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Research Article

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Bone Metastases: Epidemiological, Clinical and Therapeutic Aspects

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Abstract

Bone is a common metastatic site in many cancers. Bone metastasis is a secondary bone cancer, whose etiologies are dominated by breast cancer (50% of cases), lung, prostate, thyroid, kidney and bladder cancers. The work is part of a retrospective, descriptive and analytical epidemiological study. This study takes into account 40 patients admitted for a period of 02 years, from January 2017 to December 2019, in the medical oncology department at the Moulay Ismail Military Hospital in Meknes. Our study includes 16 women and 24 men, with percentages of 40% and 60% respectively and a sex ratio of 1.5. The mean age of discovery of bone metastases was 60 years with extremes ranging from 28 to 84 years. Bone metastases were inaugural in 5 patients (12.5%). While in the others, they were discovered during the extension workup or during the follow-up of the primary tumor in 37.5% and 50% of the cases respectively. The most frequent primary tumor in our series was prostate cancer in 13 cases (32.5%), followed by breast cancer in 11 cases (27.5%) and lung cancer in 8 cases (20%).The treatment was based on systemic treatments of neoplastic pathology according to the location and histological type of the tumor, associated with biphosphonates. 3 patients (7.5%) received surgical treatment. Antalgic or consolidation radiotherapy was delivered in 15 patients (37.5%). Overall survival calculated by the Kaplan Meier method ranged from 1 to 47 months with an average of 13.5 months.

1. Introduction

Of all the possible metastatic sites, bone is the most common. Thus, the term bone metastases or metastatic bone cancer refers to a cancer that originated in another part of the body and has spread to the bones. The aetiologies are dominated by so-called "osteophilic" solid tumours, such as breast, prostate, lung, kidney and bladder cancers. The doctor may discover bone metastases through follow-up and monitoring of a known neoplasia, or in the opposite case, these metastases may be indicative of neoplasia. Clinically, this type of metastasis is known mainly for its bone pain, pathological fractures or neurological complications. They are very often osteolytic (due to significant bone destruction), sometimes osteocondensing (due to excess bone formation) or mixed. Nowadays, the number of unidentified primary neoplasia is low. This is due to the progress made in recent years in the field of imaging, biology with tumour markers, the conditions for percutaneously directed bone biopsies, and the use of anatomopathological and immunolabelling techniques. Managing the pain of a bone fracture or pathological fracture requires a multidisciplinary assessment. This assessment initially involves the patient and his family, and subsequently includes the radiologist, pathologist, surgeon, oncologist and psychologist. The ultimate aim of this approach is to improve the patient's quality of life and prolong survival. Although considerable progress has been made in oncology, bone invasion affects 30 to 60% of cancer patients, with a fairly poor prognosis. This work is part of a retrospective and descriptive epidemiological study which includes 40 patients with bone metastases, over a period of 02 years, from January 2017 to December 2019, within the medical oncology department at the Moulay Ismail Military Hospital in Meknes.

2. Patients and Methods

2.1. Framework and Interest of the Study

The work is part of a retrospective, descriptive and analytical epidemiological study. This study takes into account all patients followed for cancer and presenting bone metastases, over a period of 02 years, from January 2017 to December 2019, within the medical oncology department at the Moulay Ismail Military Hospital in Meknes. The main objective of this study is to describe the epidemiological profile of patients with bone metastases. This work will also make it possible to specify the aetiological profile, to study the clinical characteristics and to appreciate the degree of conformity of the diagnostic, therapeutic protocols and the follow-up established within the Military Hospital moulay Ismail of Meknès, with the behaviours adopted in real daily practice.

2.2. Inclusion Criteria

We included in this study all patients treated in the medical

oncology department of the moulay Ismail hospital in Meknes who were diagnosed as having a bone metastasis of solid cancer on the basis of clinical, radiological and histological criteria.

2.3. Exclusion Criteria

Patients with: An unusable file or one containing incomplete data.
A non-metastatic bone tumour.

2.4. Collection of Data

The information on which the study will be based was essentially collected from the patients' clinical files in the archives of the oncology department of the Moulay Ismail Military Hospital in Meknes. An information sheet was drawn up in order to collect all the necessary and usable data to meet the objectives of our study.

2.5. Input and Analysis of Data

The data was entered and analysed using Microsoft Office 2016. In order to analyse the results in greater depth and to gaina better understanding of them, we carried out a descriptive analysis based on percentage calculations for the qualitative variables and measures of central tendency (mean, median) for the quantitative variables.

2.6. Ethical Considerations

The study complied with the ethical recommendations of the Declaration of Helsinki. The data were collected anonymously. Finally, we carried out a bibliographic search and compared our results with those already published in the literature.

3. Results

3.1. The Epidemiological Profile

3.1.1. Total Number of Patients

During the period covered by our study, from January 2017 to December 2019, we enrolled 40 patients with bone metastases in the oncology department of the moulay Ismail military hospital in Meknes.

3.2. Incidence of Cases by Year

This study included a sample of 40 patients being followed for bone metastases.

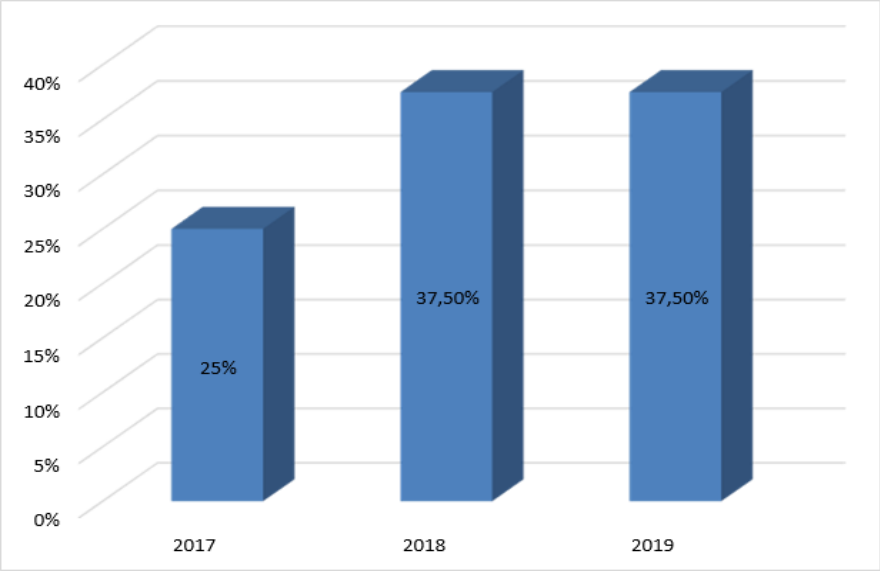

Figure 1: Incidence of Cases by Year

3.3. Gender

Our study included 16 women and 24 men, with respective percentages of 40% and 60% and a sex ratio (M/F) of 1.5.

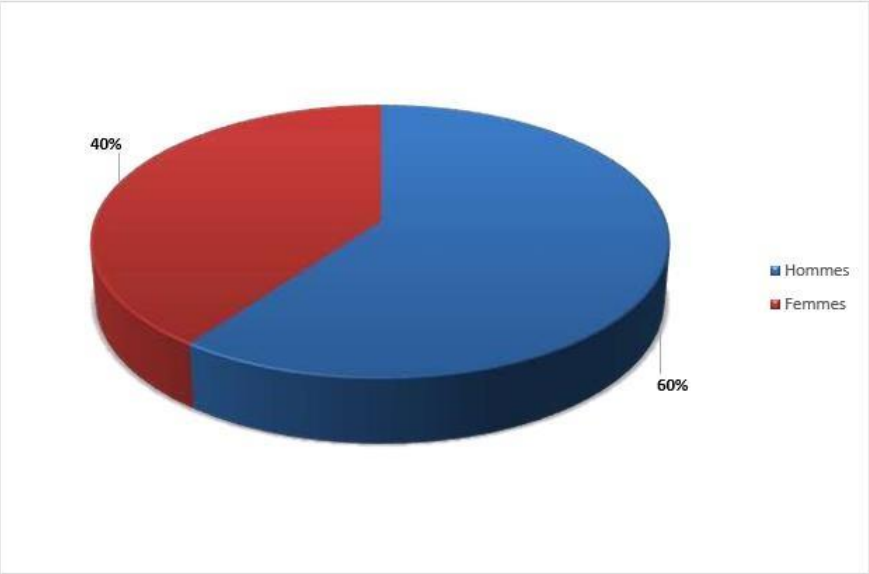

Figure 2: Breakdown of Cases by Sex

3.4. Age

In our series, the average age of discovery of bone metastases was 60 years, with extremes ranging from 28 to 84 years. As regards the distribution of our patients by age group, we note a higher frequency (30%) in the 51 to 60 age group.

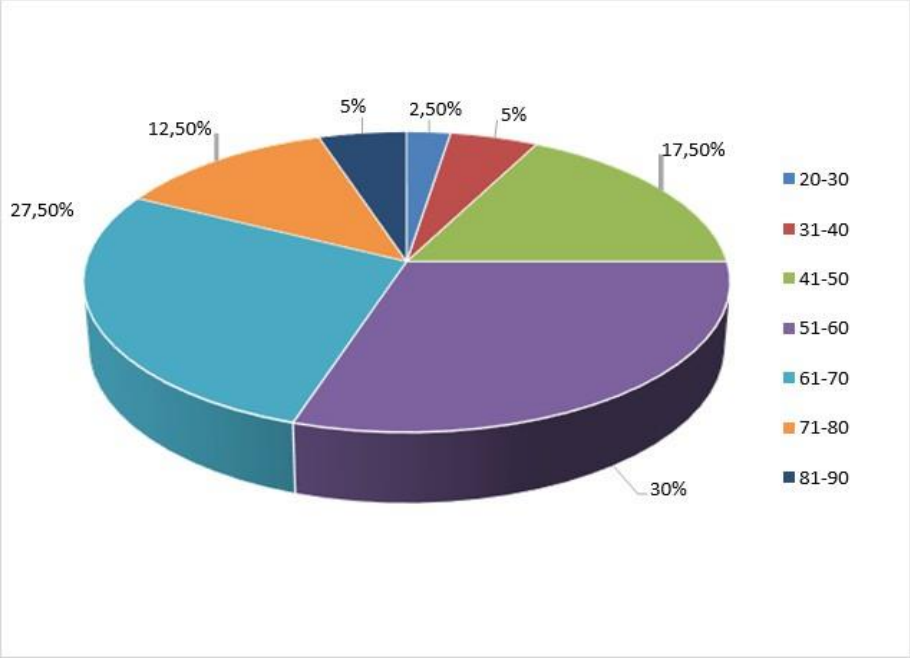

Figure 3: Breakdown of Cases by Age Group

4. The Clinical Study

4.1. Personal and Family Pathological History

Analysis of the history of the patients in our series revealed the following results:

4.2. Personal History

• Medical :

In our series, we found the following medical histories:

High blood pressure in 28 patients (70%)

Diabetes in 21 patients (52.5%)

• Toxic :

In our series, we found the following toxic antecedents:

Smoking intoxication in 23 patients (57.5%)

Alcohol consumption affected 9 patients (22.5%)

• Surgical :

In our series, 23 patients had a surgical history (57.5%), including :

10 patients underwent prostatectomy (25%),

7 patients underwent mastectomy (17.5%),

3 patients underwent thyroidectomy (7.5%),

1 patient underwent nephrectomy (2.5%),

1 patient benefited from RTUV (2.5%),

1 patient underwent Nissen fundoplication (2.5%).

