a positive scintigraphy, progressive pain on several locations or pain on an area that had been previously radiated. It cannot be applied on the acute stage of a pathological fracture or a medullary compression, but it can be administered when the emergency treatment has already been resolved.

The most common radiopharmaceuticals are strontium-89 and samarium-153. Both of them accumulate on the bone tissue with a 10:1 preference over soft tissues. This makes it possible to provide a very specific treatment for bone lesions.

Treatment with systemic radiation therapy shows pain relief in 70-75% of the patients, and it lasts for 2-4 months. In patients with a good clinical response, the treatment can be repeated.

Clinical results have been tested on different studies over the last 10-15 years. A significant improvement in pain control after the administration of radiopharmaceuticals has been observed, when compared with a placebo.

6.2.3 Orthopedic therapy

With a few exceptions, curative surgery is not a realistic objective for these patients. Their general condition needs to be assessed, together with the type and location of the tumor. Generally speaking, the treatment of pathological fractures is similar to the treatment of conventional fractures.

In view of the fact that these patients are prone to prolonged pain, the usual treatment for pathological fractures is early osteosynthesis for a precocious mobilization. However, this is not always possible, and the fractures can be controlled with radiation, hormonal therapy and chemotherapy.

There are several types of immobilization, depending on the area involved, including figure-of-eight bandages, slings or Velpeau bandage, hanging casts, splints and orthotics.

In the case of spinal involvement, patients with a neurological deficit associated to instability require early decompression and stabilization. In the case of stable lesions, they can benefit from radiotherapy and orthotics, like braces or corsets.

If the pelvis is involved, in cases in which surgery is not possible or in which it represents a high risk, the loads supported by the bone need to be limited with a walking support or with crutches.

Lesions on the femur and the tibia are usually treated surgically, but in cases in which this is not possible, the usual immobilization systems will be used.

6.3 Surgical treatment

Surgery for bone metastases requires a previous complete general and local assessment. It presents its own indications, objectives, techniques and means, and it is associated to a program for postoperative radiotherapy that follows the lines that have been previously described.

Before the operation, we must know whether the general condition of the patient allows it, as well as the estimated survival rates according to the stage of the disease and the type of original tumor. There are some carcinomas, such as thyroid carcinoma, with high long-term survival rates, in spite of the appearance of bone metastases, whereas in lung cancer, the

short-term prognosis is quite poor, with a life expectancy of a few months. The surgical approach may vary according to these data and other information regarding the metastasis, such as its location, its size and the areas it affects.

6.3.1 Spinal metastases

The objective in this case is to improve the patient's quality of life as much as possible. In view of its associated morbidity and its recovery rates, many practitioners think that patients with a minimum life expectancy of 6-12 weeks are candidates for surgery. We can divide the role of surgery into diagnostic procedures (biopsy) and therapeutic procedures.

-BIOPSY: The most accessible lesions should be biopsied, and all the areas of the spine can be easily reached. A percutaneous core-needle biopsy shows positive results in 65% of all osteolytic lesions, and in open biopsy this rate goes up to 85% of the cases.

-THERAPEUTIC PROCEDURES: Laminectomy provides an excellent improvement of pain in 75-100% of the patients, as well as neurological improvement in 50-75% of the cases. More than 95% of the patients who did not present a preoperative deficit maintained their function, more than 95% maintains mobility and 90% maintains the continence ability 3 months after surgery, while less than 40% of the patients recover these abilities once they have lost them. Risks derive from the basal situation of the patients, because of their poor nutrition and the fact that they are usually affected by thrombocytopenia and leukopenia and that they have been previously exposed to radiotherapy. For these reasons, the risk of infections or complications in the wound reaches 10-15%.

