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Radiation Oncology

Management of Bone Metastases in Breast Cancer: Experience of the Oncology - Radiotherapy Department of the Oncology and Hematology Center of the Mohammed VI University Hospital in Marrakech: About 120 Cases

Basma Mahrouch[1]*, Fatima Ezzahra Ballouk[1], Ikram Zaytoune[1], Mouna Darfaoui[1], Abdelhamid El Omrani[1], Mouna Khouchani[1]

[1]Radiation Oncology Department, Mohammed VI Teaching Hospital, Marrakesh, Morocco

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***Corresponding author:** Basma Mahrouch
Radiation Oncology Department, Mohammed VI Teaching Hospital, Marrakesh, Morocco

Abstract **Original Research Article**

A frequent side effect of several advanced cancer types, including breast cancer, is bone metastases. Patients with breast cancer may experience severe pain, fractures, and hypercalcemia as a result of bone metastases, which makes clinical management difficult and significantly shortens their overall survival (OS) time and quality of life. According to research, bone metastasis comprises complicated molecular biological processes such as invasion, osteolytic destruction, and an immunosuppressive bone microenvironment and is linked to interactions between tumor cells and the bone microenvironment. Inhibitors of bone metastasis, like Denosumab and bisphosphate, reduce bone loss and enhance the quality of life for patients with bone metastases from breast cancer. The precise biological mechanism of bone metastases is not fully understood, and the prognosis for these individuals is still bleak. There is an urgent need for more basic and clinical research to better understand the mechanism of bone metastases and create novel treatment medications.

Keywords : Breast, Cancer, Bone, Metastatic, Biphosphate, Denosumab.

INTRODUCTION

Breast cancer is currently the most common malignant tumor in women, both in Morocco and worldwide. It is also the leading cause of death from cancer in women. Its incidence is rising steadily, making it a major public health problem worldwide.

The skeleton is the site most frequently affected by metastatic disease. It is also the preferred initial metastatic site for breast neoplasia.

The management of any sign of bone metastasis (bone pain, pathological fracture, etc.) requires a multidisciplinary consultation involving the radiologist, pathologist, surgeon, oncologist and psychologist, in order to achieve the best possible treatment.

To improve these patients' quality of life, bone-targeted therapies such as biphosphonates and Denosumab are now one of the treatments of choice in bone metastases of breast cancer. These bone-modulating agents are currently transforming the course of advanced breast cancer in many patients, with a major reduction in skeletal events (pain, pathological fracture, malignant hypercalcemia, spinal cord compression) and an improvement in quality of life.

Without neglecting the role of surgical treatment in the management of bone complications, particularly pathological fractures, and of radiotherapy, which can be used for analgesic decompression or even consolidation.

The aim of this study was to determine the characteristics of the diagnostic and therapeutic management of bone metastases in breast cancer.

MATERIALS AND METHODS

This is a descriptive retrospective study, collating 120 records of patients followed for breast cancer with bone metastases, at the Oncology and

Hematology Center of the Mohammed VI University Hospital Center in Marrakech, over a period from January 2021 to December 2024.

Inclusion Criteria

In this study we included: Patients with a histological diagnosis of breast cancer.

Patients with bone metastases the diagnosis of metastasis is based on radiological and/or histological data.

All patients receive at least one treatment targeting bone metastases.

Exclusion Criteria

Male breast cancer

Patients who have not received specific treatment for bone metastases.

Data Collection

An evaluation form was drawn up for each patient (Appendix 1). Information is recorded for each patient, including sociodemographic data, histological characteristics of the primary and metastatic tumors, treatment of the primary tumor, circumstances of diagnosis of bone metastases, treatments received, therapeutic response to bone metastases, overall patient outcome and survival.

All the variables to be studied were transcribed onto an Excel database.

RESULTS

➢ **AGE:**

The mean age in our study was 68 years with a standard deviation of 10 years and extremes of 28 years and 84 years.