Family history

In our series, 18 patients had a family history of cancer, i.e. (45%).

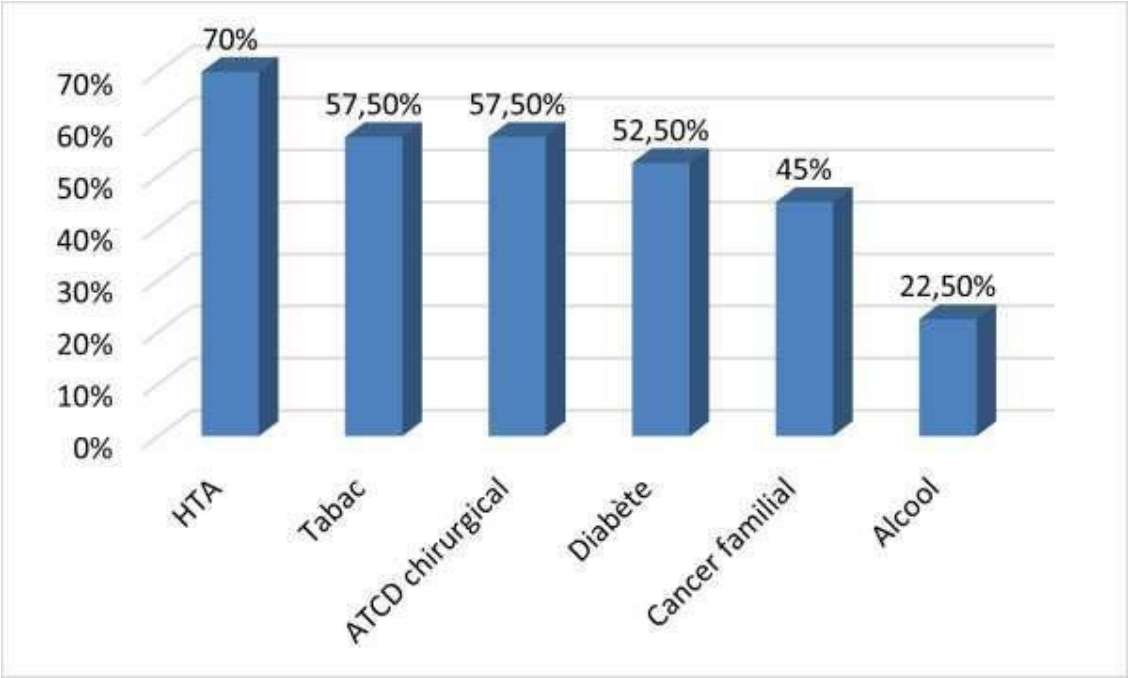

Figure 4: Distribution of Patients According to Pathological History.

5. Reason for Hospitalization

In our study, bone metastases were inaugural in 5 patients (12.5%). In the other patients, bone metastases were discovered during extension work-up or follow-up of the primary tumor (respectively (37.5%) and (50%).

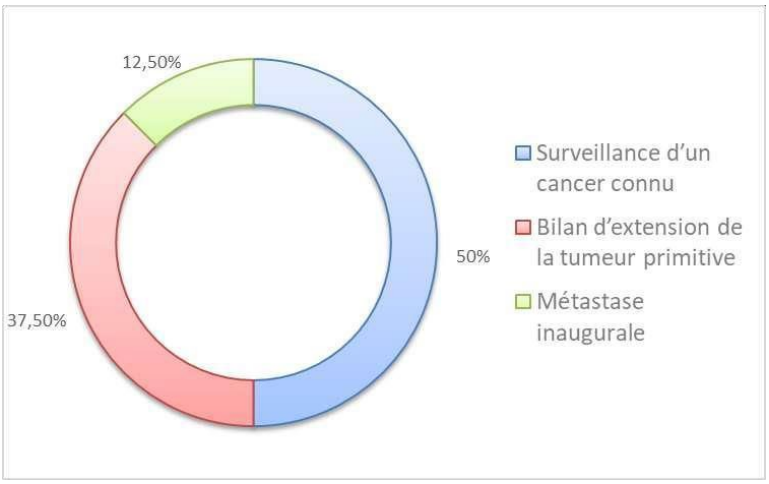

Figure 5: Breakdown of Patients by Reason for Hospitalization

6. General Condition

6.1.WHO Classification

The overall assessment of patients' general condition was carried out by the "WHO Performans Status", with the following results: half of our patients had a WHO score of 2 (20 cases, i.e. 50%), 16 patients had a WHO score of 3, i.e. 40% of cases, and 2 patients had a WHO score of 4, i.e. 5%. While 2 patients had a WHO of 0 and 1 respectively, i.e. 2.5% each.

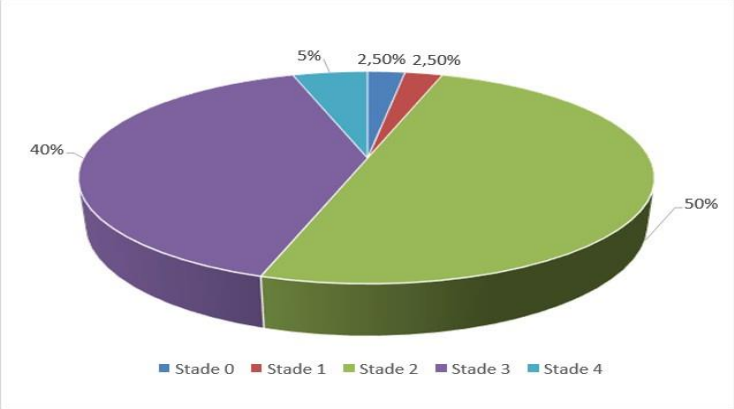

Figure 6: Distribution of Patients According to WHO Classification

7. Primary Tumors

In our series, prostate cancer is the most frequent primary tumour with (32.5%) in 13 cases, followed by breast cancer which represents (27.5%) of the total in 11 cases, lung cancer (20%) in 8 cases, then thyroid with a percentage of (7.5%) as well as UCNT of the cavum. Kidney and bladder UCNT, on the other hand, appeared **in only 1 patient**.

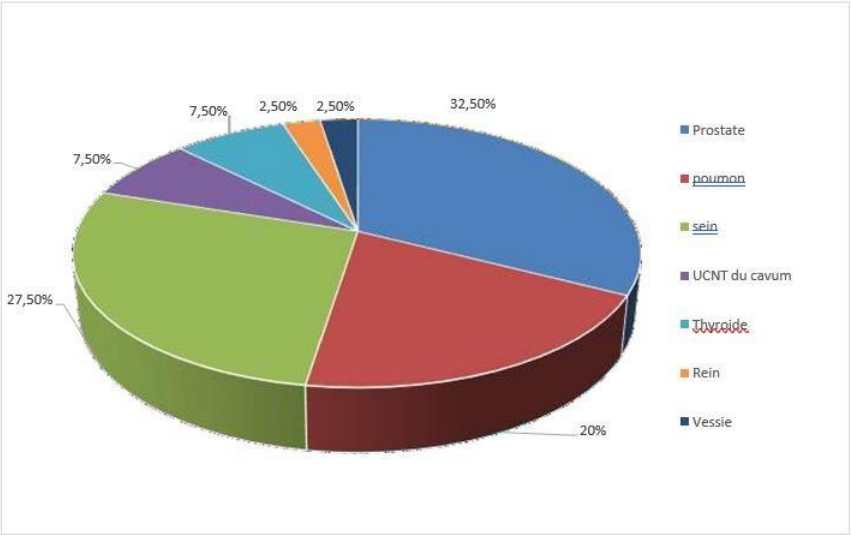

Figure 7: Distribution of Patients According to Primary Tumor

8. Bone Metastases

8.1. Circumstances of Discovery

The circumstances of discovery which have two bone metastases are clinical and paraclinical. In the patients in our study, the discovery was in the majority of cases due to clinical signs: mainly deterioration in general condition in 27 patients (67.5%) and bone pain in 21 patients (52.5%).

Each patient often presented several synchronous clinical signs. From a paraclinical point of view, bone metastases were discovered in 14 patients (35%), mainly during the work-up for extension of the primary tumor.

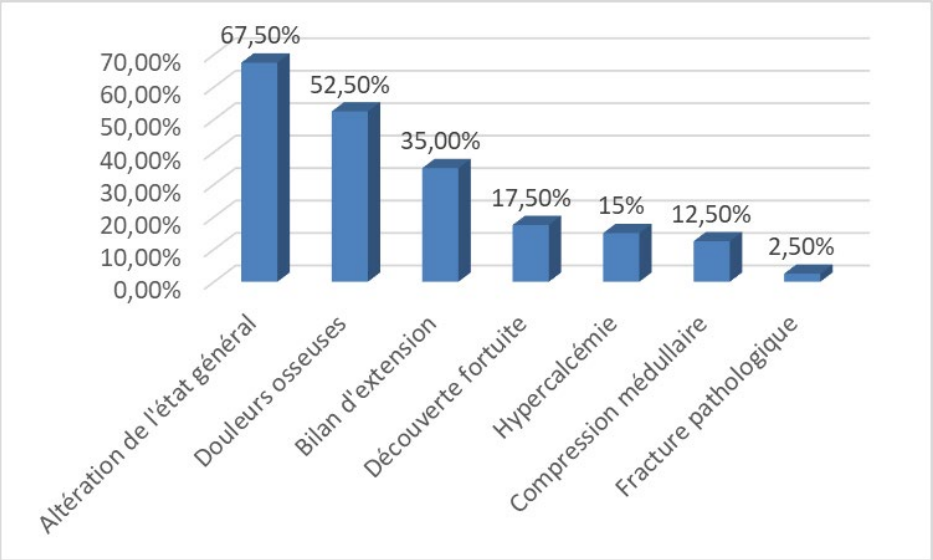

Figure 8: Circumstances of Discovery of Bone Metastases in our Series

8.2. Discovery Time

The time between the diagnosis of the primary tumour and the discovery of bone metastases varied. It was specified in 40 cases, ranging from 0 to 60 months, with an average delay of 9.4 months.