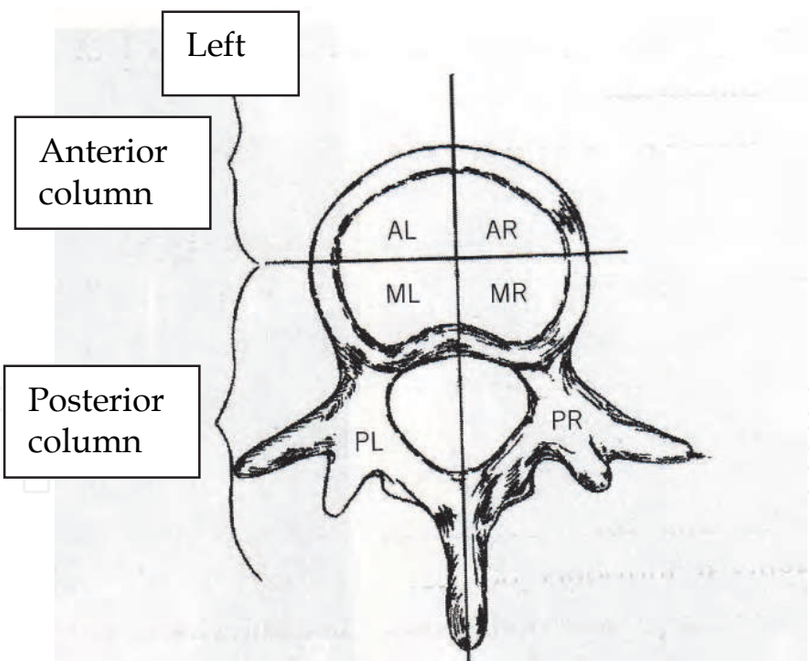

Fig. 7. Modification of Denis classification: Divison into 6 areas

With regard to indications, we can use a modification of Denis (fig. 7) classification as a reference, which subdivides each one of the three regions of the column into two parts: medial column and lateral column, thus creating 6 areas of the column. With this basis, the destruction of less than 3 areas shows a stable situation, the destruction of 3-4 areas is

considered unstable (fig. 8) and requires surgical stabilization, and destruction of 5-6 areas reveals extreme instability and requires combined antero-posterior stabilization.

