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ORIGINAL ARTICLE

Breast cancer and musculoskeletal implications - potential mechanism of dissemination

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Abstract

The purpose of this article was to analyze bone metastases as being the most common site of recurrence of breast cancer. Bone metastases secondary to breast cancer have a negative impact on patient survival, mobility and quality of life. In addition, the clinical complications of bone cancer metastases of breast cancer are associated with a significant financial burden for the individual and society.

This article summarized the implications of breast cancer musculoskeletal metastases based on clinical application in an emergency hospital, including patient workup, procedural strategy and techniques.

Keywords: metastatic breast cancer, bone, muscle, molecular subtype, survival

Introduction

Breast cancer remains the leading cause of cancer-related deaths among women, with around 95,000 deaths by 2020, accounting for 17% of all deaths from the disease. The latest statistics show breast cancer accounting for 13.3% of all new cases of cancer diagnosed in

EU-27 countries in 2020. This makes it the most common type of cancer (Fig. 1, 2). It is estimated to account for 28.7% of all new cases of cancer in women. Although the incidence rate of breast cancer has increased over the last decade, death rates have either decreased or stabilized due to earlier diagnosis and better treatment.

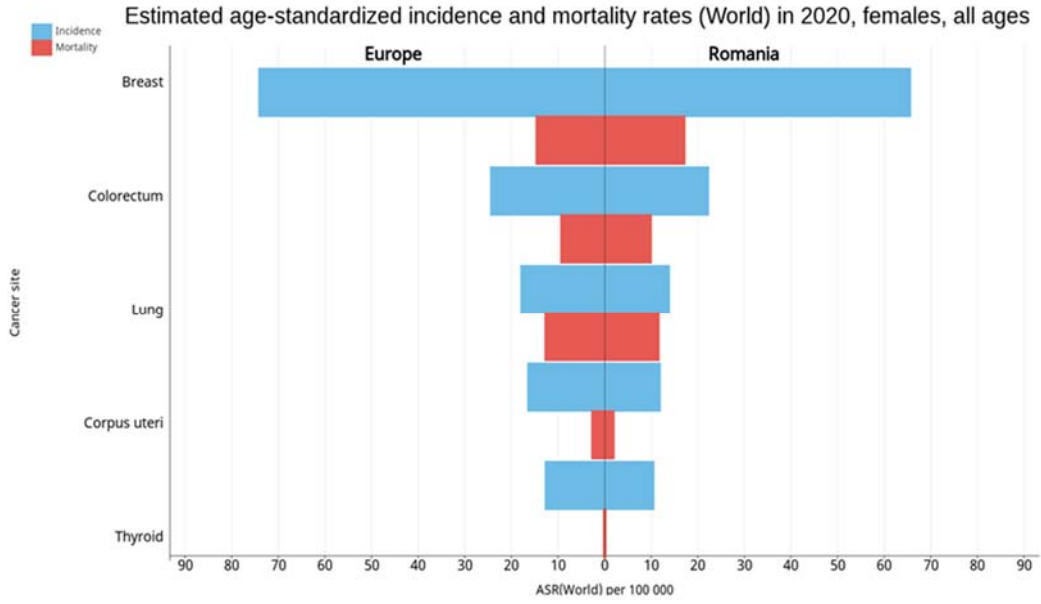


Fig. 1 *Comparison of cancer incidence and mortality rates between Europe and Romania (adapted from https://gco.iarc.fr)*