8.3.Type of Metastasis

Bone metastases were late in some cases and synchronous with the primary tumour in others, with a percentage of (55% of the population) in 22 cases compared with a percentage of (35% of the population) in 14 cases. In 4 cases of the population studied, the metastases revealed the primary tumour.

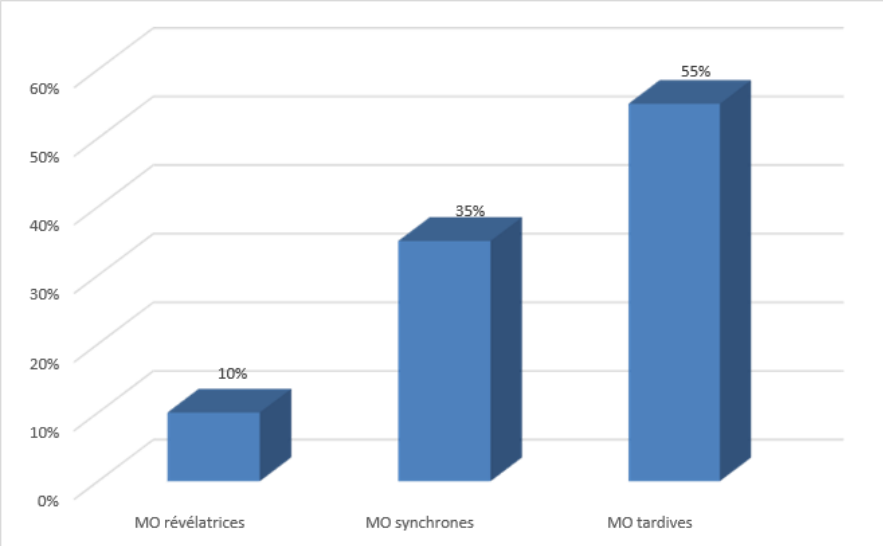

Figure 9: Types of Bone Metastases in our Series

8.4. Number of Bone Metastases

Bone metastases in our series were in the majority of cases multiple (34 cases or 85% of the population). They were single in 6 cases (15% of the population).

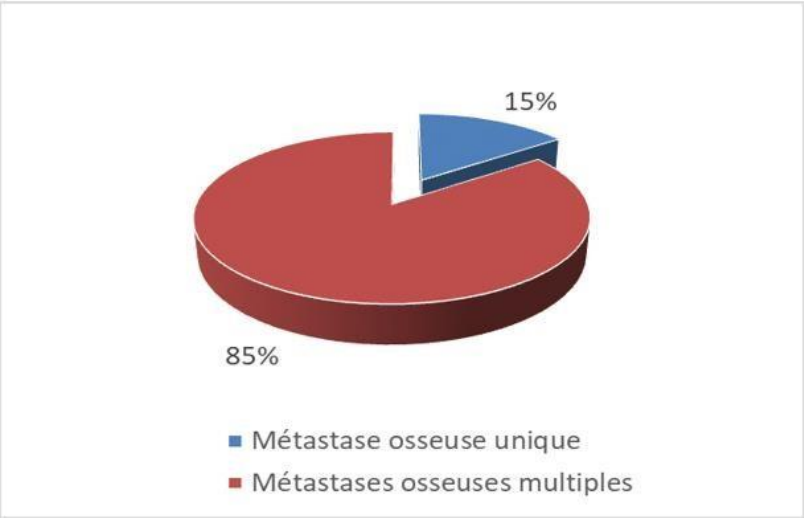

Figure 10: Number of bone Metastases

8.5. Presence of Visceral Metastases

In our patients, metastatic extension associating visceral metastases was present in 28 cases (70%).

9. Paraclinical Studies

9.1. Biology

9.1.1. Non-Specific Balance Sheet

• Blood count

Performed on all patients (100%), it showed abnormalities in only 11 patients (27.5% of the population).

• Sedimentation rate(VS)

The sedimentation rate was carried out in our entire study population. No abnormalities of SV were detected in our series.

9.2. Biochemical Markers of Bone Remodeling

• Bone formation markers(PAL)

All patients had a serum alkaline phosphatase assay, i.e. 100% of the population studied. Elevation of this marker was noted in 2 patients, corresponding to 5% of the population.

• Markers of bone resorption (Calcemia)

All patients in our study series benefited from serum calcium measurement. Hypercalcaemia was noted in 12 patients, i.e. 30% of our study population.

10. Radiology/Imaging

10.1. Radiology Examinations

• Standard X-rays

A standard frontal X-ray of the pelvis and spine was ordered in a single patient with lung cancer, and revealed multiple osteolytic lesions in the pelvis and vertebrae. In order to better analyse these lesions, this patient also underwent a CT scan, which confirmed the diagnosis.

• Computed tomography

CT scans revealed the presence of bone metastases in 24 patients in our series, i.e. 60% of the population.

• Magnetic resonance imaging

MRI was performed in 11 patients in our series, i.e. 27.5% of the population.

10.2. Nuclear Medicine Examinations

• Bone scan

Because of its high level of validation, bone scintigraphy was performed in 31 patients in our series, a percentage of 77.5%.

• Positron emission tomography

Positron emission tomography (PET scan) was performed in only 3 patients in our series, representing 7.5% of the total.

It revealed hyperfixation foci on the skeleton in the first patient, and hyperfixation foci on the vertebra in the second. Bone foci were scattered over the skeleton, vertebral bodies and sternum in the last patient.

10.3. Location of Bone Metastases

Imaging data showed that 26 patients, or 65% of the population, had bone metastases preferentially located in the spine, followed by the pelvis and ribs with percentages of 40% and 37.5% respectively.

11. Treatment

11.1. Bone Resorption Inhibitors

30 patients were treated with bone resorption inhibitors based on biphosphonates, i.e. 75% of the population.

zoledronic acid.

11.2. Systemic Treatments

In our series, 21 patients were treated with chemotherapy alone (52.5%), 12 with hormonal therapy (30%) and 1 with targeted therapy (2.5%). Hormone therapy alone was the treatment of choice in 6 patients (15% of the population).

Traitements systémiques	Nombre de cas	Pourcentage%
Chimiothérapie	21	52,5%
Hormonothérapie	6	15%
Chimiothérapie+ hormonothérapie	12	30%
Chimiothérapie+ thérapie ciblée	1	2,5%

Table 1: The Choice of Systemic Treatment in our Series.

11.3. Surgical Treatment

3 patients received surgical treatment, representing 7.5% of the study population. These were all decompressive surgeries.

11.4. Radiotherapy

14 patients underwent analgesic radiotherapy with a total dose of 30 GY over 10 sessions.

1 patient treated for breast cancer with a single spinal bone metastasis underwent stereotactic radiotherapy.

12. Evolution of Bone Metastases in our Patients

The evolution of bone metastases in the patients in our study is summarised in the table below:

Evolution des métastases osseuses	Nombre de cas	Pourcentage%
Rémission	1	2,5%
Stabilité	8	20%
Progression	31	77,5%

Table 2: Progression of bone metastases in patients in our series.

12.1. Overall Survival

Overall survival calculated by the Kaplan Meier method ranged from 1 to 47 months, with a mean of 13.5 months.

	Minimum	Maximum	Moyenne
Survie (mois)	1 mois	47 mois	13,5 mois

Table 3: Overall Survival of Patients in our Series.

13. Discussion

13.1. Physiopathology

Tumor cells can invade bone cells [1].

- Blood: this is the most common route of spread,
- By lymphatic route,
- By contiguity: much more rarely.

From a pathophysiological point of view, there are several stages involved in the formation of bone metastases: establishment of a pre-metastatic niche, chemotaxis of tumor cells and then invasion of host tissue cells [2].

These stages, which are common to all metastatic dissemination, involve various molecules (chemokines, cytokines, proteases, integrins) that enable cells to be implanted in bone tissue by stimulating cell migration to a given site. When tumour cells reach the bone site, they produce serine proteases (urokinase, plasmin, hepsin) and metalloproteinases that degrade the extracellular matrix, invading the bone marrow. This is a stage specific to bone tissue, known as homing of tumour cells into bone metastasis niches or osteomimicry [3].

After a variable period of dormancy, these tumour cells can proliferate and form tumours that disrupt bone remodelling by interfering with the normal functions of osteoclasts and osteoblasts [4]. In osteolytic metastases, tumour cells do not break down bone directly. Instead, they secrete various factors that stimulate the activity of osteoclasts and inhibit that of osteoblasts, leading to the development of osteolysis. The main factor is a parathyroid hormone-like protein called PTH-rP, which is considered to be the main player in malignant osteolysis [5]. Conversely, in osteocondensing metastases, osteoclastic activity is inhibited and osteoblastic activity is stimulated. In breast and prostate cancer, the main player in the formation of this type of metastasis is endothelin-1, which is a powerful mitogenic factor for osteoblasts. At the site of bone metastasis, there is a vicious circle in which bone resorption/formation and tumour proliferation mutually support each other [1,2]

Métastases ostéocondensantes (15%)	Métastases ostéolytiques (75%)	Métastases mixtes (10%)
Prostate (70%)	Sein +++	Sein
Sein (10%)	Poumon ++	Poumon
Tumeurs carcinoïdes	Rein	Col utérin
Vessie	Thyroïde	Ovaire
Tumeurs neuroendocrines	Vessie	Testicule
Nasopharynx	Tube digestif	Tube digestif
Médulloblastome	Mélanome	
Carcinomes mucineux digestifs	Sarcome d'Ewing	
	Myélome multiple	

Table 4: Main Cancers Causing Condensing, Lytic or Mixed Bone Metastases.

13.2. Anatomical Pathology

Although the diagnosis of bone metastases is based on a combination of clinical, biological and radiological factors, it is the anatomopathological study of a bone biopsy specimen that confirms the diagnosis [6]. In the case of a single metastasis, histology can be used to distinguish the metastasis from a sarcoma or haematological disease, thus allowing therapeutic management to be initiated [7]. Diagnostic biopsy is most often performed by trocar biopsy, more rarely by surgery. When the context (clinical, radiological) is strongly suggestive of the diagnosis of bone metastases, histological confirmation may be carried out intraoperatively during the therapeutic procedure [8].

Biopsy can be used:

• Histological diagnosis of the tumour,

• Referral to primary cancer in certain cases,

• The possible identification of therapeutic targets: such as the search for overexpression of hormone receptors and HER2 by immunohistochemistry in the case of adenocarcinoma of breast origin.

Macroscopic aspects:

Consistency: may be firm, soft, fibrous or encephaloid. Colour: varies according to the tumour of origin:

• Whitish, greyish or haemorrhagic: pointing to kidney or thyroid cancer.