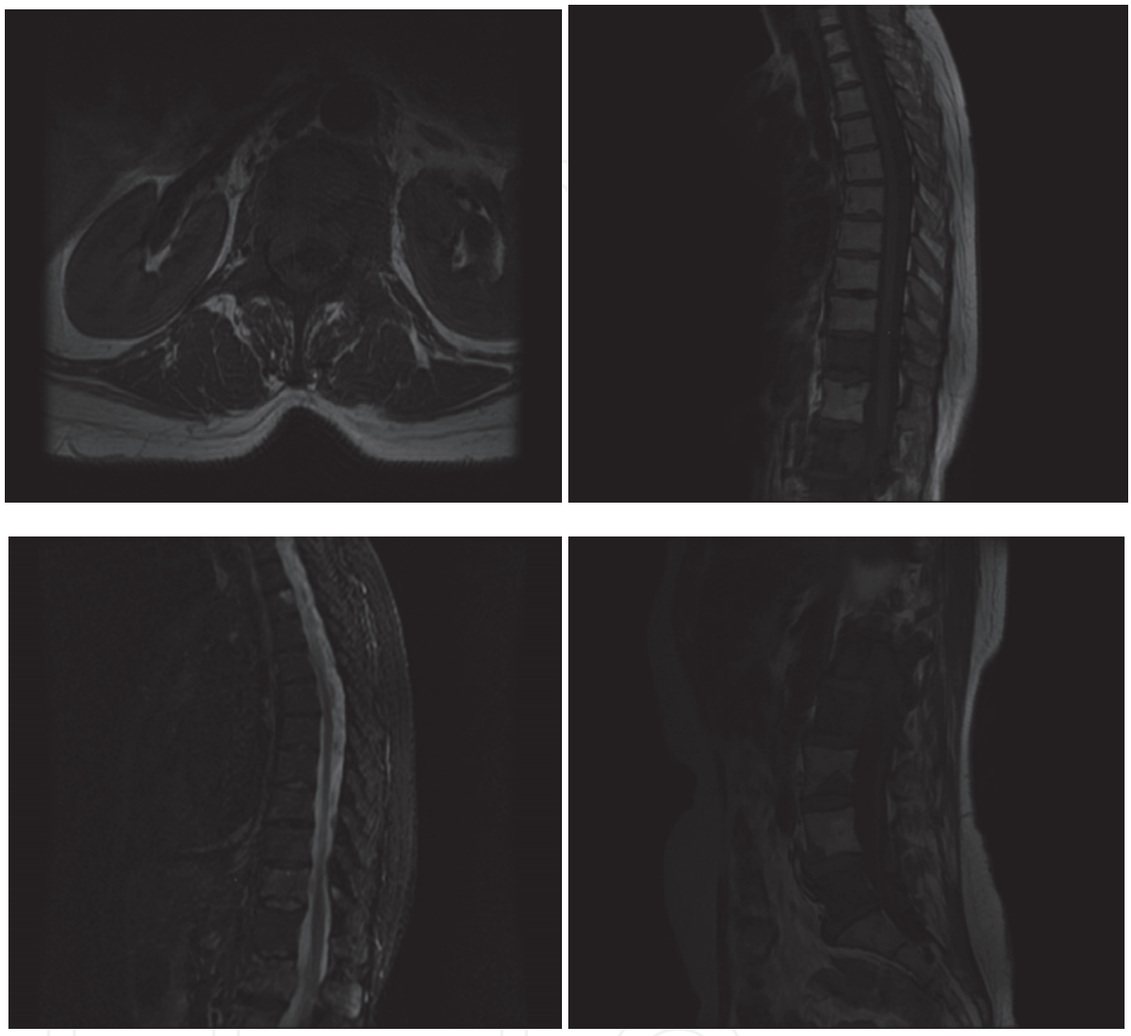

Fig. 8. Unstable vertebral lesion on L1, in a patient with multiple metastases

Primary surgical intervention is indicated when the chances of an adjuvant therapy providing a long-term response are low. Secondary surgery is indicated when symptoms are still present in spite of treatment of fractures or instability after treatment, as well as for the post-therapeutic progression of the tumor and medullary compression.

Corticoids are used due to their anti-edema effect on neurological lesions, and they are never used alone, except in cases in which the general condition of the patient does not allow a different choice.

Radiotherapy is indicated in patients with intense pain with no medullary involvement or with a neurological deficit that shows a slow and incomplete onset and progression, whenever osteoarticular spinal instability (which is the key element for the indication of surgery) has been ruled out. In cases in which short-term prognosis is poor or when surgery is contraindicated due to the general condition of the patient, radiotherapy is the only option.

6.3.2 Non-spinal metastases

The surgical treatment of pathological fractures has been proven to reduce the complications associated to metastatic bone disease, and to improve the patient's pain, independence and ability to walk, as well as longer survival rates.

-PELVIS AND ACETABULUM: The complex anatomy and approach of the pelvis make surgery a difficult task, and other palliative techniques, such as arterial embolization of the metastasis or radiotherapy may be indicated in the first place. These treatments are an ideal choice if the lesion affects isolated areas of the ischium, the pubis, the sacro-iliac region and the iliac wing. However, they are not effective on the periacetabular area, which is subject to lots of mechanic efforts, and which requires surgical reconstruction