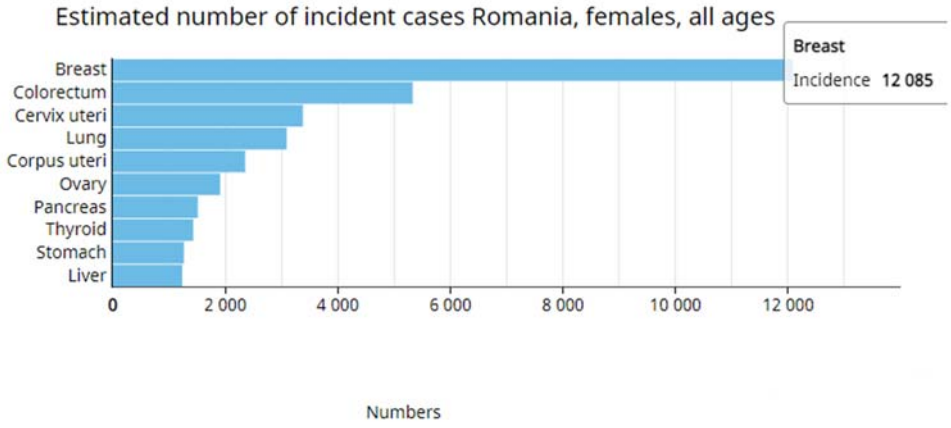


Fig. 2 *Comparison of the incidence between cancer sites in women of all ages in Romania in 2020*

Breast cancer is characterized by frequent metastases to the skeleton, ending the normal process of bone remodeling and causing bone degradation. Osteolytic lesions are the result of osteoclast activity. However, osteoclast differentiation and activation are mediated by osteoblastic production of RANKL (NFkB ligand receptor activator) and several osteoclastogenic cytokines. Osteoblasts themselves are adversely affected by cancer cells: increased apoptosis and a decrease in the proteins needed to form new bones. Thus, bone loss is due to both increased activations of osteoclasts and suppression of osteoblasts [1].

Cachexia associated with breast cancer is due to elevated inflammation, including high levels of interleukin (IL)-6, as well as increased oxidative stress [2]. These same factors are also linked with the development and progression of tumors. Furthermore, skeletal muscle ryanodine receptor 1 (RyR1) intracellular Ca2+ release channels, required for skeletal muscle coupling excitation-contraction, becomes oxidized in the setting of bone metastases, resulting in reduced muscle function [3].

Breast cancer is known to be a heterogeneous disease with a wide range of different subtypes and stages that lead to different treatment responses and disease-specific outcomes, including sites of dissemination.

Considering biomarkers, the various subtypes of breast cancer can be identified primarily by immunohistochemistry (IHC) and the expressed gene pattern. Depending on the fluorescent in situ hybridization profile (FISH) or immunohistochemical profile, breast cancer can be classified as follows, according to the recommendations of the American Society of Clinical Oncology/ ASCO/ CAP) [4]:

- Presence of estrogen receptor (ER) = ER-positive;
- Presence of progesterone receptor (PR) = PR-positive;
- Presence of receptor for human epidermal growth factor 2 (HER2) = HER2-positive;
- Triple-negative (defined by the absence of ER, PR and HER2) - representing ~ 20% of all cases of breast cancer; it is associated with poorer prognosis and reduced survival due to early metastases in other organs and lack of targeted therapies.

Genetically speaking, breast cancer is classified into four major intrinsic molecular subtypes with prognostic and therapeutic implications:

- luminal type A - includes ER-positive and/ or PR-positive tumors, but HER2-negative and is reported to have a higher propensity to develop bone metastasis;
- luminal type B - includes ER-positive and/ or PR-positive and HER2-positive tumors in only 30% of cases;
- HER2 - includes ER-negative, PR-negative, but HER2-positive tumors;
- basaloid - includes ER-negative, PR-negative and HER2-negative tumors.
- From a morphological point of view, breast carcinoma is classified as follows:
  - invasive ductal carcinoma (CDI) of no special or otherwise unspecified type (NOS) is the most common (40-75%) histological type of invasive breast cancer. Although common, CDI NOS is not well defined at all, and the 2012 World Health Organization (WHO) classification defines CDI NOS by exclusion as "a heterogeneous group of tumors that do not have sufficient characteristics to be classified as a specific histological type". In addition to the NOS CDI, the WHO classification includes 21 special subtypes with distinct morphological features, of which:
  - invasive lobular carcinoma (CLI) is the most common (5-15%);
  - tubular, mucinous and papillary carcinomas usually have excellent clinical results compared to the 2 subtypes described above and do not always require chemotherapy.

