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Research Article

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Different Prognosis of Bone Metastasis in Breast Cancer Patients Molecular Subtypes: Luminal-A Luminal-B

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ABSTRACT

The aim of study It was unclear whether breast cancer subtypes are associated of bone metastasis probability. In molecular subtypes among post-treated patients (hormone-receptor-positive breast cancer), considering statistical frequency of stages, and their prognostic significance.

Methods and Materials: 101 women (I, II, III stages; hormone-receptor-positive), who underwent bone scintigraphy before and after treatment, were retrospectively studied. The study was performed with radiotracer Tc99m MDP, intravenous injection. BS data were correlated with molecular subtype (Luminal-A, Luminal-B) and stage.

Results: According to the stages, molecular subtypes and bone metastasis was revealed:
In the I stage - 32 (20,0%) patients: luminal A - 30 (93.7%) patients, among them with metastasis 12 (40%) cases; luminal B - 2 (6.2%) patients with metastasis 0 (0%) cases (p=0.282).

II stage - 83 (51.9%) patients: luminal A = 71 (85.5%) patients, among them with metastasis - 43 (60.5%) cases; luminal B - 12 (14.4%) patients; among them with metastasis -3 (25%) cases (p=0.022)

III stage =45 (28.1%) patients: Luminal A 38 (84.4%) patients, among them with metastasis - 30 (78.9%) cases; luminal B - 7 (15.5%) patients; among them with metastasis - 1 (14.2%) case (p=0.001)

Conclusion: Breast cancer subtypes are associated with different metastatic patterns and confer different prognostic impacts. Among breast cancer patients molecular subtype luminal A has a high probability of spreading metastasis in bone, but there is more positive prognosis, rather than in luminal B type, that is much more rare and aggressive molecular subtype.

Taking into consideration molecular subtypes and stages of breast cancer is very important, as both of them are significant prognostic factors of disease, which might be helpful in the most cases.

Keywords: Molecular subtype luminal - A has a high probability of spreading metastasis to the bone system, rather than in luminal B type, Molecular subtype luminal _A has more positive prognosis in dynamic observation, rather than in luminal B type

Introduction

According to data provided by the World Health Organization, Breast cancer ranks first among oncological diseases in the female population (30%). According to the data of 2020, 2.3 million new cases of cancer were revealed in the world. Globally, the number of deaths from breast cancer reaches 685,000. 7.8 million women in the world live with this disease. About 90% of breast cancer deaths are related to disease recurrence or disease complications caused by metastatic lesions. According to experts prognosis, by 2030, without additional interventions, new cancer cases will reach 21.7 million and deaths will reach 13 million; Nearly one-third of patients with early-stage breast cancer at the time of first diagnosis suffer from metastatic disease during lifetime [1]. About 7% of patients with initially diagnosed breast cancer already present with metastatic disease at time of first diagnosis [2]. The molecular Types of the primary tumor usually remain in the metastases. The management of metastatic disease is often based on the receptor status of the primary lesion. However, differences between the receptor status of the primary tumor and the metastases exist [3]. It is known that the role of hormones, mainly estrogens, in the development of breast cancer, hormone-

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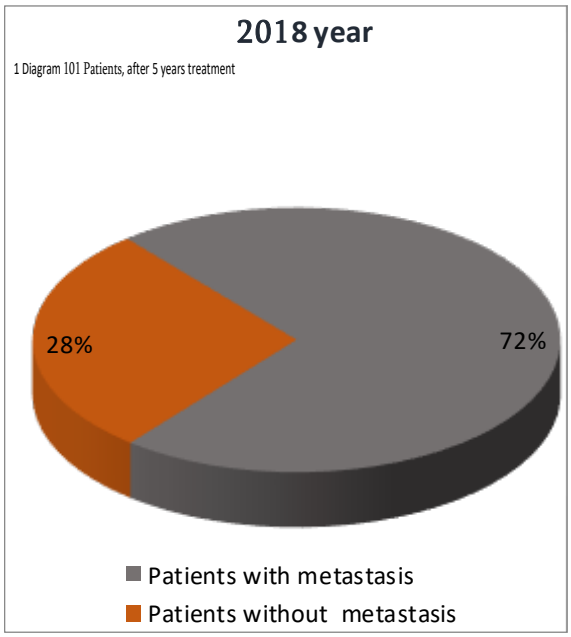
sensitive tumors are mainly found in cancers developed from the ductal epithelium of the mammary gland (79%). Molecular breast cancer subtypes are associated with different models of metastatic behavior and provide different information about the prognosis [7-9]. Cancer cells contain proteins (receptors) to which the hormone (estrogen/progesterone) binds and stimulates cell growth. as well as the prognosis difference between primary and metastatic breast cancer patients of different subtypes, have remained to be fully defined. Luminal molecular type breast cancer represents the majority of breast cancer cases and despite relatively good prognosis, its heterogeneity creates problems with a proper stratification of patients and correct identification of the group with a high risk of metastatic relapse. According to the different sources molecular subtypes Luminal A, Luminal B have different rates of metastatic bone lesions and have different prognoses. Triple-negative breast cancer is relatively rare, often occurs at a young age (under 30 years), and is characterized by a more aggressive spreading on bone system is less common (15%) [4-7].