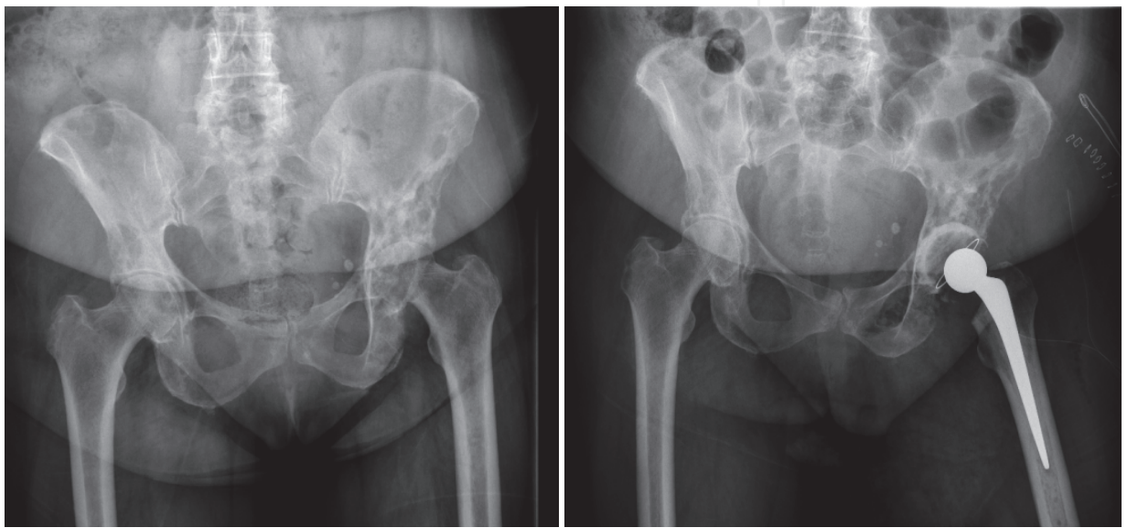

Fig. 9. Total hip arthroplasty

The reconstruction of periacetabular destructive lesions is extremely rare and complex. The results are not as fast or as spectacular as those achieved in other areas, and complications may be more frequent and serious. For these reasons, the choice of patients and techniques must be particularly careful.

The possibilities of surgery will depend on the extent of the periacetabular destruction. In cases of slight or moderate destruction, the initial treatment may be isolated radiotherapy, and if it fails, then curettage of the lesion is indicated. The new space should be filled with bone cement and a conventional total hip replacement should be inserted. There are several different metallic materials that can provide stability for the area, such as acetabular anti-protrusio rings and mails that prevent the pelvic invasion of bone cement. In cases of serious or severe destruction, the same methods can be applied, and there is also the possibility of performing wide resections associated with the implantation of massive bone allografts as a replacement, taking into account the fact that a total hip replacement will always be inserted in the end.

- PROXIMAL THIRD OF THE FEMUR: This is the most common location for metastases that affect long bones. The most common techniques used are hip arthroplasty (fig. 9) , pin osteosynthesis or open osteosynthesis
- DIAPHYSEAL LESIONS: The most commonly affected bones are the femur and the humerus, in order of frequency, and the proximal and medial portions are more

common than the distal area. In the femur, the functional impact is more relevant, because this bone is subject to more demanding mechanic efforts, particularly when walking.

In diaphyseal bone metastases, the treatment of choice is an osteosynthesis of the bone as wide and stable as possible, covering all weak areas, even anticipating the foreseeable progression of the disease.

Already during the 50s and 60s, some authors published studies that highlighted the advantages of internal fixation of pathological fractures, compared with other classic procedures, such as complete rest for a long period of time and orthotics or external immobilization techniques that were more or less complicated. These authors proposed the stabilization of pathological fractures with intramedullary nails as well as their prophylactic use in some cases of lithic lesions that were at risk of fracture, associated with postoperative radiotherapy. These are the same grounds observed in the current treatments, albeit with the materials and procedures of that time. The results in the improvement of pain and immediate function were already promising back then.

The subsequent introduction of endomedullary locking nails represented a qualitative step towards the rotational and global stability of the result. It prevented a collapse of the bone defect that was created by the metastasis with a short, safe and barely aggressive intervention that did not require a surgical approach of the metastatic. Also, early radiation therapy could be applied, because the scars were not near the radiated area.

Giannoudis used locking nails in 30 pathological and imminent fractures of the femoral diaphysis and he achieved enough stability for a painless or almost painless mobilization of the patients in all cases. Other authors present case series with similar results. The results of this technique are the same for humeral diaphysis.

The potential dissemination of tumor cells due to endomedullary procedures is a matter of some controversy. Although some authors report isolated cases of local spreading after the use of these techniques, other studies proved that the moment in which the pathological fracture takes place is the one in which the possibility of tumor dispersion via the blood significantly increases. For this reason, when the prophylactic nailing reduces the risks of a fracture, it also reduces the possibility of dissemination. There are few reported cases with these complications in the clinical practice.