Detection of breast cancer metastases

At present, detection of breast cancer metastases relies on:

- clinical manifestations (such as new breast lumps, pain in the bone, chest or

abdomen, dyspnea and constant headaches);
- biopsies of affected organs (Fig. 3, 4);
- radiological evaluations and other imaging methods (such as mammography, ultrasound, MRI and CT examinations (Fig. 5-8) for the detection of relapse in breast cancer, bone scintigraphy, liver echography and chest X-ray);
- serum tumor markers (evaluation of serum carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA) and breast cancer-associated antigen 115 D8/ DF_3 (CA15.3));
- analysis of circulating tumor cells (CTCs), which has shown promise in filling the gaps left by other diagnostic methods. CTCs are tumor cells originating from primary sites or metastases that circulate in the patients' bloodstream and are very rarely found in healthy individuals [5]. CTCs are firstly isolated and enriched through either morphological (separating CTCs according to size discrepancies, density) or immunological techniques (which are the most widely used methods, they employ immunomagnetic isolation using either epithelial cell-specific markers that are generally expressed in all tumor cells, or tumor markers expressed by specific types of cancer). After isolation, the origin of the CTCs is identified using nucleic acid-based methods, such as quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR), or cytometry-based methods, such as flow cytometry and enzyme-linked immunospot assay technology.

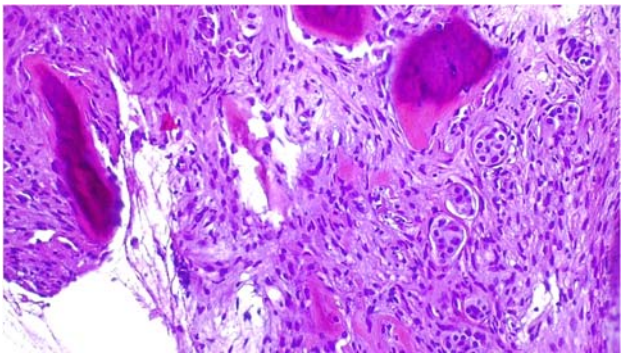


Fig. 3 *The tumor proliferation completely occupies the bone marrow, having a destructive effect on the bone lamellae. Tumor cell groups are surrounded by desmoid fibrous stroma. Hematoxylin-Eosin stain × 200 (personal archive of Dr. Dumitru)*

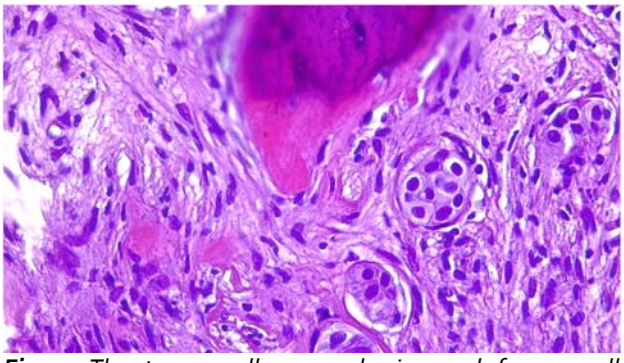
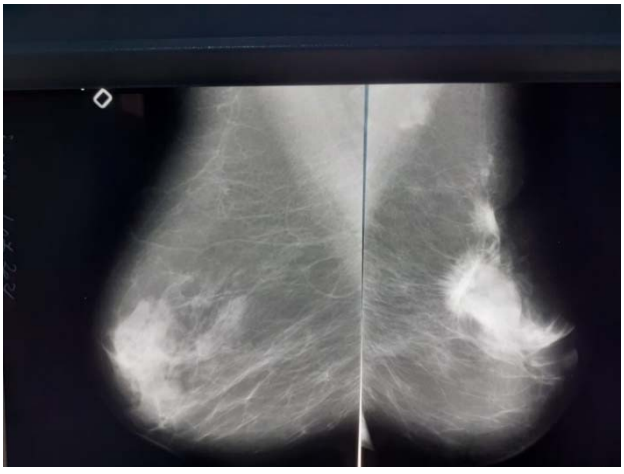


Fig. 4 *The tumor cells are cohesive and form small compact nests or pseudoglandular structures distorted by the surrounding fibrous stroma. The tumor cells have large, tachycromatic nuclei with slightly irregular borders. Microscopic features are highly suggestive of a bone metastasis of breast carcinoma of no special type (invasive ductal carcinoma). Hematoxylin-Eosin stain × 400 (personal archive of Dr. Dumitru)*