• Blackish: pointing to melanoma.

• Yellowish: metastasis of hypernephroma.

Form: depends on whether the metastasis is osteolytic or osteocondensing.

• Osteolytic form: this is the most frequent form, the tumour is represented by rounded or polycyclic islands occupying the medullary bone and which may extend as far as the cortical bone.

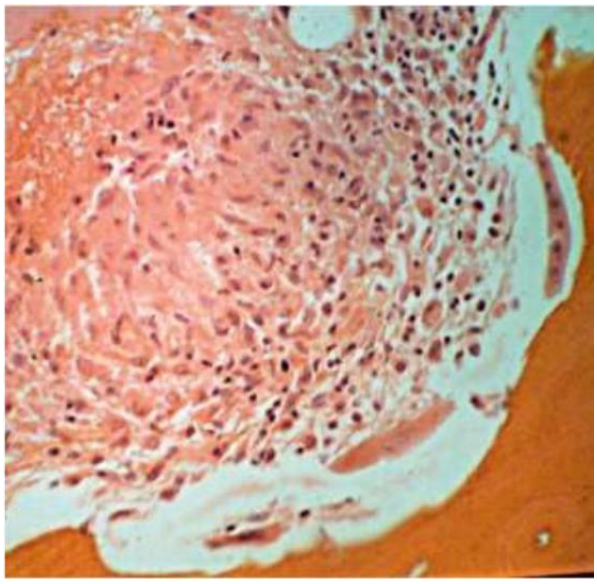

Figure 11: Osteolytic Metastasis of Breast Cancer (solochrome staining). Islands of tumor cells and Multinucleated Osteoclasts Resorbing the Bone Trabecular Meshwork [9,10].

• Osteocondensing form: this is a much rarer form, most often of prostatic origin. The metastasis is represented by a remodelling of the bone structure with medullary densification and cortical thickening.

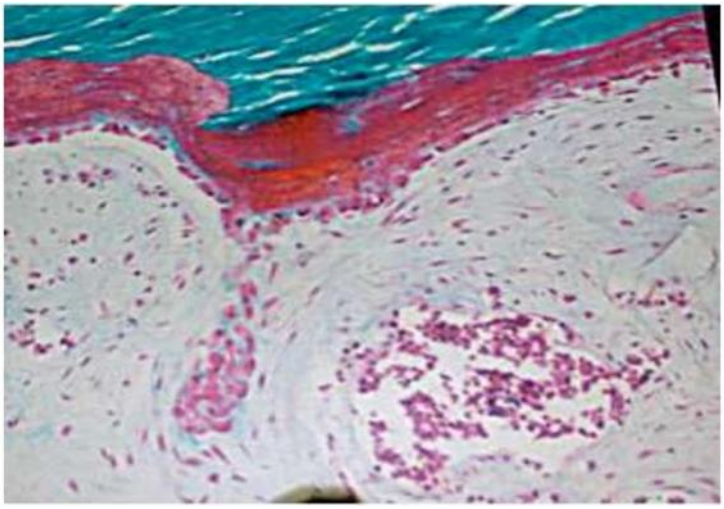

Figure 12: Prostate Cancer Metastasis (Goldner stain). Osteoblasts recruited by cells within a Stroma Synthesizing excess tissue [10]

• Mixed form: frequently found in breast cancer, characterised by the coexistence of both osteolytic and osteoblastic processes.

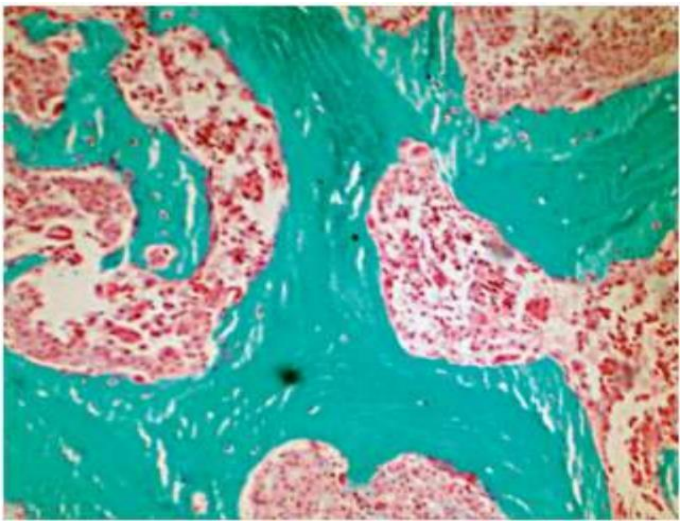

Figure 13: Breast Cancer Metastasis (Goldner stain). Invasion of the bone Metastasis by Neoplastic cells. Numerous Osteoclasts Resorb the bone Trabeculae Initially thickened by a Paraneoplastic Construction Phenomenon [10].

14. Microscopic Aspects

The diagnosis is obvious when neoplastic epithelial tissue is present. The tumour tissue is usually identical in architecture to the primary tumour. It is rare for the metastasis to be less differentiated, and exceptional for it to be more differentiated. The bone structure is generally altered. It may be rarefied by excessive osteoclastic resorption (osteolysis), or be the site of abundant new formation of bone trabeculae (osteoformation) [11]. Bone metastases may be normal or show non-specific changes (hyperplasia, hypereosinophilia, increase in granular elements) or be the site of myelofibrosis [5,9,12].

14.1. Bone Metastases

14.1.1. Circumstances of Discovery

Bone metastases can be diagnosed in three circumstances:

• Follow-up and monitoring of known neoplasia: this is the most frequent presentation, particularly for breast cancer.

• Assessment of extension of the primary tumour.

• Inaugural bone metastases: the most frequent primary tumours identified at the origin of these inaugural metastases are the prostate, lung and kidney. Breast metastases are rarely inaugural.

14.2. Clinical Manifestations

The clinical manifestations of bone metastases include :

14.2.1. Bone Pain

Pain is the main revealing symptom. It may be of the bone or the roots. Pain is described as violent, permanent, of variable location, evolving in attacks and resistant to the usual analgesics. They are mainly nocturnal and osteocopic, with an inflammatory rhythm and increasing intensity [13]. According to the study by M.Vandecandelaere, pain was present in 80% of patients in our study, and in 52.5% of patients [14].

14.2.2. Pathological Fractures

It is a frequent sign, and may be a progressive event in the course of a known bone metastasis, or the revealing fact of the metastasis. They may be spontaneous or secondary to harmless

trauma. One or more fractures occur in 5 to 15% of patients with bone metastases [15]. Osteolytic lesions are more prone to pathological fractures than osteocondensing lesions. According to the study by M.Vandecandelaere, fractures were present in 11% of patients. However, in our study, they were present in only 2.5% of the study population [14].

14.2.3. Functional Impotence

Partial or total loss of function of a limb or limb segment in the event of intense pain or fracture.

14.2.4. Bone Swelling

It is much rarer, with Conroy identifying it in only 3.3% of cases. It affects superficial bones such as the skull, scapula, clavicle, ribs and especially the sternum.

14.2.5. General Signs

Changes in general condition often accompany bone metastases, manifested by weight loss and asthenia. Occasionally, bone metastases may be revealed by digestive disorders (nausea, vomiting, diarrhoea), neuropsychological disorders (torpor), cardiac disorders, polyuria and dehydration, caused by neoplastic hypercalcaemia [16].

14.2.6. Neurological Signs

Neurological involvement is common, revealing bone metastasis in more than 10% of cases. Depending on the level and type of tumour development, this may be a spinal cord compression syndrome, a cauda equina syndrome or a radicular compression syndrome. These syndromes may be evolutionary events in the course of a known metastasis, or the revealing fact of the metastasis [17]. According to neurological abnormalities were present in 37% of patients. In our study, neurological abnormalities were revelatory in 5 cases, i.e. 12.5% of the population.

14.3. Paraclinical Manifestations

From a paraclinical point of view, there are several bone metastases, the main ones being:

14.4. Biological Abnormalities

• Blood Count

A blood count is essential for diagnosing cytopenias induced by diffuse bone marrow invasion: thrombocytopenia is the most common (risk of haemorrhage), followed by anaemia (asthenia, dyspnoea, risk of ischaemic stroke) and leucopenia (risk of infection). Occasionally, in the absence of any other cause, the discovery of cytopenias on a biological work-up may lead to the diagnosis of bone metastases by carrying out an additional aetiological work-up (imaging, osteomedullary biopsy) [18]. In our study, haemograms were performed in all patients (100%), and showed abnormalities in only 11 patients (27.5% of the population).

• Calcaemia

Serum calcium is an indicator of osteoclastic activity. Studies have shown its value in identifying bone metastases in cancer patients and its correlation with the extent of bone damage [19, 20].

The disturbance in phosphocalcic metabolism varies according to whether the metastasis is lytic (hypercalcaemia with normal phosphaemia) or condensing (sometimes hypocalcaemia). All patients in our series had serum calcium levels measured. Hypercalcaemia was noted in 12 patients, i.e. 30% of our study population.

• Bone formation markers (PAL)

An elevated serum LAP level is suggestive of the presence of bone metastases, particularly in prostate cancer, and less so in breast and lung cancer [21,22]. However, the sensitivity of this assay is low because the existence of bone metastases is not always accompanied by an increase in LAP [23,24]. The specificity of this assay is also poor because LAPs increase in other pathologies such as certain liver diseases (hepatobiliary pathologies, liver metastases, etc.) or when certain chemotherapies are administered. Serum total alkaline phosphatase was measured in all patients (100% of the total). Elevation of this marker was measured in 2 patients (5% of the population).

• Tumor Markers

Although they sometimes provide information for the diagnosis of cancer.

The main advantage of tumour markers is their ability to reflect changes in overall tumour mass over time in the same patient [11]. They are therefore not specific to metastatic bone disease. Of all the tumour markers described and validated as such, serum measurement of CA15-3 in breast cancer and PSA in prostate cancer appear to be the most interesting in the context of bone metastases [25]. Because of their lack of specificity for BONE METASTASES, tumour markers have shown very little value in improving the diagnosis of bone metastases or their complications, and are therefore not recommended in this indication [26].

14.5. Discovery Time

The time between diagnosis of the primary tumour and discovery of bone metastases varies. According to a study by Marie Vandecandelaere, the time to discovery of bone metastases varies from 0 to 55 months, with an average of 36 months, i.e. 3 years after diagnosis of the primary tumour. In our series, this delay was specified in 40 cases for which it varied from 0 to 60 months with an average delay of 9.4 months.

Séries	Délai de découverte des métastases osseuse (mois)		
	Minimum	maximum	moyenne
Marie.V et al. N=132	0	55	36
Notre étude N=40	0	60	9,4

Table 5: Time to Discovery of bone Metastases by Series.