The effectiveness of surgical stabilization of diaphyseal bone metastases of the long bones is out of question, as well as the value of associated radiation therapy after surgery. Townsend presents better functional and long-term results, a lower number of re-interventions due to malfunctioning of the internal fixation and a higher average survival rate in patients that arte treated with surgical stabilization and radiation therapy, compared with patients who only underwent surgery for pathological and imminent fractures of the femur.

In spite of the excellent results obtained with internal fixation followed by radiation therapy. These results are not always stable. The progression of the tumor leads to a failure of surgical stabilization in more than 10% of the cases. The most important risk factor is prolonged survival after surgery. There are other factors that tend to increase the risk of a re-intervention, such as kidney carcinoma as a primary tumor, femoral location, due to a higher mechanic effort, and osteosynthesis surgery, compared with prosthesis.

After an analysis of these data we can observe the need to identify patients with prolonged survival prospects, in order to adapt the therapeutic approach. In these cases, an intervention on the metastatic site and a resection of the affected bone fragment and subsequent reconstruction are indicated. The reconstruction with bone cement was common during the

80s and 90s, but massive intercalary bone allografts are more common nowadays. Postoperative radiation therapy is more effective, because it reduces the size of the tumor mass. There is a clear improvement in the mechanic capability and the stability of the internal fixation, with better and more durable results regarding the function of the bone.
This approach changes in epiphyseal and metaphyseal lesions. Osteosynthesis becomes less effective, and it is replaced by prosthesis. Whenever there is a mainly epiphyseal involvement, the solution is its resection and the implantation of a conventional articular cemented graft, both on the hip and the shoulder. The use of cement and long rods is useful in the prevention of the consequences of a later appearance of other metastatic sites. In cases in which the affected metaphyseal area is large and requires a wide bone resection, there are special resection grafts or composite bone allografts (prosthesis plus graft).
-HUMERUS: This is the second most commonly affected bone in the limbs after the femur. The initial symptom is usually a pathological fracture or pain associated to an imminent fracture. However, as this is not a load-bearing bone, sometimes the lesions reach a very large size. Standard procedures include arthroplasty and osteosynthesis.

7. Discussion

Colorectal cancer affects 6% of the population in western countries along their lives, and it is the third cause of cancer-related death in the world, both for men and women. More than one third of the patients develop a metastasis during the course of the disease, but only a small fraction of them would benefit from a potentially curative surgery. Approximately 50% of the patients with cancer die within 5 years after the diagnosis, due to cancer-related problems. These deaths are due to complications in distant metastases. (Schlüter, et al. 2006) The most common locations for these metastases are the liver, the peritoneum and the lung. Bone metastases in colorectal cancer are rare. (Kose, et al 2009).
The skeleton is the most common organ for metastasis of other tumors, however, and it has a high prevalence in breast and prostate cancers. These two tumors represent 80% of all cases, and the high incidence of bone metastases leads to high morbidity rates. There are other types of cancer that also tend to present bone metastasis, although not as often, such as multiple myeloma and lung cancer. Bone metastases, however, are rare in colorectal cancer. In general terms, the incidence of these metastases, according to the literature, ranges between 5.6% and 10.1%. (Kose, et al 2009).
Malignant colorectal tumors do not evolve with a primary extension to the bone. Thus, bone metastases are less common than in other types of cancer. 70% of patients with a stage IV breast cancer present bone metastasis, compared with 10% of patients with colorectal cancer. Bone metastases of colorectal cancer do not appear if the tumor has not metastasized on the liver or the lung first.
The location of colorectal cancer established a recurrence pattern and a dissemination mechanism of the tumor. The colon has intra-peritoneal segments (covered with serous membrane) in the cecum, the transverse colon and the sigmoid colon, as well as extra-peritoneal segments (without a serous membrane) in the posterior area, the ascending colon, the descending colon and both flexures.
When the colon carcinoma is located on the intra-peritoneal areas, it has a high risk of peritoneal dissemination. Tumors located on the extra-peritoneal segments tend to a direct dissemination towards the retroperitoneal organs, such as the kidney, the ureter or the pancreas. (García Plaza, 2003)

Tumors of the rectum usually invade perirectal tissue, such as the base of the bladder, the prostate or the vagina. Tumors located on the lower third of the rectum drain the superior hemorrhoidal vein towards the portal venous system, via the inferior mesenteric vein. These tumors commonly lead to hepatic metastases.