➢ **HISTORY OF BREAST CANCER :**

In our study, 9 patients had a family history of breast cancer, whereas 111 patients had none

➢ **Menopausal Status**

Menopausal patients represent 67% (86 cases) and 19% (43 cases) are still in the genital activity period

➢ **Performance Status (WHO)**

The general condition of our patients was generally assessed according to the WHO score expressed from 0 to 4

- WHO 0 represents 10% of cases
- WHO1 represents 79% of cases
- WHO2 represents 10% of cases
- WHO 3 represents 1% of cases
- No patient with WHO 4

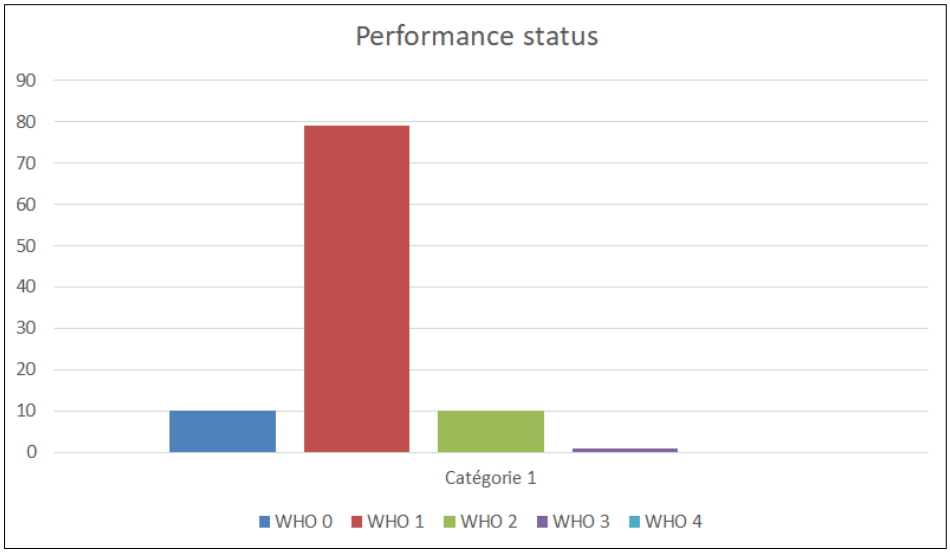

Figure 1: Performance status WHO

Metastatic Breast Cancer

Size of Primary Tumour:

The distribution of primary tumours, synchronous or metachronous, according to size was as follows:

- Tumors smaller than 2 cm (T1) accounted for 12.5% or 15 patients
- Tumors 2 cm to 5 cm (T2) accounted for 35% or 42 patients
- Tumors larger than 5 cm (T3) accounted for 19.1% or 23 patients
- Tumors extending to the wall (T4) accounted for 33.3 or 40 patients

Lymph Node Status

The majority of patients had a positive clinical lymph node status at the time of diagnosis, estimated at 87.5%; with 40 patients classified as N1, 48 as N2, 16 as N3, while 15 patients had no lymph node involvement N0.