15. Type of Metastasis

Bone metastases can be

• Metachronous or synchronous with a known tumour,

• Revealing, requiring investigation of the primary tumour. The most frequent type varies from one series to another.

In our study, bone metastases were metachronous in 22 cases (55% of the population). They were synchronous with the primary tumour in 14 cases (35% of the population). In 4 cases, the metastases revealed the primary tumour.

15.1. Imaging

15.1.1. Standard Radiography

Because of its low sensitivity, radiography is not a good screening method because 30-50% of the bone framework must be destroyed for radiological signs to appear, so a normal radiograph does not rule out bone metastasis. X-rays are therefore useful in the case of an imminent pathological fracture [27,28].

X-rays are recommended for patients presenting with pain on palpation, weight-bearing or mobilisation [29]. Because of their very low cost, low radiation exposure and easy access, standard X-rays are still frequently used to detect or characterise bone metastases.

Schematically, three types of radiological lesions can be described: osteolytic, osteocondensing and mixed [30].

• Osteolytic type

It is the most frequent and the most responsible for pathological fractures.

Osteolysis of cortical bone is slow, but is detected earlier because of the very large difference in density between healthy and pathological bone.

Osteolysis of cancellous bone is more rapid, but it takes a loss of 50% of bone mass for the lesion to become detectable.

Lodwick and others have described three types of tumour osteolysis: Type I: round or oval geographic osteolysis with clear contours.

• Ia: limited by a border of marginal condensation.

• Ib: without marginal condensation, mainly seen on the skull and long bones.

• Ic: osteolysis with blurred boundaries and a narrow transitional zone.

Type II: moth-eaten or worm-eaten osteolysis, formed by the juxtaposition of numerous small lacunae and micro geodes, giving a very irregular area with blurred contours.

Type III: permeative osteolysis, with multiple fissures giving the cortex a laminated appearance.

• Osteocondensing type :

This osteoblastic, "candle-spotted" type is uncommon and less responsible for pathological fractures, and is especially suggestive of prostate cancers.

Characterised by areas of bone condensation, with blurred, homogeneous or discretely heterogeneous contours, with disappearance of the normal structure of the bone [31].

• The mixed type :

It is fairly frequent, but rare from the outset, and is characterised by the juxtaposition of osteolytic foci and osteocondensing foci, giving a mottled and inhomogeneous appearance. The transition from the lytic type to the condensing type reflects reparative osteogenesis and is therefore a sign of treatment efficacy [32].

15.2. Bone Scintigraphy

Bone scintigraphy is the most widely used method for detecting bone metastases, as it enables the entire skeleton to be visualised within an acceptable timeframe and at reasonable cost. 99mTc-methylene diphosphonate or 99mTc MDP (technetium-99m biphosphonates) is the most commonly used tracer [33]. It is a sensitive technique, positive before the bone framework is destroyed, often abnormal several months before the radiological translation of a lesion, making it possible to detect metastases without clinical or radiographic translation [34]. It is reliable for detecting osteoblastic metastases, which most often appear as multiple, asymmetric foci of hyperfixation, mainly located in the axial skeleton [35]. The method is less sensitive for detecting tumours with little or no osteoblastic reaction or aggressive lesions with rapid bone destruction [35]. Lytic lesions may appear as hypofixations or may be invisible, resulting in false negatives [29,36].

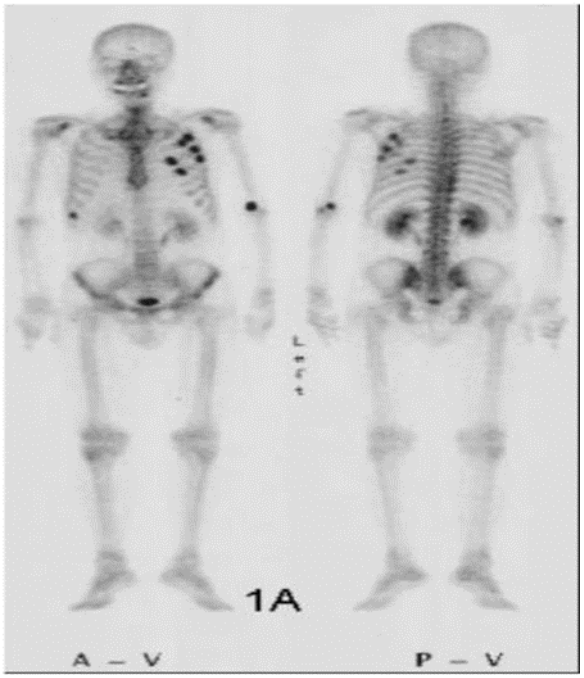

Figure 14: Anterior and posterior bone scan images, revealing left humeral and costal metastases [36].

15.3. Computed Tomography

Used as a second-line treatment, especially in cases where there is a discrepancy between standard radiography and bone scintigraphy. More sensitive than standard radiography, because it avoids the effects of superimposition, it highlights cortical damage and explores areas that are difficult to access with standard radiography, such as the base of the skull, the spine, the sacrum and the pelvis [36].

CT is also useful for assessing the response to treatment of bone lesions, for determining the precise location and extent of metastases, and for performing image-guided biopsies [31].

However, only limited areas can be scanned at any one time and a CT scan cannot therefore be used for whole-body screening because of the high level of radiation emitted by this technique, which is its main limitation in terms of bone metastases [30,37,29].

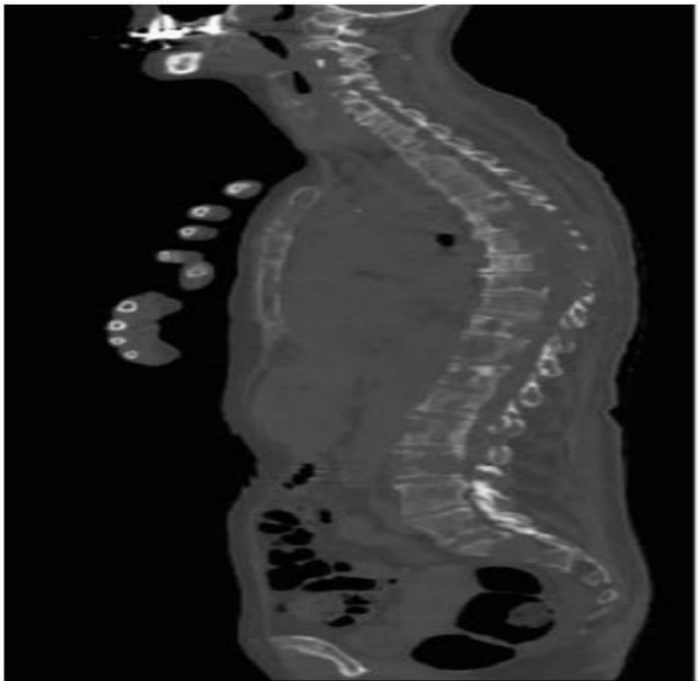

Figure 15: Bone window CT scan reconstructed in the sagittal plane. Staggered osteolytic spinal metastases, some of which invade the posterior wall [37].

16. Magnetic Resonance Imaging

MRI is more sensitive than standard X-rays and CT scans, allowing intraosseous and soft tissue extension to be explored, and haematopoietic or adipose bone marrow to be visualised. However, it lacks specificity, and many lesions may show changes in signal, masquerading as bone metastases [38]. MRI is useful in cases of suspected bone metastases with normal scintigraphy, or in cases of discrepancy between a normal X-ray with increased tumour markers and a positive scintigraphy [39]. It is also used as a reference for post-radiotherapy follow-up to better assess the effectiveness of treatment, and for demonstrating compression of bone or spinal metastases in patients presenting neurological symptoms [40].

ytic bone metastases appear in T1 as a nodular hyposignal with clear or extensive borders, and in T2 as a hypersignal with enhancement on injection of gadolinium. As for condensing metastases, whatever the sequence used, the appearance is frank and marked hyposignal [9,41,17,37].

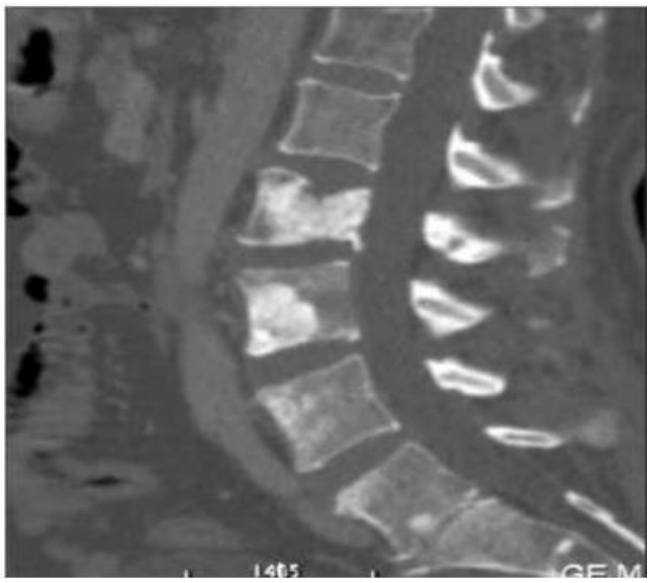

Figure 16: Lumbar MRI. Condensing metastases of prostate cancer affecting L2 (fractured), the anterior half of the body of L3, the superior-anterior angle of L4 and the inferior plateau of L5 (condensing nodule) [10].

17. Positron Emission Tomography-Scanner

Two radiopharmaceuticals can be used, 18F-fluoro-deoxy-glucose (18FDG) or less often 18F-sodium fluoride, injected intravenously. FDG is a glucose analogue that is taken up by tumour cells, phosphorylates and then traps inside these cells. These cells have a high level of metabolic activity, consuming a lot of glucose, and are eager for FDG [17]. FDG-PET is a mainstay of staging in many malignant tumours. Although 18F FDG-PET can detect lytic, blastic and mixed lesions. PET-scanner allows objective assessment of the response to treatment by comparing the value of hyper metabolism on the different examinations.

A decrease in metabolic activity on PET and increased attenuation on CT due to an osteoblastic reaction indicate a positive response to treatment. An increase in metabolic activity and an increase in osteolysis correspond to cancer progression [42].