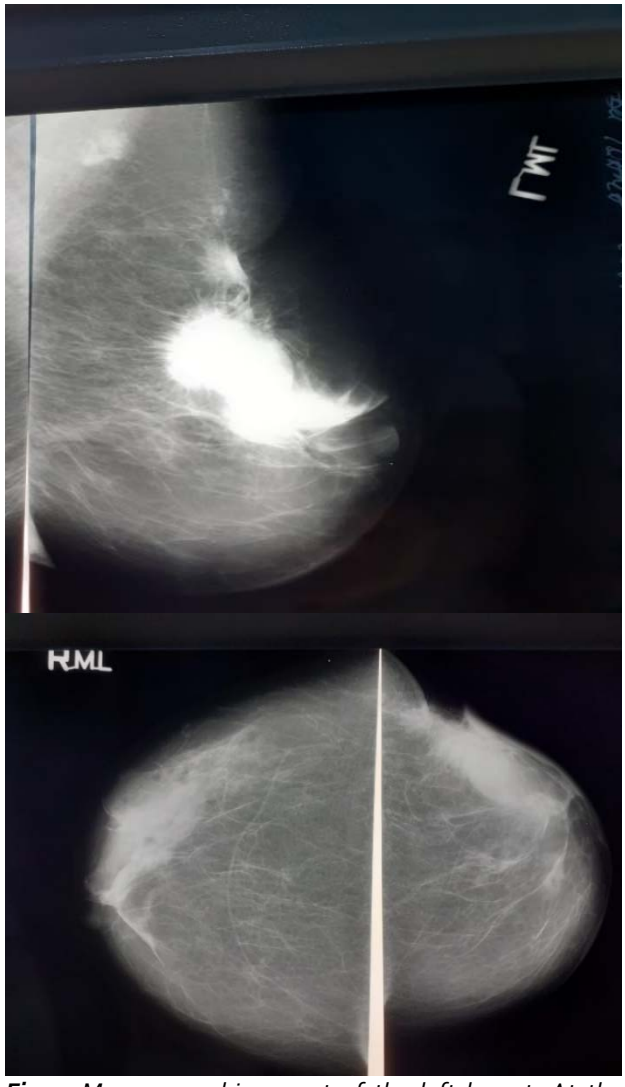
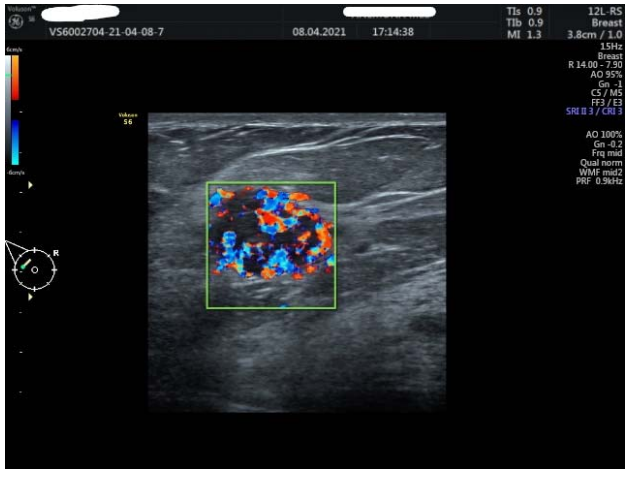


Fig. 5 *Mammographic aspect of the left breast. At the intersection of the external quadrants, there are two stellar opacities, with skin retraction, accompanied by adenopathic block in the left armpit (B.I.R.A.D.S. score = 5 - oncological lesions) (Dr. Șerboiu's personal archive)*



