Title:

Higher rate of progesterone receptor positivity in skeletal metastases of breast cancer with a pathological fracture versus those without fracture

Short title:

Pathological fractures linked to increased progesterone receptor positivity in breast cancer metastases

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Influence of receptor status and proliferation index in skeletal metastases of breast carcinoma on pathological fracture occurrence
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Abbreviation list:

ASCO/CAP - American Society of Clinical Oncology/College of American Pathologists
BC - Breast cancer
CT - Computed tomography
ER - Estrogen receptor
FISH - Fluorescence In Situ Hybridization
HER2 - Human epidermal growth factor receptor 2
Ki67 - Ki67 proliferative index
MRI - Magnetic resonance imaging
PR - Progesterone receptor
PET - Positron emission tomography
SM - Skeletal metastases
SINS - Spinal instability neoplastic score
SPSS - Statistical Package for the Social Sciences

Novelty and Impact:

Few studies so far investigated the relationship between hormone and HER2 receptors in breast cancer metastatic tissue with the occurrence of a pathological fracture. Our results showed that skeletal metastases of breast cancer with a pathological fracture have a significantly higher rate of progesterone receptor positivity compared to those with no fracture. Determining the progesterone receptor status in skeletal metastases may identify high-risk groups for fracture occurrence and guide surgical and hormonal therapy.

ABSTRACT

Identifying risk factors for fracture occurrence in breast cancer (BC) skeletal metastases (SM) may guide the management of such bone deposits. There is sparse evidence regarding receptor status in SM and their relationship to fracture occurrence. This study aimed to determine the relationship between estrogen (ER), progesterone (PR), and HER2 receptor status and Ki-67 index and fracture occurrence in SM of BC. 152 samples of SM of BC obtained from individual patients were evaluated. The status of the aforementioned receptors and Ki67 index were determined in SMs samples. Their expression was compared between SM that did and did not develop a fracture. Ninety-one cases had pathological fracture at the SM site, and 61 did not. Patients who sustained a pathological fracture had a higher rate of PR positivity at their SMs as compared to those with no fracture. There was no significant difference between the two groups concerning ER, HER2+, or Ki67 status. SMs secondary to BC with a fracture are more likely to be PR positive than those with no fracture. Determining the receptor status in SMs may identify high-risk groups for fracture occurrence, and determining the PR status may also guide surgical and hormonal therapy.

Keywords:

pathological fracture; skeletal metastases; breast cancer; hormone receptor; progesterone

1. INTRODUCTION

Breast cancer (BC) is the leading cancer site in women with an incidence in Europe and North America of 85-94/100,000. [1] Although early diagnosis and contemporary treatment have improved the survival rates of BC patients remain second to lung cancer as a cause of cancer deaths. Such a high mortality rate is due to the early dissemination of cancer cells, especially in bone, with skeletal metastases (SM) reported in 65-75% of patients. In 5-6% of patients SMs are identified at the same time as the initial diagnosis of BC. [2]

A devastating complication of SM is the occurrence of a pathological fracture which impairs the patient's quality of life and can adversely affect the survival rate. [3] Hence, great effort is put into the early diagnosis and treatment of SM using radiological investigations such as whole-body bone scintigraphy, positron emission tomography (PET) along with a more focussed assessment of suspicious lesions using plain radiographs, computed tomography (CT) scan and magnetic resonance imaging (MRI).

Identifying SM at high risk for fracture allows early intervention to minimize the risk of fracture occurrence. Fracture risk scores for skeletal metastases have been described and are used in clinical practice including the Mirels` score for long bones and the spinal instability neoplastic score (SINS) for vertebrae. [4, 5] Mirels`score is based on plain radiographs and scores the site of metastasis, its size, the radiological type of lesion (lytic, mixed, blastic), and the pain it causes, each scored from 1 to 3 points. The SINS scores 6 components namely the location, pain type (none, mechanical, non-mechanical), radiological type, spine alignment, vertebral body collapse, and posterolateral involvement each scored from 0 to 3. Both scores are used for treatment guidance, especially in decision-making for prophylactic surgery of SM.

In addition to clinical and radiological parameters, it may also be that histological analysis of metastatic tissue may guide as to the risk of pathological fracture occurrence. It is recognized that the status of various tissue receptors and other cellular markers in the breast cancer tissue is related to the aggressiveness of the disease and the effectiveness of breast cancer treatment which raises the possibility that the status of these in metastatic disease may influence the risk of pathological fracture occurrence. These include the progesterone receptor (PR), estrogen receptor (ER), the human epidermal growth factor receptor 2 (HER2), and Ki67 proliferative index. [6, 7, 8, 9] However, although the status of these receptors is routinely reported in primary breast cancer biopsy analysis and used to guide treatment, this is not a routine practice for SM. Studies reported that the receptor status in SM may differ from that in their primary tumour, [10, 11, 12, 13] which emphasizes the importance of pathohistological and immunohistochemical analysis of metastatic tissue.