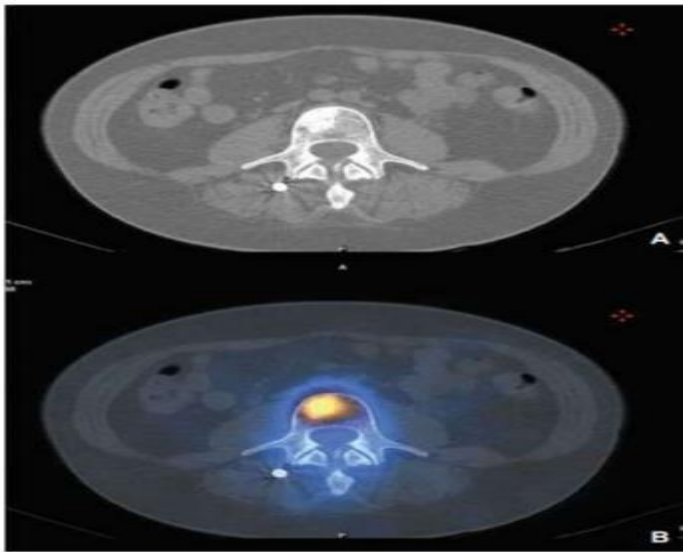

Figure 17: Corporal Osteocondensing Lesion

A. Axial section CT scan: right anterolateral corporal condensation. B: hypermetabolic lesion in the condensation zone [43]. In the series by Sun et al of 273 patients with bone metastases, the results showed that the preferred site was the spine, with a percentage of patients with bone metastases in the pelvis (22%), followed by the ribs (20%). In the study by Villemain et al of 100 patients, the most frequent sites were the spine (29%), pelvis (25%) and ribs (18%) [20,44]. This is in line with the results of our study. On the other hand, all authors agree on the preferential location of the spine, before the pelvis and ribs.

Séries	Rachis (%)	Bassin (%)	Côtes (%)
Vilemain et al. N=100	29%	25%	18%
Sun et al N=273	42%	19,5%	15,7%
Seguira et al. N=118	56,3%	30,1%	38,4%
Notre série N=40	65%	40%	37,5%

Table 6: Location of Bone Metastases According to Series

17.1. Histology

In most cases, the existence of a previously diagnosed cancer does not require histological proof of the metastatic nature of the bone lesions [45]. Histological analysis of bone metastases is essential in 2 circumstances: Absence of primary tumour: isolated, revealing bone metastases, If there is a long interval between the diagnosis of a localised tumour and the occurrence of bone metastases, raising the problem of a possible second metachronous cancer [14].

The key to diagnosis in these cases is biopsy. Most often of pelvic or spinal location, bone metastases are easily accessible. The biopsy may be performed ≪ open surgery ≫ or percutaneously under radiological control in the majority of cases. It is performed under scopic or CT control using true-cut needles or trocars. Samples must be taken from the border zone between the tumour and the bone, in order to avoid the necrotic areas usually located in the centre of the lesion. The yield is excellent and tumour material can be obtained in over 90% of cases [46]. In accordance with the study by Destombe et al. In 107 of the 152 patients, one or more bone biopsies were taken to identify the primary cancer. The anatomopathological results of the bone biopsies were in favour of adenocarcinoma in more than 50% of cases (54.2%).

17.2. Treatment

The treatment of bone metastases is mainly palliative, and forms part of a multidisciplinary management strategy, given the numerous therapeutic possibilities involving the radiologist, anatomopathologist, surgeon, oncologist, psychologist and above all the cooperation of the patient and family [47].
The management of bone metastases must take into account the patient's overall survival time and must meet several objectives:
• Pain control
• Maintaining independence and physical activity
• Combating osteolysis
• Preventing and treating bone complications.
Various treatments are available to deal with it: surgery, radiotherapy, anti-tumour drugs, biphosphonates and denosumab, cementoplasty and destruction by radiofrequency [15].

17.3. Bone Resorption Inhibitors

• Biphosphonates
Biphosphonates are part of the therapeutic arsenal for the management of bone metastases [48]. Biphosphonates are antiosteoclastic agents are stable analogues of inorganic pyrophosphate which reduce bone resorption by inhibiting osteoclast activity [15].

Indications for biphosphonates in metastatic bone disease [49]. Treatment of malignant hypercalcaemia. Palliative treatment of malignant osteolysis, with or without hypercalcaemia, in addition to specific treatment of the primary tumour. Analgesic action in polymetastatic patients with diffuse pain. 75% of the population were treated with biphosphonates, i.e. a number of 30 patients in our study. This is consistent with the results of Sekine et al, a study of 773 patients with bone metastases secondary to solid tumours [50]. 507 patients received zoledronic acid, i.e. 66% of the study population.

• Denosumab
Denosumab is a human monoclonal antibody directed against a cytokine called RANK-ligand (RANKL) [51]. RANKL binds to its receptor on the surface of osteoclasts and stimulates their formation, activity and survival. By mimicking the action of osteoprotegerin, denosumab blocks the RANK ligand and its binding to the RANK transmembrane protein located on the osteoclast [52]. By inhibiting this primordial signalling pathway in cancer osteolysis, denosumab hinders the vicious circle of bone resorption [15,53].

17.4. Systemic Treatments

17.4.1. Chemotherapy

Carcinological treatment with chemotherapy is the standard treatment for bone metastases [54]. This therapeutic method is useful for primary cancer, but is not very effective for bone lysis

[55]. Chemotherapy for bone metastases is most often used in combination with hormone therapy or after hormone therapy has been discontinued [56,57].

17.4.2. Hormone Therapy

This is a major palliative treatment, aimed at metastases from hormone-dependent cancers, in particular breast and prostate cancers. It aims to prevent the occurrence of bone metastases in the first instance, to limit their dissemination in the second instance and to avoid their complications in the last instance [58].

It is administered by :
Or in the form of corticosteroid therapy: in moderate doses so as not to aggravate bone fragility, improves general condition and acts on pain. Or in the form of hormone therapy: mainly represented by antioestrogens, aromatase inhibitors in breast cancer, anti-androgens, GnRH analogues and oestrogens in prostate cancer.

17.4.3. Analgesic Treatment

Pain is the first symptom of bone metastases. Analgesics should be prescribed as soon as the first painful symptoms appear, and should follow the classic steps defined by the WHO [59]. Co-algesics such as corticosteroids, neuroleptics, antidepressants and muscle relaxants can also be of great help [60]. Analgesic treatment is always indicated for bone metastases, most often as a complement to other treatments [61].

17.4.4. Surgical treatment

This is palliative surgery, which is not intended to treat the cancer, but simply to restore function [62]. Surgical treatment should be indicated at an early stage in patients who are in good general condition and able to withstand what may be major surgery [63]. The quality of the assessment of extension is essential, particularly CT for extension into the bone and soft tissues, MRI for vascular relationships, and scintigraphy for other bone locations [64].

17.4.5. Aims and Principles

Duparc[43] is credited with defining the principles and aims of surgery for bone metastases. The main aim of surgical treatment is to [65-67].

• Complete elimination of pain by ensuring strict mobilisation of the fracture site.
• Maintain or re-establish bone continuity using osteosynthesis or the addition of a prosthesis.
• Ensuring the best possible function for the limbs by allowing them to mobilise and regain support.
• The result must be achieved immediately, without having to wait for the often uncertain consolidation of the bone.
• Facilitate the continuation of anti-cancer treatment by eliminating the harmful effects of fractures.
• Ensuring patients' psychological well-being.
• Last but not least, the mechanical survival of the osteosynthesis or prosthesis must not be less than the survival of the patient.

18. Radiotherapy

Radiotherapy is one of the major methods available for treating bone metastases, alongside drug treatment and surgery. Bone metastases are often radiosensitive, and radiotherapy is now an essential adjunct to treatment. Radiotherapy is indicated to: Relieve metastatic pain. Improving the patient's quality of life. Stop tumour progression in irradiated bone. Limiting the risk of fractures.

18.1. Resources and Techniques

Radiotherapy treatment uses either high-energy external radiotherapy or internal metabolic radiotherapy [68].

18.2. External Radiotherapy

External radiotherapy is widely used for both analgesic and consolidative purposes [20]. Several retrospective studies have highlighted its effectiveness in the treatment of pathological fractures and, above all, in their prevention. It allows recalcification and better consolidation of the fracture site [69]. Dose and fractionation have been the subject of numerous trials [70,71]. However, several studies have been carried out to determine the optimal radiotherapy regimen for bone metastases, delivering fractionated irradiation of 30 Gy in ten sessions as the standard treatment in symptomatic forms [72-74]. The average time taken to achieve maximum analgesic efficacy from the end of radiotherapy is 3-4 weeks. There is often a resurgence of pain during the first sessions, which can be prevented or relieved by corticosteroids. The side effects of radiotherapy depend on the site treated. These side effects (oesophagitis, nausea, vomiting, diarrhoea) may occur during radiotherapy and continue for 2 to 3 weeks after the end of treatment. One particular modality is hemicorporeal radiotherapy, which, in hyperalgesic and extensive forms, consists of irradiating the entire upper or lower hemisphere, where most of the metastases are found [75].

18.3. Metabolic Radiotherapy

Metabolic radiotherapy consists of cytotoxic intravenous injections of a radionucleotide (samarium-153 or strontium-89) which binds to hydroxyapatite, follows the calcium pathway in the body and binds to bone sites with increased metabolic activity, thus delivering beta irradiation with analgesic action on several bone sites at once. An analgesic effect is obtained in 65% to 70% of cases [51,76-79]. Unfortunately, the cost of the treatment remains high, which is a factor limiting its widespread use [80,81].

18.4. Indications

External radiotherapy is indicated mainly in the case of single or few osteolytic bone metastases located in a well-limited anatomical region [82]. Metabolic radiotherapy is indicated in the case of osteo-condensing metastases and as a complement to external radiotherapy in multi-metastatic patients [83].

18.5. Overall Survival

In the trial by Decroisette et al [15]. The mean survival of patients was 6.6 months, ranging from 1 to 32 months. In our series, mean survival was 13.5 months, ranging from 1 to 47 months. This significant difference in mean survival is explained by the high incidence of bronchial cancers in the Decroisette series.

Survie (mois)	Minimum	Maximum	Moyenne
Decroisette et al. N=200	1	32	6,6
Notre étude N=40	1	47	13,5

Table 7: Overall Survival by Series.

19. Conclusion

Bone metastases are a frequent reason for hospitalisation in oncology settings. Due to the high incidence of bone metastases, the management of bone metastases is increasingly becoming a clinical concern. Therapeutic options can very often be combined to improve patients' quality of life [84]. Multidisciplinary discussion is the cornerstone of an optimal therapeutic decision [85]. The morbidity and mortality associated with the treatment of bone metastases, and the economic burden of treatment, mean that prevention is justified. New compounds, such as denosumab, are being added to this approach. At the same time, a better understanding of the mechanisms of osteolysis will pave the way for new treatments [29]. This work on bone metastases has enabled us to distinguish its various epidemiological, clinical, therapeutic and prognostic aspects. Computed tomography (CT) and bone scintigraphy remain the most commonly used examinations in our context, both for diagnostic purposes and for post-treatment follow-up. Treatment, apart from carcinological treatment, is based on symptomatic drugs, radiotherapy and surgery (radiofrequency, cementoplasty) [86,87]. Targeted therapy has significantly improved the prognosis of cancers [88].