Bone metastases cause fractures, spinal cord compression, and hypercalcemia effect the patient's quality of life. Accurate assessment and timely elimination of skeletal complications improve the patient's quality of life. Therefore, it's very important to reveal incidence of bone lesions in molecular subtypes (according to the stages) for disease prognosis [8,9].

Bone scan (BS) is very sensitive, easily performing, screening method for detection of bone metastasis; This method reveals (Tc99 Methildiphosphonat - MDP) small blastic activity, before visible structural changes [10].

The purpose of this study is to determine the association between molecular subtypes and metastatic patterns and their impact on prognosis the Surveillance, Epidemiology and end Results database.



Patients and Methods

In Todua Clinic Radionuclide department, BS was performed on 1,737 patients (2018). We retrospectively selected 101 patient stages- I, II, III with a 5-year history of breast cancer, who underwent treatment (operative: sectoral or complete resection, radiation therapy, chemotherapy, targeted therapy, hormone therapy). The age of the patients ranged from 37 to 77 years (average age 55 years). The studies were conducted with SIEMENS cameras: Symbia intevo (Hybrid) and Symbia Evo. Radiopharmaceutical Technetium99m-methyl diphosphonate (99mTc MDP) was used for the research, which was administered Iv 500-750 mbq. The whole body scan was performed after 3 hours from injection. The table movement speed was 9 cm in 1 minute. BS data were correlated with molecular subtype (Luminal-A, Luminal-B), stage, and grade. In doubtful cases BS results were correlated with MRI or CT.

Results/Discussion

101 patients who were diagnosed with breast cancer (stage I, II, III) in 2018 were selected according to our retrospective study. Bone scan data were analyzed before and after (5 years) treatment. Histomorphology- Invasive ductal carcinoma revealed in 95% of patients, (the most frequent morphological form of breast cancer), while papillary and medullar carcinoma were detected in 5% of patients.

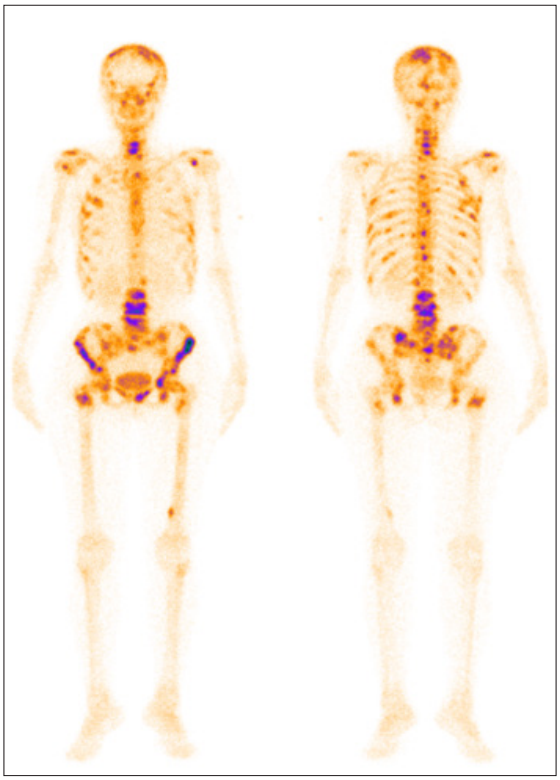
In our study, luminal A was detected in 71 (70%) of 101 patients, of which metastatic lesions of the bone system were found in 49 (34%) patients. Luminal B was detected in 29 (30%) of 101 patients, and metastatic lesions of the bone system were seen in 8 (9%) cases.