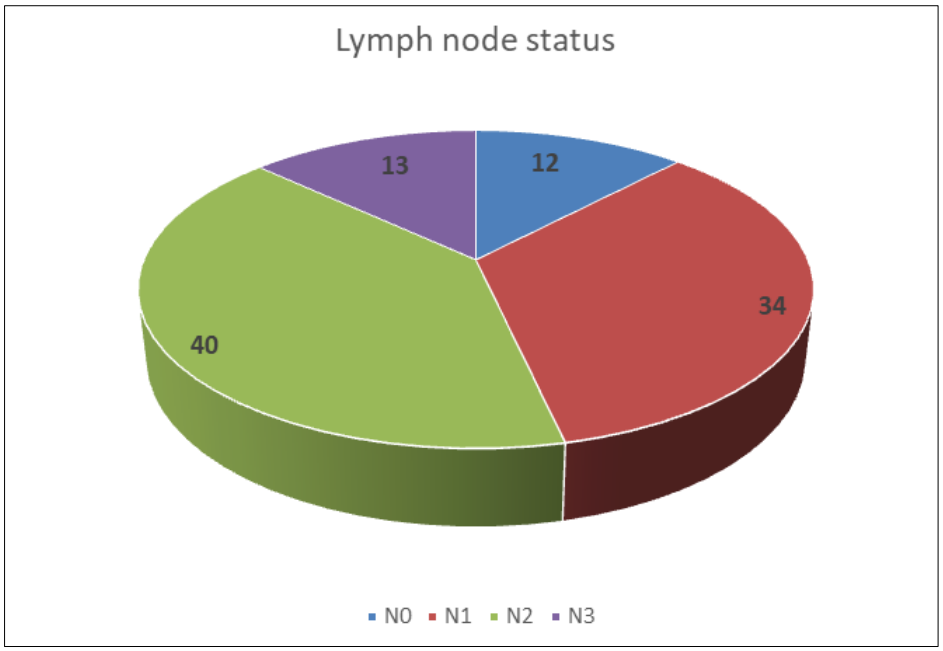

Figure 2: Graphic representation of lymph node status

Histological Type

Histologically, infiltrating ductal carcinoma predominated, accounting for 96.6% (116 patients), while infiltrating lobular carcinoma represented only 3.33% (4 patients).

S.B.R grade of Primary Tumour

The majority of patients had SBR grade II tumours, i.e. 82 patients with a rate of 68.3%, 17 patients had SBR grade III tumours, i.e. 14.1% of cases. Grade SBR I was found in 10 patients (8.3%).

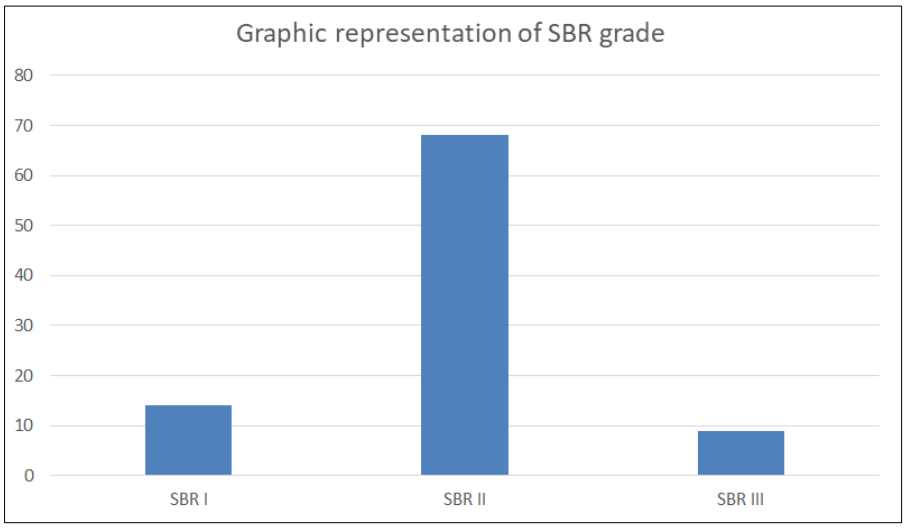

Figure 3 : Graphic representation of SBR node

Molecular Classification

According to immunohistochemistry results, 13% of patients were triple-negative and 86.6% were luminal tumors.

Molecular subtypes (A or B) could only be specified in 21 patients whose tumors were characterized by Ki67 expression.

Thus, Luminal (B) cancer represents 37%, and Luminal(A) represents only 31% of Luminal tumours, and is not determined for the others.

Bone Metastases:

Location:

Bone metastases were predominantly spinal, with 35 cases involving the cervical spine (42% of cases), 22 cases involving the lumbar spine (26.4% of cases) and 13 cases involving the dorsal spine (15.6% of cases). In the case of spinal metastases, there were 41

cases of posterior arch involvement (49.20%) and 56 cases of vertebral compression (67.2%). The other bone locations were the ribs with 10 cases (12.0%), the iliac bone with 18 cases (21.60%) and the sternum with 7 cases (8.4%).