There is sparse evidence regarding receptor status in SM and the relationship of such receptors to fracture occurrence, hence this study was performed. The aim of this study was to determine the ER, PR, HER2 status, and Ki67 index in SM of BC with fracture vs. those with no fracture to thus determine whether there is any role in these factors in guiding as to the risk of pathological fracture occurrence.

2. MATERIAL AND METHODS

2.1 Clinical data

This was a retrospective, observational study that evaluated clinical, radiological, and pathohistological data in patients presenting with SM secondary to breast cancer. Patients treated at a regional reference centre for bone and soft tissue oncology over ten-year period (June 2011 to June 2021) were evaluated. Female patients with biopsy-proven metastatic breast cancer were included. Male patients and those surgically treated outside the reference center, as well as those with incomplete medical data, were excluded. Similarly, only lesions with completely determined ER, PR, HER2, and Ki67 status in the skeletal metastasis were included.

Bone lesions that presented with a pathological fracture were routinely biopsied at the fracture site in most cases along with the operative procedure of fracture treatment. Furthermore, bone lesions not associated with a fracture were biopsied if their primary origin was unknown or uncertain. SM with no fracture was biopsied if the time interval from the primary breast cancer diagnosis was long and was thus considered that the lesion may not be related to that primary or if the patient had been diagnosed earlier with more than one primary tumour. In those with multiple SM, the most suitable bone with regards to accessibility was selected for biopsy.

Clinical data were collected from patients' records. Radiological evaluation of SM was performed using plain radiographs, CT, and skeletal scintigraphy, and the results for these were assessed and reported. The immunohistochemical profile (PR, ER, and HER2 status) and Ki67 proliferative index were analyzed as described below.

2.2 Immunohistochemistry

Serial sections, 5 μm thick, were cut for immunohistochemical analysis of ER, PR, HER2, and Ki67 using US Food and Drug Administration approved primary rabbit monoclonal antibodies (Ventana Medical Systems, Oro Valley, Arizona, USA; PR [1E2 clone], ER [6F11 clone], HER2 [4B5 clone], and Ki-67 [M7240 Clone MIB-1, dilution 1 : 100; Dako]). Positive and negative controls were included for each case. The slides were evaluated according to the ASCO/CAP guidelines. [14, 15] For PR and ER the percentage and intensity of positively stained tumour cells were measured and the score was calculated by adding these two values for a total of 0 to 8. The percentage of positive tumour cells was divided into 6 categories, 0 - negative, 1 indicating <1%, 2 - 1%-10%, 3 - 11%-33%, 4 - 34%-66%, and 5 - 67%-100% (Figure 1). The intensity of positive tumour cells was averaged across the predominant area and scored 0 indicating no staining, 1 - weak staining, 2 - moderate staining, and 3 - strong staining. HER2 slides were analyzed for the intensity of staining and percentage of stained cells and classified as negative (score 0 or 1+), equivocal (score 2+), or positive (score 3+). For equivocal cases, immunohistochemical analysis was repeated, and if still unchanged, fluorescence in situ hybridization (FISH) was performed. Tumour cells with nuclear staining were considered positive for Ki-67 and were reported as a percentage of the overall cells. [16]

2.3 Statistical analysis

Statistical analysis was performed using SPSS v.28.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data are expressed as a percentage of a group for discrete measures. A normal distribution of continuous numerical data was analyzed using the non-parametric Kolmogorov-Smirnov test. For categorical data t-test was used and where it was not applicable, non-parametric statistical Pearson's chi-squared test and Mann-Whitney test were utilized. The odds ratio and 95% Confidence Intervals were also calculated. Statistical significance was established at the $p<0.05$ level.

3. RESULTS

3.1 Demographic and clinical characteristics

152 patients were included for analysis, with a mean age of 61.4 years (range 33-83, SD=10,37, 95%CI ±1.649). Localized bone pain and limitation of the movement were the most common complaints at the SM site. In this series 99/152 (65.1%) patients had a confirmed diagnosis of breast cancer prior to the SM biopsy, whilst in 53/152 (34.9%) the diagnosis of BC was made for the first-time following bone biopsy. In those with previously diagnosed breast cancer, the mean time from the primary breast cancer diagnosis to the diagnosis of SM was 75.7 months (range 4-264, SD=61.47, CI95% ±15.99). The duration of symptoms related to the SM until pathological fracture varied from 1 day (in patients with sudden pathological fractures and no previous complaints) to 60 months (mean of 4.4 months, SD=8.15, CI95% ±1.297). A total of 91 (59.9%) cases had a pathological fracture at their skeletal metastasis whereas 61 did not. The demographics between these groups were similar (Table 1.).