The value of surgery at the metastatic stage is very limited except in the case of complications (spinal cord compression, etc.) [89]. Bone complications (spinal cord compression, hypercalcaemia, pathological fractures, vertebral compression) affect quality of life and pose public health problems due to the high cost of their management [90]. Research into other therapeutic options and ongoing studies into bone metastases should enable us to propose an appropriate treatment in the coming years.

References

1. Clézardin, P. (2008). Pathogenesis of bone metastases. *Rheumatism Review , 75* (4), 327-331.
2. Conroy, T., Malissard, L., Dartois, D., Luporsi, E., Stines, J., & Chardot, C. (1988). Natural history and development of bone metastasis. Apropos of 429 cases. *Bulletin du cancer, 75*(9), 845-857.
3. Gouin, F., Moreau, A., Guicheux, J., Passuti, N., & Heymann, D. (1999). Pathophysiology of tumor osteolysis. Journal of Orthopedic and Reconstructive Surgery of the Motor System , 85 (1), 58-68.
4. " A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer - Carducci - 2007 - Cancer - Wiley Online Library". https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.22996 (accessed Feb. 11, 2021).
5. " Mechanisms of Bone Metastasis | NEJM". https://www.nejm.org/doi/10.1056/NEJMra030831 (accessed Nov. 26, 2020).
6. Alcalay, M., Azais, I., Brigeon, B., Babin, P., Vandermarcq, P., & Debiais, F. (1995). Stratégie du diagnostic étiologique des métastases osseuses inaugurales. *Revue du rhumatisme (Ed. française), 62*(10), 675-686.
7. Fernández, A., Hernández, A., Martínez, L., Urbistazu, J., Saldivia, F., Prince, J., & Mora, E. V. (2008). Metástasis óseas en adenocarcinoma de mama. *Revista Venezolana de Oncología, 20*(4), 181-185.
8. Roodman, G. D. (2004). Mechanisms of bone metastasis. *New England journal of medicine, 350*(16), 1655-1664.
9. E. Masson, "Aspects histo et cytopathologiques des métastases osseuses des Prostate cancers", EM-Consulte. https://www.em- consulte.com/article/193646/article/aspects-histo-et-cytopathologiques-des- metastases- (consulted on Nov. 26, 2020).
10. A. Constantin, A. Cantagrel, M. Laroche, and B. Mazières, Rheumatology for the practitioner. Elsevier Health Sciences, 2018.
11. Bubley, G. J., Carducci, M., Dahut, W., Dawson, N., Daliani, D., Eisenberger, M., ... & Wilding, G. (1999). Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *Journal of Clinical Oncology, 17*(11), 3461-3467.
12. "Revue du rhumatisme - Vol 71 - n° 5 - EM consulte". https://www.em- consulte.com/revue/REVRHU/71/5/table-des-matieres/ (consulted on Nov. 26, 2020).
13. Goldwasser, F. (2013). Bone metastases in bronchopulmonary cancers. *Revue des Maladies Respiratoires Actualités , 5* (5), 538-546.
14. Vandecandelaere, M., Flipo, R. M., Cortet, B., Catanzariti, L., Duquesnoy, B., & Delcambre, B. (2004). Métastases osseuses révélatrices: étude comparative à 30 ans d'intervalle. *Revue du rhumatisme, 71*(5), 390-396.
15. Decroisette, C., Monnet, I., Berard, H., Quere, G., Le Caer, H., Bota, S., ... & Chouaid, C. (2011). Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601). *Journal of thoracic oncology, 6*(3), 576-582.
16. "Bone metastases - Canadian Cancer Society". https://www.cancer.ca/fr-ca/cancer-information/cancer-type/metastatic-cancer/bone-metastases/?region=qc (consulted on Feb. 11, 2021).
17. Algra, P. R., Bloem, J. L., Tissing, H., Falke, T. H., Arndt, J. W., & Verboom, L. J. (1991). Detection of vertebral metastases: comparison between MR imaging and bone scintigraphy. *Radiographics, 11*(2), 219-232.

18. Nicolini, A., Ferrari, P., Sagripanti, A., & Carpi, A. (1999). The role of tumour markers in predicting skeletal metastases in breast cancer patients with equivocal bone scintigraphy. *British journal of cancer, 79*(9), 1443-1447.
19. Berruti, A., Dogliotti, L., Gorzegno, G., Torta, M., Tampellini, M., Tucci, M., ... & Angeli, A. (1999). Differential patterns of bone turnover in relation to bone pain and disease extent in bone in cancer patients with skeletal metastases. *Clinical Chemistry, 45*(8), 1240-1247.
20. Alataş, F., Alataş, Ö., Metintaş, M., Çolak, Ö., Erginel, S., & Harmanci, E. (2002). Usefulness of bone markers for detection of bone metastases in lung cancer patients. *Clinical biochemistry, 35*(4), 293-296.
21. Hegele, A., Wahl, H. G., Varga, Z., Sevinc, S., Koliva, L., Schrader, A. J., ... & Olbert, P. (2007). Biochemical markers of bone turnover in patients with localized and metastasized prostate cancer. *BJU international, 99*(2), 330-334.
22. Takeuchi, S. I., Arai, K., Saitoh, H., Yoshida, K. I., & Miura, M. (1996). Urinary pyridinoline and deoxypyridinoline as potential markers of bone metastasis in patients with prostate cancer. *The Journal of urology, 156*(5), 1691-1695.
23. Seibel, M. J., Koeller, M., Van der Velden, B., & Diel, I. (2002). Markers of bone turnover do not predict bone metastases in breast cancer. *Clinical Laboratory, 48*(11-12), 583-588.
24. Yokoyama, T., Yamamoto, M., Shima, K., Suzuki, K., Sako, C., Ito, G., ... & Maeda, M. (2005). Clinical usefulness of serum pyridinoline cross-linked carboxyterminal telopeptide of type I collagen for diagnosis of bone metastases in patients with primary lung cancer. *Respirology, 10*(3), 300-304.
25. Robertson, J. F., Jaeger, W., Syzmendera, J. J., Selby, C., Coleman, R., Howell, A., ... & Blamey, R. W. (1999). The objective measurement of remission and progression in metastatic breast cancer by use of serum tumour markers. *European Journal of Cancer, 35*(1), 47-53.
26. A. Auperin et al, Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *Centre for Reviews and Dissemination (UK), 2010.*
27. Leflot, L., Le Pointe, H.D., Lenoir, M., Ariche-Maman, S., & Montagne, J.P. (2005). Imaging diagnosis of bone tumors. *EMC-Locomotor System , 38* (1), 1-16.
28. Daou, A. (2014). Study of primary malignant bone tumors in the orthopedic and trauma surgery department of the CHU-GABRIEL TOURE. About 20 cases.
29. Choi, J., & Raghavan, M. (2012). Diagnostic imaging and image-guided therapy of skeletal metastases. *Cancer Control, 19*(2), 102-112.
30. "Imagerie ostéo-articulaire (2 volumes) LAREDO Jean Denis, MÉTASTASES OSSEUSES RVAN Gérard, WYBIER Marc", Librairie Lavoisier. https://www.lavoisier.fr/livre/medecine/imagerie-osteo-articulaire-2- volumes/laredo/descriptif-9782257155436 (accessed Nov. 25, 2020).
31. Buthiau, D., Antoine, EC, Lapresle, P., Wechsler, B., Missenard, G., Misset, JL, ... & Ziza, JM (1999). Clinical imaging of osteosclerotic metastases. *The Journal of Internal Medicine , 20* (4), 353-364.
32. Hage, W. D., Aboulafia, A. J., & Aboulafia, D. M. (2000). Incidence, location, and diagnostic evaluation of metastatic bone disease. *Orthopedic Clinics of North America, 31*(4), 515-528.
33. de Beaulieu, M. A., & Paycha, F. (2015). Évaluation d'un protocole d'acquisition de la scintigraphie osseuse en mode TEMP/TDM 3 champs de vue dans un contexte oncologique et rhumatologique. *Médecine Nucléaire, 39*(6), 486-501.
34. Paycha, F., Girma, A., & Granier, P. (2010). Démarche sémiologique en TEMP/TDM osseuse. Une approche diagnostique intégrée de l'imagerie hybride. *Médecine Nucléaire, 34*(8), 490-511.
35. F. Giammarile, "Bone scintigraphy", Medecine Nucleaire. Imagerie Fonctionnelle et Metabolique, vol. 30, March 2006, Accessed: Jan. 31, 2021. [On- line]. Available at: https://www.osti.gov/etdeweb/biblio/20758470.
36. Brown, M. L., Collier, B. D., & Fogelman, I. (1993). Bone scintigraphy: part 1. oncology and infection. *Journal of Nuclear Medicine, 34*(12), 2236-2240.
37. Murphy Jr, W. A. (1991). Imaging bone tumors in the 1990s. *Cancer, 67*(S4), 1169-1176.
38. Lecouvet, F., Tombal, B., Malghem, J., Berg, B.V., & Simoni, P. (2008). Whole-body MRI as a tool for detecting bone metastases. *Journal of Radiology , 89* (10), 1291.
39. Berg, B. C. V., Lecouvet, F. E., Galant, C., Maldague, B. E., & Malghem, J. (2005). Normal variants and frequent marrow alterations that simulate bone marrow lesions at MR imaging. *Radiologic Clinics, 43*(4), 761-770.
40. Sugimura, K., Kajitani, A., Okizuka, H., Sugihara, M., Mizutani, M., & Ishida, T. (1991). Assessing response to therapy of spinal metastases with gadolinium-enhanced MR imaging. *Journal of Magnetic Resonance Imaging, 1*(4), 481-484.
41. "Journal of Radiology - Vol 89 - No 10 - EM consulte". https://www.em- consulte.com/revue/jradio/89/10/page/3 (accessed Nov 25, 2020).
42. Schneider, J. A., Divgi, C. R., Scott, A. M., Macapinlac, H. A., Seidman, A. D., Goldsmith, S. J., & Larson, S. M. (1994). Flare on bone scintigraphy following Taxol chemotherapy for metastatic breast cancer. *Journal of Nuclear Medicine, 35*(11), 1748-1752.
43. E. Masson, "Traitement chirurgical des métastases osseuses", EM-Consulte. https://www.em-consulte.com/article/1272750/traitement-chirurgical-des- metastases-osseuses (accessed March 01, 2021).
44. A. Villemain, "Identification of clinico-biological predictive factors for the occurrence of bone events in bone metastatic bronchial cancers", other, University of Lorraine, 2014.
45. Cronin, C. G., Cashell, T., Mhuircheartaigh, J. N., Swords, R., Murray, M., O'Sullivan, G. J., & O'Keeffe, D. (2009). Bone biopsy of new suspicious bone lesions in patients with primary carcinoma: prevalence and probability of an alternative diagnosis. *American Journal of Roentgenology, 193*(5), W407-W410.
46. Decroisette, C., Galerneau, LM, Hominal, S., & Chouaid, C. (2013). Epidemiology, management and cost of bone metastases from bronchopulmonary cancers (excluding spinal metastases). *Revue des maladies respiratoryes , 30* (4), 309-315.
47. Langlais, F., Belot, N., Thomazeau, H., Huten, D., Lambotte, J. C., & Dreano, T. (2005). Tumeurs malignes osseuses du genou: exérèse et reconstruction. *EMC-Rhumatologie-*