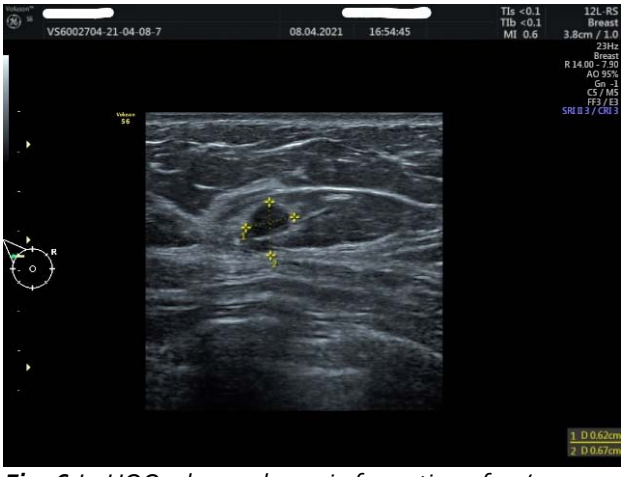


Fig. 6 *In UOQ - hypoechogenic formation of 12/ 14 mm, irregular contour, with macro- and microcalcifications inside, intense Doppler signal, accompanied by axillary extension of the gland, by a hypoechogenic nodular formation (intraparenchymal ganglion), B.I.R.A.D.S. score = 4c - highly suspicious ultrasound lesion (personal archive of Dr. Şerboiu)*

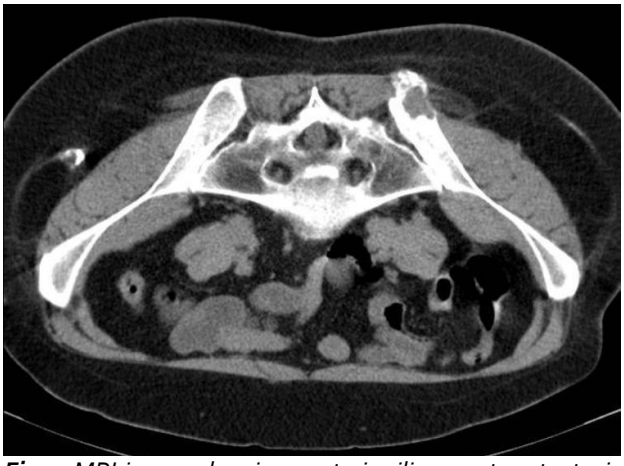


Fig. 7 *MRI image showing posterior iliac crest metastasis in a 52-year-old female secondary to breast adenocarcinoma, 9 years after chemotherapy, radiotherapy and primary tumoral resection (Department of Orthopedics and Traumatology - University Emergency Hospital, Bucharest, Romania)*

Most breast cancer patients are consistent with overexpression of hormone receptors (ER+/ PR+), and are treated with endocrine therapies:

- Aromatase inhibitors (AIs) block estrogen production. The most common AIs are anastrozole, letrozole, and exemestane.
- Other drugs block estrogen's effects by binding to the estrogen receptor.

Tamoxifen is a selective estrogen receptor modulator (SERM), and fulvestrant is a selective estrogen receptor degrader (SERD).

- Surgical interventions such as ovarian ablation will eliminate ovarian function and estrogen production.
- Lastly, ovarian suppression can also be induced through drugs such as goserelin or leuprolide. *Premenopausal breast* cancer patients treated by ovarian suppression with goserelin have increased bone loss (10.5%) 6 years after a 2-year treatment regimen compared with women receiving a traditional adjuvant chemotherapy regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (6.5%). The onset of bone loss is significant (21% decreased bone density compared with age-matched fertile women) [**6**].