At the time of the SM diagnosis, 81 patients (53.3%) had a SM in only one bone and 71 patients (47.7%) in two or more bones. The most frequently involved bone was the femur in 71 cases (46.7%), followed by the spine in 67 (44.1%) and the pelvis in 39 (25.6%). The femur was the most frequently fractured bone, in 55 cases (60.4%). Mixed SM (with osteoblastic and osteolytic components) were seen in 101 cases (66.4%) and lytic SM (isolated osteolysis), in 51 (33.6%) (Table 2.). No relationship was found between the lesion's radiological appearance and fracture occurrence ($p=0.117$).

In 67 (44.1%) cases an isolated SM biopsy was performed whereas in 85 (55.9%) cases other concomitant surgical procedures were performed as part of the fracture treatment. These additional surgical procedures included stabilization with or without corpectomy of the affected vertebra (21), stabilization of long bone with or without resection (18), resection of the long bone segment and implantation of a tumor mega-prosthesis (26), and hemiarthroplasty or total hip arthroplasty (20).

3.2 Immunohistochemistry

Overall, 71 (46.7%) biopsy samples were positive for PR (PR+), 117 (76.9%) for ER (ER+), and 57 (37.5%) for HER2 (HER2+).

In the group with pathological fracture PR+ metastases were seen 49 (53.9%) patients versus 22 (36.1%) in those without fracture ($p<0.05$). We further analyzed the PR score along with the intensity of expression and percentage of positive cells (Table 3.). The PR score was significantly higher in those with a pathological

fracture ($p<0.05$), and this was mainly due to the percentage of positive cells ($p<0.05$) rather than staining intensity ($p=0.066$).

In the group with pathological fracture 71 (78%) were ER+ and in the group without fracture 46 (75.4%) were positive (OR=1.16, CI95%=0.54-2.49, p=0.708). HER2 was positive in 32 (35.2%) cases with fracture and in 25 (41%) without (OR=0.78, CI95%=0.40-1.52, p=0.468). The mean Ki67 value was 23.4 for all SM (range 1-90, SD 17.94, CI95% ±2.852). The mean value was 22.9 in SM with pathological fracture and 24.2 in those without fracture (p=0.542).

4. DISCUSSION

Our results showed that SMs of breast cancer with a pathological fracture had a significantly higher rate of PR positivity and PR scores as compared to those with no fracture. Moreover, our findings show that the association between the PR score and fracture occurrence depends on the percentage of stained cells and not on the staining intensity. The latter is in line with previous reports that recommend that ≥1% of hormone receptor-positive tumour cells presence should be considered as hormone receptor-positive tumor. [14]

Breast cancer is the most common type of cancer in women, with 2.3 million women diagnosed globally with the disease and 685 000 deaths in 2020. [17] The occurrence of distal metastatic disease is the main cause of breast cancer-related mortality. Breast cancer can metastasize to several organs in the body, with bone being the most common site, accounting for 60-80% of metastatic cases [18] and with a median survival of 3 – 5 years. [19]

Metastatic breast cancer can cause destruction of the normal skeletal structure and function, resulting in skeletal-related events, including severe bone pain, pathological bone fracture, spinal cord compression, and hypercalcemia, which may lead to reduced quality of life and survival. [20] Under normal circumstances, bone metabolism is a well-balanced process between osteoblasts and osteoclasts, regulated by various cytokines and steroid sex hormones, including estrogen and progesterone. [21] Disrupted levels of these hormones together with their downstream receptor signalling may lead to an abnormal bone composition and facilitate the development of SM.

Primary breast cancers and/or metastatic deposits may be biopsied before any treatment to confirm the diagnosis of malignancy and also to establish the expression of three receptors namely PR, ER, and HER2. The expression of these receptors may help clinicians formulate an individualized management plan for each breast cancer patient, and determine the order of the various treatment modalities in this plan (such as surgery, chemotherapy, endocrine suppression therapy, and biological anti-HER2 treatment). Discordance in the PR and/or ER, and HER2 status between primary and metastatic breast cancer has been described more than 30 years ago, [22] but only recently this important feature of the disease is coming into focus. [23] With discordant rates ranging from 18% to 56% for PR and ER status and 6% to 48% for HER2 status, obtaining a biopsy from metastatic lesions rather than simply relying on the characteristics of the primary breast tumour seems of substantial clinical importance. [24] When the status of primary and metastatic tissues are discordant, the consensus of the American Society of Clinical Oncology (ASCO)/ College of American Pathologists (CAP)

clinical practice guideline is to use the PR, ER and HER2 status of the metastasis to direct therapy if supported by the clinical scenario of the individual patient. [25]