Orthopédie, 2(4), 335-354.
48. Paycha, F., Maia, S., Ayachi, N., Grossin, M., & de Vernejoul, M. C. (2007). Quelle est la signification des anomalies observées en scintigraphie osseuse?: Retour sur les mécanismes de fixation des bisphosphonates-(99mTc). *Médecine nucléaire, 31*(7), 356-365.
49. Sadot, S., & Campone, M. (2008). Aspect thérapeutique des métastases osseuses du cancer du sein: rôle des bisphosphonates. *Revue du rhumatisme, 4*(75), 339-342.
50. Sekine, I., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y., & Tamura, T. (2009). Risk factors for skeletal-related events in patients with non-small cell lung cancer treated by chemotherapy. *Lung cancer, 65*(2), 219-222.
51. Henry, D. H., Costa, L., Goldwasser, F., Hirsh, V., Hungria, V., Prausova, J., ... & Yeh, H. (2011). Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of Clinical Oncology, 29*(9), 1125-1132.
52. "A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. | Clinical Cancer Research". https://clincancerres.aacrjournals.org/content/12/4/1221.short (accessed Feb. 11, 2021).
53. Fizazi, K., Lipton, A., Mariette, X., Body, J. J., Rahim, Y., Gralow, J. R., ... & Jun, S. (2009). Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *Journal of Clinical Oncology, 27*(10), 1564-1571.
54. Kimura, H., Tsuchiya, H., Shirai, T., Nishida, H., Hayashi, K., Takeuchi, A., ... & Tomita, K. (2009). Caffeine-potentiated chemotherapy for metastatic osteosarcoma. *Journal of Orthopaedic Science, 14*(5), 556-565.
55. "Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies - Chiara D'Antonio, Antonio Passaro, Bruno Gori, Ester Del Signore, Maria Rita Migliorino, Serena Ricciardi, Alberto Fulvi, Filippo de Marinis, 2014". https://journals.sagepub.com/doi/full/10.1177/1758834014521110 (accessed Feb 11, 2021).
56. Meyers, P. A., Heller, G., Healey, J., Huvos, A., Lane, J., Marcove, R., ... & Rosen, G. (1992). Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *Journal of Clinical Oncology, 10*(1), 5-15.
57. Booth, S. (Ed.). (2006). Palliative care consultations in advanced breast cancer. Oxford University Press.
58. Drouin, S. J., Roupret, M., Davin, J. L., & Soulie, M. (2009). Medical castration in the treatment of locally advanced or metastatic prostate cancer: an update. *Progres en Urologie: Journal de L'association Francaise D'urologie et de la Societe Francaise D'urologie, 19,* S15-9.
59. Caillet, J. B. (2008). Prise en charge des douleurs de métastases osseuses. *Revue du rhumatisme (Ed. française), 75*(6), 536-541.
60. Mantyh, P. W. (2014). Bone cancer pain: from mechanism to therapy. *Current opinion in supportive and palliative care, 8*(2), 83-90.
61. Mercadante, S. (1997). Malignant bone pain: pathophysiology and treatment. *Pain, 69*(1-2), 1-18.
62. "Soft tissue attachment to orthopaedic implant materials - ProQuest". https://search.proquest.com/openview/85ae543fb54d3ba87c3e1f75a869d7c1/ 1?pq-origsite=gscholar&cbl=2026366&diss=y (consulted on Feb. 11, 2021).
63. "Pathologie chirurgicale T3 Chirurgie de l'appareil locomo teur", Unithèque. https://www.unitheque.com/pathologie-chirurgicale- chirurgie- appareil-locomoteur/elsevier-masson/Livre/1360 (accessed Nov. 25, 2020).
64. "Management of spinal metastases from bronchopulmonary cancer - ScienceDirect". https://www.sciencedirect.com/science/article/abs/pii/S0761842513000594 (consulted on Feb. 05, 2021).
65. Broos, P. L. O., Rommens, P. M., & Vanlangenaker, M. J. U. (1992). Pathological fractures of the femur: improvement of quality of life after surgical treatment. *Archives of orthopaedic and trauma surgery, 111,* 73-77.
66. Hoskin, P. J. (1995). Radiotherapy in the management of bone pain. *Clinical Orthopaedics and Related Research®, 312*, 105-119.
67. Salai, M., Rahamimov, N., Pritch, M., Rotstein, Z., & Horoszowski, H. (1997). Massive bone allografts in the treatment of pathologic fractures due to bone metastases. *Journal of surgical oncology, 66*(2), 93-96.
68. Blake, G. M., Gray, J. M., Zivanovic, M. A., McEwan, A. J., Fleming, J. S., & Ackery, D. M. (1987). Strontium-89 radionuclide therapy: a dosimetric study using impulse response function analysis. *The British Journal of Radiology, 60*(715), 685-692.
69. Bradley, N. M. E., Husted, J., Sey, M. S. L., Sinclair, E., Li, K. K., Husain, A. F., ... & Chow, E. (2008). Did the pattern of practice in the prescription of palliative radiotherapy for the treatment of uncomplicated bone metastases change between 1999 and 2005 at the rapid response radiotherapy program?. *Clinical Oncology, 20*(5), 327-336.
70. "Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems | SpringerLink." https://link.springer.com/article/10.1007/s00520- 013-1887-3 (accessed Feb 11, 2021).
71. " The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in Spain - POCKETT - 2010 - European Journal of Cancer Care - Wiley Online Library." https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365- 2354.2009.01135.x (accessed Feb. 11, 2021).
72. Gross tumor volume and clinical target volume in radiotherapy: bone metastasis]. - Abstract - Europe PMC". https://europepmc.org/article/med/11715322 (accessed Feb. 11, 2021)
73. Rose, C. M., & Kagan, A. R. (1998). The final report of the expert panel for the radiation oncology bone metastasis work group of the American College of Radiology. *International Journal of Radiation Oncology* Biology* Physics, 40*(5), 1117-1124.
74. Feng, Z. F., Liu, X., Liu, Z. M., Song, H. S., & Tang, R. M. (2009). Efficacy of hypofractionated radiotherapy combined with docetaxel for treatment of bone metastasis

of lung cancer. *Nan Fang yi ke da xue xue bao= Journal of Southern Medical University, 29*(7), 1442-1444.
75. George, B., & Maronne, J. M. (2009). Characteristics and typology of cancer-related pain. *Journal africain du cancer/ African Journal of Cancer, 1,* 147-153.
76. Porter, A. T., McEwan, A. J. B., Powe, J. E., Reid, R., McGowan, D. G., Lukka, H., ... & Yardley, J. (1993). Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *International Journal of Radiation Oncology* Biology* Physics, 25*(5), 805-813.
77. Achahbar, F. (2010). Bone metastases of the limbs (About 27 cases).
78. Robinson, R. G., Preston, D. F., Spicer, J. A., & Baxter, K. G. (1992, January). Radionuclide therapy of intractable bone pain: emphasis on strontium-89. In *Seminars in nuclear medicine* (Vol. 22, No. 1, pp. 28-32). WB Saunders.
79. Tessonnier, L., Ciais, C., Valerio, L., Fontana, X., Carrier, P., Chaborel, JP, ... & Darcourt, J. (2007). Analgesic treatment of painful bone metastases by vectorized internal radiotherapy. *Nuclear Medicine , 31* (5), 262-270.
80. Ouboukdir, R., Ghfir, I., & Ben Rais, N. (2011). Bone scintigraphy with 99mTc-HMDP in the staging of lung cancer-about 136 cases. MEDECINE NUCLEAIRE-IMAGERIE FONCTIONNELLE ET METABOLIQUE, 35(4), 219-223.
81. Pradier, O., Bouchekoua, M., Albargach, N., Muller, M., & Malhaire, J. P. (2008). How to irradiate bone metastases?. *Cancer Radiotherapie: Journal de la Societe Francaise de Radiotherapie Oncologique, 12*(8), 837-841.
82. Hoskin, P. J., Price, P., Easton, D., Regan, J., Austin, D., Palmer, S., & Yarnold, J. R. (1992). A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. *Radiotherapy and Oncology, 23*(2), 74-78.
83. Sl, B. (1992). Dose estimation in strontium-89 radiotherapy of metastatic prostatic carcinoma. *J Nucl Med., 33*, 1316-1323.
84. Lipton, A., Fizazi, K., Stopeck, A. T., Henry, D. H., Brown, J. E., Yardley, D. A., ... & Jun, S. (2012). Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *European journal of cancer, 48*(16), 3082-3092.
85. " Clinical Features of Metastatic Bone Disease and Risk of Skeletal Metastases rbidity | Clinical Cancer Research." https://clincancerres.aacrjournals.org/content/12/20/6243s.short (accessed Feb. 11, 2021).
86. Sze, W. M., Shelley, M. D., Held, I., Wilt, T. J., & Mason, M. D. (2003). Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy–a systematic review of randomised trials. *Clinical Oncology, 15*(6), 345-352.
87. Anselmetti, G. C., Manca, A., Ortega, C., Grignani, G., DeBernardi, F., & Regge, D. (2008). Treatment of extraspinal painful bone metastases with percutaneous cementoplasty: a prospective study of 50 patients. *Cardiovascular and interventional radiology, 31*, 1165-1173.
88. Dupuy, D. E., Liu, D., Hartfeil, D., Hanna, L., Blume, J. D., Ahrar, K., ... & DiPetrillo, T. (2010). Percutaneous radiofrequency ablation of painful osseous metastases: a multicenter American College of Radiology Imaging Network trial. *Cancer: Interdisciplinary International Journal of the American Cancer Society, 116*(4), 989-997.
89. "Full article: Surgery for skeletal metastases in lung cancer". https://www.tandfonline.com/doi/full/10.3109/17453674.2011.552779 (consulted on Feb. 05, 2021).
90. Al Husaini, H., Wheatley-Price, P., Clemons, M., & Shepherd, F. A. (2009). Prevention and management of bone metastases in lung cancer: a review. *Journal of Thoracic Oncology, 4*(2), 251-259.