The recurrence pattern for rectal cancer is not the same as for the colon cancer. The local recurrence of the rectal colon is usually isolated, and it is not accompanied by a disseminated disease, contrary to colon cancer, in which local recurrence is associated to a disseminated disease in most of the cases. This phenomenon is explained by the fact that the recurrence of colon is detected at the same time that dissemination, whereas in rectal cancer, the detection of the recurrence takes place before that stage, due to the limited pelvic space and the accessibility of the exploration. (García Plaza, 2003).

The recurrence pattern of colon cancer is characterized by a rate of local recurrence that ranges between 1 and 19%, a 5-16% rate of local recurrence associated to distant metastasis, and a 12-22% rate of systemic recurrence. The recurrence pattern of rectal cancer is: local recurrence rate of 7-33%, local and systemic recurrence rate of 7-30% and systemic recurrence rate of 6-19%. The increase in the incidence of local recurrence can be attributed to an increased difficulty in securing safe margins in the pelvis, and to the high number of lymphatic ducts located on the mesorectum. The location for the recurrence of rectal cancer depends on the location of the primary tumor. Local recurrence is predominant in lesions of the middle and lower third, and the systemic recurrence is more common in lesions of the upper third, similarly to the recurrence pattern of colon cancer (García Plaza, 2003).

Bone metastases are more common in patients with primary rectal cancer than in patients with primary colon cancer. (Bonnheim, et al.1986)

A higher incidence of patients with pulmonary and bone metastases (16.1%) has been observed, compared with the number of patients with bone metastases alone (6.4%). There has been a decrease in the number of patients with hepatic metastases. (Sundermeyer et al. 2004, 2005).

A study carried out by Roth et al. showed that there is no time pattern, in spite of the individual variables of the degree and sequence of involvement of organs affected by metastasis between colorectal cancer patients. Colorectal tumors do not spread mainly towards the bones. This is a particular characteristic in colorectal cancer; bone metastases are more common in other types of cancer.(Roth et al 2008).

A lower incidence of bone metastases in colorectal cancer with regard to other carcinomas suggests that the behavior of colon cancer is different to other types of tumors. (Roth et al 2008).

An experimental study carried out by Schlüter et al. shows for the first time that the organ-specific formation of colorectal metastases appears to be mainly mediated by specific interactions between circulating carcinoma cells and the vessel wall of potential target organs. (Schlüter et al 2006). On the other hand, a correlation was found between the metastatic potential of colon carcinoma cells and their ability for cell adhesion within potential target organs. For the first time, they directly observed circulating tumor cells within the pulmonary microcirculation in situ and they found specific cell adhesions without size restriction comparable to the liver sinusoids, whereas cells were unable to arrest within the renal and other capillaries in situ. Further studies are required to investigate the underlying molecular mechanisms of these specific adhesive interactions in metastatic target organs.

A review of literature shows that colorectal cancer metastasizes first on the liver or the lung, which contain dense capillary beds that can trap the tumor cells and insert them in these organs. The environment of a specific organ and its influence on the adherence of tumor cells can also have an influence on the effectiveness of the spreading of the tumor. This is what happens more frequently with colorectal cancer patients in the liver and the lungs.(Schlüter et al 2006).