PR and ER are both critical steroid hormone receptors employed to predict response and hence the suitability of endocrine suppression therapy (including tamoxifen, aromatase inhibitors such as Anastrazole, Letrozole, and Exemestane), as well as provide prognostic information. About 70-80% of both primary breast cancers and metastatic breast cancers to the bones are hormone receptor-positive. Hormone receptor-positive breast cancers tend to have the highest probability of developing bone metastases. [26] HER2 is a receptor tyrosine kinase on the plasma membrane of breast cells, it is overexpressed in 25-30% of breast cancers and it is usually associated with the amplification of the Erb-B2 gene. HER2 overexpression plays an important pathogenic role in breast cancer, as it provides the cancerous cells with potent proliferative and anti-apoptosis signals, being the main driver of tumour development and progression in this subset of breast cancer. [27]

Breast cancer is a heterogeneous disease that encompasses multiple biologically distinct entities with specific biological behaviours and pathological features. It was previously shown that the receptor status of primary BC tissue may influence the development of SMs and their radiological features (sclerotic or lytic) [8]. The influence of receptor status on patient survival after pathological fracture and the outcome of surgical treatment is also well documented. Triple-negative tumours (PR/ER/HER2) are the most aggressive, whilst PR-positive primary breast cancer shows more aggressive features in comparison to ER-positive lesions. [28, 29] Since PR and ER regulate each other`s expression, various combinations of these receptors and HER2 receptor differ in their prognosis, with single PR+ (ER-) and HER2- patients having poorer prognosis than PR+ and ER+, also than single ER+ (PR-) in same HER2- subtype. [30]

Although various national and international guidelines exist as to the management of early and metastatic breast cancer, to the best of our knowledge, none of these guidelines provides any guidance as to how the receptor status of the SMs of these patients may help in the selection process by the orthopaedic surgeon of the patients who are at high risk of pathological fractures and therefore require bone fixation. Our results showed that SMs of breast cancer with a pathological fracture had a significantly higher rate of PR positivity and PR scores as compared to those with no fracture. Moreover, our findings show that the association between the PR score and fracture occurrence depends not on the staining intensity but on the percentage of stained cells. These findings raise the possibility that the progesterone status of metastatic bone lesions may help identify SM at high risk for fracturing. Such an approach may supplement existing predictive clinical and radiological scores such as the Mirels`and SINS scores. [4, 5]

Limitations of this study include its retrospective design and the lack of a complete cohort of breast cancer cases. However, despite its limitations, this study assessed a large number of patients to allow meaningful conclusions and guide clinical decision-making. Since tumour tissue in SM can differ from the primary tumour, the significance of this study is that it shows the potential value of routine biopsy of SMs and establishing their receptor status. Long bone SMs found to be PR+, especially SMs in the femur, may benefit from prophylactic stabilization to minimize the risk of fracture. PR positivity may also guide hormone therapy for such bone lesions either as the principal or post-surgery treatment.

In SMs of BC, PR positivity may confer an increased risk for fracture, especially in the femur. This may be taken into consideration with regard to the prophylactic surgical treatment of SM or guide hormone therapy of such lesion.

5. ETHICS STATEMENT

The study was approved by the Ethical Committee of the Medical Faculty, University of Belgrade, number 1322V-3, and the research was carried out in compliance with the 1964. Declaration of Helsinki. It was conducted retrospectively as data analysis of an existing data bank without any additional experiment on human or animal tissue. Informed Consent to Participate and Consent to Publish were obtained from all participants or if participants are under 18, from a parent and/or legal guardian.

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7. ADDITIONAL INFORMATION

7.1 Authors' contributions

SR was responsible for designing and writing the protocol, conducting the search, collecting surgical data, reviewing other studies in this field, extracting and analyzing data, interpreting results, and writing the report. MC contributed to analyzing and interpreting the results. CC analyzed and interpreted the results and helped write the report. LS was responsible for pathologic diagnostics, collecting pathological data, analyzing and interpreting results, and writing report. GD took part in collecting and analyzing radiological data and analyzing and interpreting results. DD contributed to collecting pathological data and took part in analyzing and interpreting results. LM helped collect surgical data and review studies at writing the report. BM conducted the statistical analysis and helped analyze and interpret the results. JS took part in designing and writing the protocol, supervising pathological data, reviewing previous studies, and analyzing and interpreting results. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

7.2 Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

7.3 Competing interests

The authors declare that they have no conflict and competing interests.

8. FIGURE LEGEND

Figure 1. (A) Typical morphology of metastatic breast cancer into the bone (H&E, 4x), (B) Bone trabeculae surrounded by tumor tissue (H&E, 20x) (C-H) Percentage of PR positive tumor cells were divided into 6 categories: (C) 5/ indicating 67%-100%; (D) 4/ 34%-66%; (E) 3/ 11%-33%; (F) 2/ 1%-10%, (G) 1/ <1%, (H) 0/ negative) (PR, 20x).