In the I stage - 32 (20,0%) patients: luminal A - 30 (93.7%) patients, among them with metastasis 12 (40%) cases; luminal B - 2 (6.2%) patients with metastasis 0 (0%) cases (p=0.282).

II stage - 83 (51.9%) patients: luminal A = 71 (85.5%) patients, among them with metastasis - 43 (60.5%) cases; luminal B - 12 (14.4%) patients; among them with metastasis -3 (25%) cases (p=0.022)

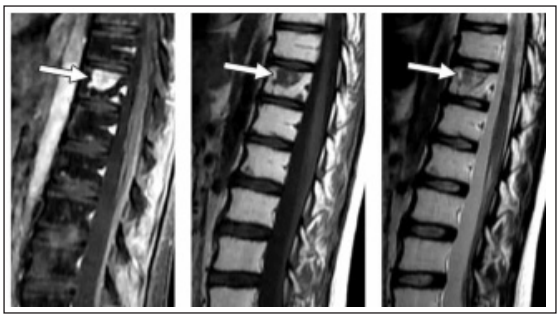
III stage -45 (28.1%) patients: Luminal A 38 (84.4%) patients, among them with metastasis - 30 (78.9%) cases; luminal B - 7 (15.5%) patients; among them with metastasis - 1 (14.2%) case (p=0.001)

Molecular Subtypes	ER/PR	Metastasis %
Luminal A	• ER/ PR-+positive • HER2- negative.	101 → 7 (70%)
Luminal B	• ER/ PR-positive or one of them neg • HER2-positive (or HER2-neg)	101 → 29 (30%)

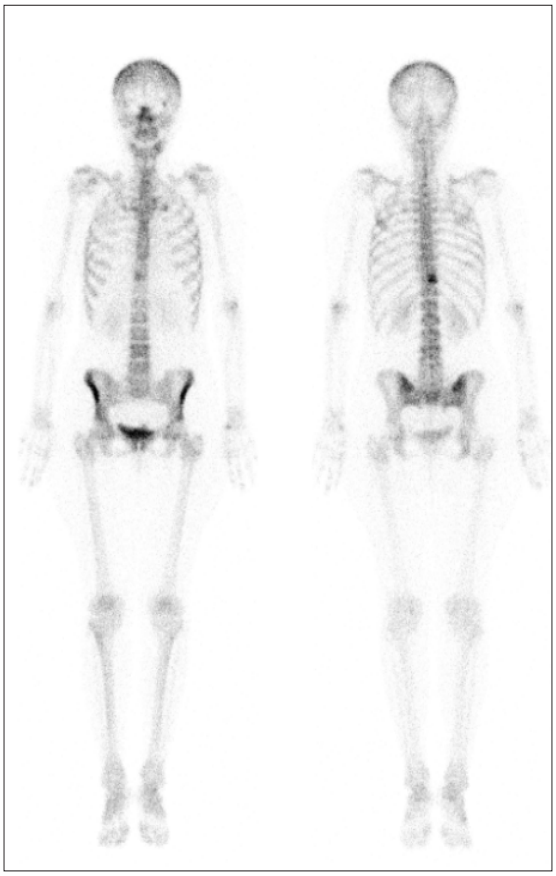


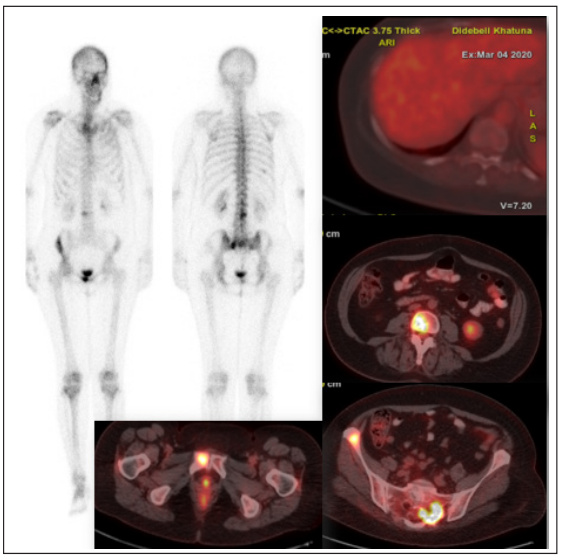
[Figure 1] Woman 55 year old, 4 years ago diagnosis: breast cancer stage II, ductal-invasive carcinoma G2, ER/PR(+), Her2neu-neg, treatment: chemotherapy, hormone therapy, (5 years later), currently complains of pain in the spine and chest area. Bone scan shows multiple metastatic lesions.