Associations with Other Metastases:

On the basis of the CT scans performed as part of the extension work-up for each patient with metastatic breast cancer, we identified 4 metastasis locations: lung, bone, liver and brain. In first place were lung metastases, with 65 patients affected (87.1%), accounting for 47.1% of metastases. In second place were bone metastases, with 47 patients affected (68.4%), accounting for 32.6% of metastases. In third place, liver metastases were found in 29 patients (38.2%), accounting for 20.1% of metastases. Cerebral metastases were the least frequent, affecting 3 patients (3.9%) or 2.1% of all metastases.

Management of Bone Metastases:

Surgery:

Of our patients, 20% underwent at least one surgical procedure, mainly for bone fractures or medullary compression.

Radiotherapy: 78% of patients underwent radiotherapy for analgesic or decompensatory purposes.

Biphosphonates: Biphosphonates were used in 81% of patients.

Anti-RANK Ligand Antibodies: Used in 22% of patients.

DISCUSSION

Breast cancer has surpassed lung cancer to become the most common tumor worldwide [1], and approximately 70% of patients with advanced breast cancer will develop bone metastasis [2]. The spine is the most common site of bone metastasis (BM) in patients with breast cancer [2]. Once bone metastasis occurs, it is rarely treated successfully and increases the risk of bone-related morbidities, such as pain, pathological fracture, hypercalcemia, and spinal cord compression, which substantially decrease the quality of life of cancer patients [3]. An understanding of the molecular mechanisms underlying bone metastases of breast cancer is the basis for developing effective targeted drugs and improving the quality of life of patients.

Patients with solid tumors of the prostate, lung, kidney, breast, or colon frequently have bone metastases [4]. In patients with metastatic breast cancer, bone metastases are the most frequent location of metastasis, accounting for 60–75% of initial diagnoses [5]. According to a population-based study, between 2010 and 2013, 3.6% of all patients with an initial diagnosis of breast cancer and 62.5% of patients with an initial diagnosis of metastatic breast cancer had an initial diagnosis of bone-related breast cancer.

Furthermore, hormone receptor-positive patients (HR+/human epidermal growth factor receptor 2 (HER2-): 57.6%; HR+/HER2+: 12.9%) accounted for 70.5% of patients with bone metastases [5]. A median of 55% of patients who experienced distant metastases during follow-up had bone metastases, and 12% of patients with stage I–III breast cancer experienced bone metastases over a 5-year follow-up, according to one systematic review and meta-analysis.

To check for the existence of bone metastases, studies have employed bone scans and advanced imaging methods such computed tomography (CT) and magnetic resonance imaging (MRI) [6]. One study found that 38.5% of patients with breast cancer had SREs in the first year following the diagnosis of bone metastasis (95% CI: 36.0–41.0%), 20.3% of patients with advanced breast cancer had bone metastases in the first year following diagnosis, and 1.9% of patients had bone metastases in the first year following the initial diagnosis of breast cancer (95% CI: 1.7–2.0%) [7].

In one 12-year Korean cohort study, the cumulative incidence of SREs (defined as pathological fracture, spinal cord compression, surgery, or RT to bone) in breast cancer patients was 47%. This was higher than the reported rates of 31.4% for prostate cancer patients and 38.0% for multiple myeloma patients [8]. Every three to six months, there are major SREs that lower patients' quality of life and ultimately cause them to die as a result of bone problems and their treatment [9].

The survival rate of patients with bone metastasis is relatively higher; the median survival time of breast cancer patients with bone metastasis depends on age, race, grade, breast cancer subtype, concurrent metastasis in other visceral sites, and treatment (surgery and chemotherapy), ranging from 13 to 47 months Patients with breast cancer, especially those with HR+ breast cancer, had a higher survival rate than those with other solid tumors. The highest survival rate (92.5% at 4 years) was seen in patients with the HR+/HER-2- subtype, followed by those with the HR+/HER-2+ subtype (90.3%) and HR-/HER2+ subtype (82.7%). In contrast, the lowest survival rate was seen in patients with triple-negative breast cancer (77.0%, including those in early and advanced stages), which fell to 11.2% among patients with stage IV triple-negative breast cancer [29]. Patients with triple-negative breast cancer frequently develop metastases, particularly visceral metastases, which are linked to a poor prognosis [10].