Recent studies have revealed that the patients who receive adjuvant or neo-adjuvant therapy show an increased rate of bone metastases. A rare location is the brain: an estimated 6% of the patients present bone and brain metastases. The prognosis is closely related to the dissemination potential of the tumor through lymph and blood. This dissemination occurs in 10-15% of the cases, regardless of the existence of a complete resection of the primary tumor, and it is closely related to the histological degree of the lesion. It affects the liver via the portal system, and the liver is the organ in which metastases are mainly detected. However, higher survival rates in colon cancer have led to an increasingly frequent appearance of metastases in locations that were previously rare. Sundermeyer et al., in a review of 1,020 patients diagnosed with colon cancer, found up to 10% of bone metastases and a 3% of brain metastases, mainly in patients that had been subject to multiple systemic treatments and with pulmonary involvement. (Sundermeyer et al. 2004, 2005). The development of bone metastases is associated to more precocious stages at diagnosis or with metachronic metastases, compared with patients who were diagnosed with a stage IV disease. Time between diagnosis and the development of a metastatic disease was long in patients with bone and brain metastases, although survival rates for the development of metastatic disease was similar. There are two possible explanations: On the one hand, the microscopic metastatic disease may be present at diagnosis and it remains inactive for long periods of time due to the particular interaction between the tumor and its microenvironment. On the other hand, it may very well be that many patients with bone and brain metastases will never develop a clinical metastatic disease in these areas. (Sundermeyer et al. 2004, 2005).

8. Acrometastasis

Acrometastases are metastases to the hands or the feet. They are very rare, and they represent between 0.3% and 3% of all bone metastases, and their frequency is variable according to different authors, between 15% and 84%. Hand metastases of a colorectal cancer are even rarer (fig. 10), and there are almost no references to it in the medical literature (Ben Abdelghani et al., 2008; Flynn CJ et al., 2008)

Benign lesions are common on the hand, but malignant lesions are very rare. Acrometastases are usually the first manifestation of a hidden neoplasia that, in most cases, leads to a diagnostic error and a wrong treatment. (Desmanet et al, 1991)

Acrometastases are difficult to diagnose. They are frequently mistaken for a benign disease, osteomyelitis, rheumatoid arthritis, gout, fractures, synovitis or glomus tumor, among others. Most of the bone metastases located on the hands affects the phalanges and they come from a lung cancer in the first place, followed by breast cancer. Acrometastases of colon cancer and urinary tract cancer are usually found on the foot; hand acrometastases are exceptionally rare. (Méndez López et al, 1997)

Nozue et al. reviewed the treatment and prognosis of patients with colorectal cancer and bone metastases. Out of 928 patients in the study, only 1.3% of the patients (12 patients)

presented these metastases, which were in an advanced stage in all cases. Most of the primary tumors were located in the spine and the pelvis. The survival rate for these patients was very poor, with an average of 5 months and a 1-year survival rate of 20%. (Nozue et al, 2002)