The percentage of distribution in multifocal metastatic lesions is as follows: chest and ribs 37%; Lumbar segment 26%, pelvis 16%, limbs 15%, skull 6%. (most often in the spine: chest -45%, waist -30%, neck -15, sacral area-10%)



[Figure 2] 42-year-old woman diagnosed with: breast cancer 7 years ago, stage I, morphologically ductal-invasive carcinoma G2, ER/PR (+), Her2neu-neg, treatment was performed: right-sided sectoral resection, radiation therapy, hormone therapy (5 years), currently in control laboratory study revealed high level of marker. In control research bone scan revealed focal uptake in vertebra Th 10 (mts?), additional was performed MRI which revealed mts damage in this area.





[Figure 3]. 39-year-old woman. Diagnosed: right breast cancer 5 years ago, stage IIb, ER/PR (+) morph: ductal-invasive carcinoma. Treatment was performed: right-sided mastectomy, chemotherapy, hormone therapy (5 years). Currently, in blood high level of markers. Progression of disease. BS and PET/CT FDG revealed increased uptake metastatic lesions in bone.

Among the complaints, a large number of patients mentioned pain (80%) and limitation of movement (40%), according to our observation, pain was not always related to the degree of bone damages, but rather depended on the localization of the metastatic focus. Pain was mostly experienced by patients who had damage in the spine (thoracic, lumbar) and pelvic bones.

Discussion

In most cases, the generation of breast cancer metastatic lesions may last for months, years or even decades prior to becoming a clinically detectable metastasis [16]. While the underlying mechanisms remain to be fully elucidated, it is known that metastasis is a process that begins with the detachment of tumor cells from the primary tumor [17]. Pre-emptive identification of patients at risk of distant metastases can improve the effectiveness of early diagnosis and interventions, and enhance the monitoring of the preferred location for metastasis in breast cancer patients. Biopsies are rarely performed to confirm the diagnosis of metastatic disease, even in the case of an interval of many years from initial diagnosis to relapse. Nevertheless, therapeutic decisions on the systemic therapy for advanced breast cancer with hormone blocker therapy, cytotoxic or targeted agents are often based on the biological information of the patients' original receptor status of the biopsy or surgery at time of the initial diagnosis. However, certain characteristics of the receptor status such as ER, PR, status may change [20]. Heterogeneity between primary cancer and metastatic lesion might be based on recently gained biological characteristics that enable tumor cells to wander through the circulatory and lymph system, in order to metastasize to distant organs [21,22]. Additionally, a more difficult IHC staining process in some metastatic tissues, especially in the bone, might play a role, pretending the loss of any receptor because of methods for decalcifying the bone biopsies. Available data suggest that the common methods for decalcifying the bones do not hamper the analysis of tumor phenotype and do not affect the IHC evaluation [23-24]. The conventional model of breast cancer progression is based on the paradigm that breast cancer passes through several stages from an in situstage to an invasive stage, followed by dissemination to the lymph nodes and distant organs [25]. Our study primarily focused on the conventional model, postulating new ideas on the common understanding diagnostic of breast cancer metastasis.

Conclusion

Breast cancer subtypes are associated with different metastatic patterns and confer different prognostic impacts.

Studies have shown that Luminal A occurs more often among hormone-positive tumors and is characterized by less damage to the bone system than Luminal B. prognostic value were determined in the case of Luminal A, the high probability of spreading the disease in the bone system was more noteworthy than in the case of Luminal B type.

Our research proved that most of patients where diagnostic in stage II, but metastasis was revealed in stage III, we have seen prognostic risk factor of bone metastasis in stage III. Taking into consideration molecular subtypes and stages of breast cancer is very important, as both of them are significant prognostic factors of disease, which might be helpful in the most cases.

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