In 81.4% of patients with metastatic cancer, bone pain was recorded, making it the most frequent consequence of metastatic bone disease [11]. Increased osteoclast activity causes pathological alterations in bone neuropathy and mechanosensitive pain from bone

loss, which are both part of the complicated process of metastatic bone pain [12]. When stretching, bone distending pain may also be a result of tumor infiltration into the periosteum [13]. Bone pain can also result from spinal cord compression, radiation, surgery, or pathological fractures [14]. Hypercalcemia is the most prevalent and deadly metabolic complication in cancer patients.

A poor prognosis is predicted by malignant tumor-related hypercalcemia, which is frequently seen in patients with breast cancer, multiple myeloma, squamous cell carcinoma, and other primary tumors and is documented in 20–30% of cancer patients along the course of the disease [15]. The most frequent causes are excess 1, 25-dihydroxy vitamin D synthesis, osteolytic cytokine generation, and malignant humoral hypercalcemia mediated by PTHrP [16].

Pathologic fracture, which affects 17–50% of women, is a relatively late consequence of bone involvement linked to endocrine therapy medications, including aromatase inhibitors, and bone metastases. It causes pain, deformity, loss of movement, paralysis, and death [17]. The risk of cardiovascular events, including venous thromboembolism (VTE), which is linked to higher mortality, is increased when a tumor spreads to the bone.

Therapies for Bone Metastasis

Bone-Modifying Agents

In order to prevent SREs (bone pain, pathological fractures, hypercalcemia, and bone marrow compression) in patients with bone metastases, as well as to delay the onset of the first SREs and decrease subsequent SREs, the FDA currently approves two classes of medications: bisphosphonates (represented by zoledronic acid (ZOL)) and the targeted medication denosumab.

ZOL

Several clinical trials have confirmed the efficacy of anti-osteoclastic bisphosphonates to stop bone loss after adjuvant breast cancer treatment. In preclinical models, bisphosphonates have been demonstrated to directly decrease angiogenesis and tumor growth [18]. By preventing farnesyl diphosphate synthase and protein prenylation, ZOL, a third-generation bone-targeting bisphosphonate, partially reduces the absorptive activity of osteoclasts. Osteoporosis in postmenopausal women, bone loss in patients with bone metastases from breast cancer [17], bone loss from cancer treatment in premenopausal women with early-stage breast cancer, and musculoskeletal symptoms associated with aromatase inhibitors in postmenopausal women with breast cancer [19] are all prevented by ZOL.

Denosumab

In postmenopausal women with osteoporosis and bone metastases from multiple myeloma or breast cancer, denosumab, a human-derived monoclonal antibody that targets RANKL, effectively and safely inhibits bone resorption and lowers the risk of SREs by competing with RANK on the osteoclast surface for RANKL binding [17, 18].

External Irradiation

The most frequent reason for palliative radiotherapy in individuals with breast cancer is bone metastases. Palliative radiotherapy aims to reduce spinal cord compression, minimize neurological symptoms, relieve pain, and stabilize and recalcify bone metastases. Radiation damage ultimately reduces tumor burden, osteolytic processes, and pain (by disrupting biomolecular pain regulation pathways) in patients with bone metastases [20].

Surgery

The majority of procedures offer palliative care to reduce pain, stabilize bone metastases, restore functional activity and weight bearing capacity, and enhance quality of life. Comprehensive excision may be able to cure a few isolated bone metastases. Clinicians from many specialties, including radiation, orthopedics, and oncology, must decide on the surgical technique and extent of resection based on the patient's overall health, tumor location, and prognosis [20].

CONCLUSIONS AND PERSPECTIVES

The therapeutic arsenal for the management of bone metastases is constantly evolving, more interdisciplinary than ever, with the association of techniques from different specialties, suggesting the interest of a dedicated multidisciplinary consultation meeting.

Declaration of Conflicting Interests

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