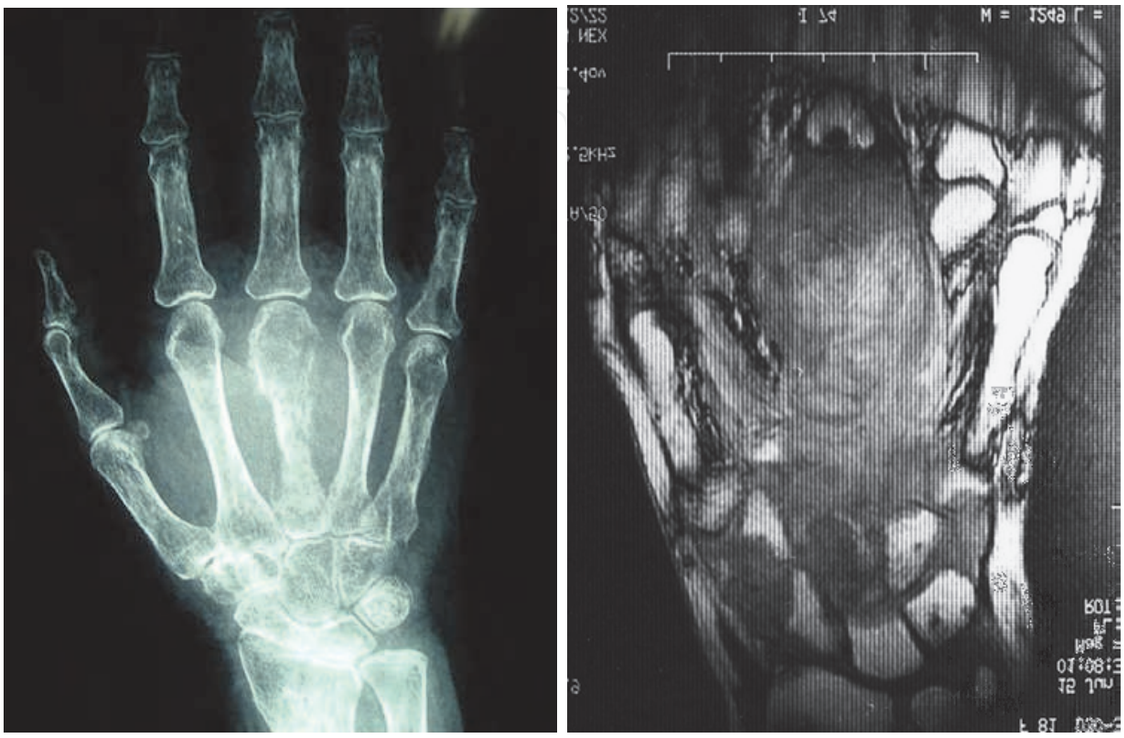

Fig. 10. a) Osteolytic lesion on the third metacarpal bone with permeative pattern and pathological fracture, b)The lesion shows large involvement of soft tissue

The mechanisms of dissemination are not well known. Some authors have stated that they spread via the lymphatic nodes, whereas others say that they spread via the blood. The embolization of the tumor requires certain conditions for the development of a metastasis. There are different factors that have been suggested for the accumulation of tumor cells on the limbs, such as traumatisms, temperature gradients, hormonal factors, local hemodynamic factors or immune factors, as well as the properties inherent to the metastasizing cell. These metastases usually leave the articulations intact. (Chang et al., 2001)

The most common location on the hands is the phalanges, and the right hand is more common than the left hand, although 10% of the patients showed bilateral metastases. (Healey et al, 1986) showed that most of the patients presented lesions on their dominant hand, because it receives more blood and it is more prone to traumatisms. It seems that the chemotactic factors that come after traumatisms may cause the cellular migration and the bone adherence. The third finger is the most common one in the medical literature, and the distal phalange is the most commonly affected. The metacarpus, the proximal phalange and the middle phalange are the next most common locations for acrometastasis.

Acrometastasis is more common in men, with a 2:1 ratio, probably due to a higher incidence of lung carcinoma.

The acrometastases usually appear in an advanced stage of the disease (Borobio, et al. 2010). For this reason, the prognosis is poor, and the objective is to alleviate pain. The therapeutic options include amputation, radiation therapy, curettage, cementation, chemotherapy and wide excision. (Spiteri et al., 2008)
The median age of acrometastasis patients was 58 years.

9. Conclusion

Bone metastasis from colorectal cancer are uncommon (10-23% in autopsy cases), usually present late in the natural history of metastasic disease, and is associated with liver or lung metastasis. Acrometastasis are reported to be 0,3-3% of all the bone metastasis.
Cancers to the rectum and cecum are accompanied by bone metasatasis more frecuently than cancers of other porcions of the colon. Signet-ring cell carcinoma show a high incidence of bone metastasis.
Pain is the most common symptom of bone metastasis. As a result of the loss of bone density, bones affected become prone to fracture and injury.
Testing for bone metastasis includes X-ray, bone scanning; open biopsy is necessary to establish the diagnosis, exclude osteomyelitis and allow treatment. Early diagnosis is important for improving quality of life in this patients.
Therapeutic management of this condition includes chemotherapy, radiotherapy and surgery, but because of survival after onset of bone metastasis is very poor, palliative treatment is the aim.

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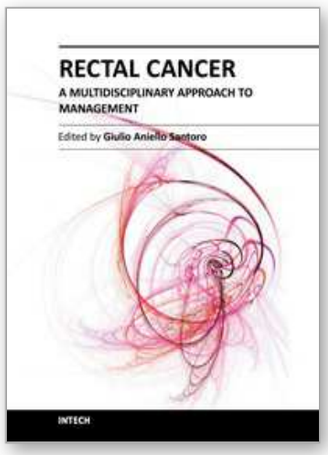

Rectal Cancer - A Multidisciplinary Approach to Management
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Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

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