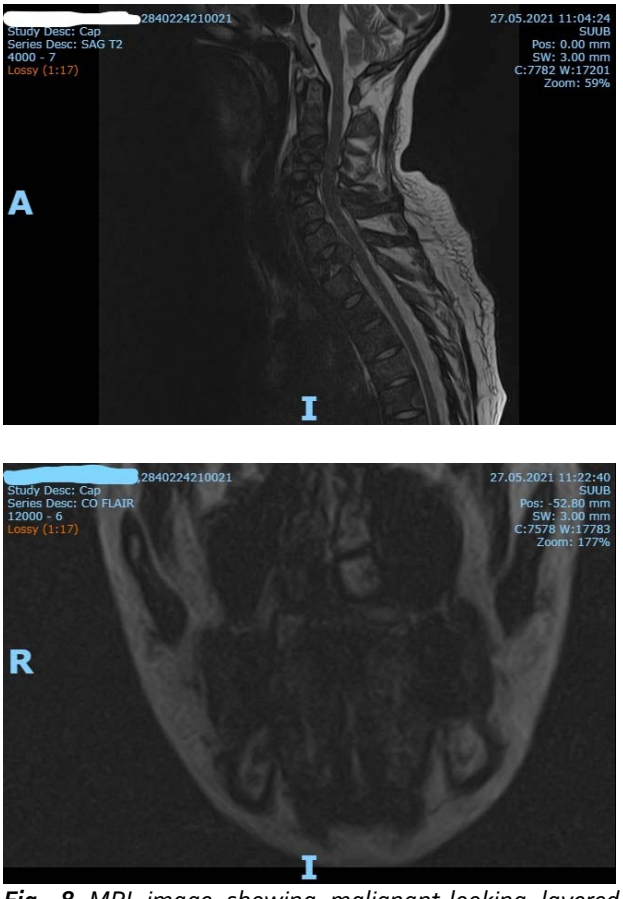


Fig. 8 *MRI image showing malignant-looking layered cervical vertebral compressions at the level of C3-4-5, tumor mass causing intracanal compression at T1 level and mandibular metastases in a 37-year-old female diagnosed with NST invasive breast cancer*

Muscle implications - mechanisms and clinical manifestations

Muscle wasting is a commonly observed phenomenon in the setting of cancer [7]. As muscle is lost, patients may initially be considered sarcopenic, but as the muscle loss progresses, patients may be diagnosed with cachexia. Sarcopenia is clinically defined as the presence of low skeletal muscle mass and either 1) low muscle strength, 2) low muscle function, or 3) low muscle performance. A recent international consensus process led by experts in medical cachexia defined it as weight loss of at least 5% or more in 12 months or less in the presence of underlying illness, plus three of the following criteria:

- decreased muscle strength;
- fatigue;
- anorexia;
- low fat-free mass index;
- abnormal biochemistry (increased inflammatory markers [C-reactive protein > 5.0 mg/ L, IL-6 > 4.0 pg/ mL], anemia [< 12 g/ dL], and low serum albumin [< 3.5 g/ dL]) [8].

Bone implications - mechanisms and clinical manifestations

Severe osteodynia, pathologic fractures, and nerve compression are the three most common symptoms of bone metastasis and are associated with poor outcome and reduced life quality. Metastasis through blood plays a major role in distant metastases in breast cancer, and so the rich blood flow in the bone marrow and the stream of blood from the breast to the skeleton via the vertebral-venous plexus significantly increases the risk of cancer metastases to bone. Also, the bone is suggested to be a large collection of growth-stimulating factors including fibroblast growth factors, platelet-derived growth factors, and bone morphogenetic proteins. These factors, released and activated in bone, could

stimulate growth of tumor cells and act as a fertile ground for metastasis formation. Although bone metastases are common in metastatic breast cancer, the preferential metastases sites of breast cancer were reported to be different based on the biomarkers' status:

-HR+ or HER2 - breast cancers are more likely to have skeletal involvement among patients with breast cancer recurrence. The mechanism regarding the preference of bone metastasis for HR+ breast cancer remains unknown. However, some studies pointed out that this phenomenon may be associated with tumor dormancy [9] (dissemination of breast cancer cells takes place long before the detection of cancer metastases and a part of these cells might survive and become dormant in bone marrow). The dormant cancer cells with positive expression of HR, which are hormone responsive, could be reactivated by steroid hormone and they subsequently develop metastasis disease in bone).

Materials and methods

The aim of the present retrospective analysis was to deter¬mine the prevalence of musculoskeletal metastases in patients diagnosed with breast cancer. The patients who met our criteria were divided into multiple groups based on the biomarkers, genetical and morphological characteristics. Thus, the studied population consisted of 440 suspected cases, out of which 112 cases were confirmed. The patients were referred to the Departments of Obstetrics Gynecology and General Surgery, University Emergency Hospital Bucharest. An informed consent was obtained from all patients. Patients' medical charts were retrospectively evaluated for clinical and laboratory data. Clinical data collection was based on a standardized inter¬view completed by all the patients presenting with features of breast cancer.

In the first stage of statistical evaluation, descriptive tests were applied while monitoring the morphological pattern, type of biomarkers present and the presence or absence of musculoskeletal metastases in the studied group.

Results

In the analysis of the cases admitted to the Department of Obstetrics Gynecology and General Surgery of the University Emergency Hospital Bucharest from January 2015 to June 2021, we identified 112 cases with breast cancer, which was histologically confirmed (Chart 1).

Five cases also asso¬ciated other synchronous cancers (Chart 2), whereas 4 cases had confirmed musculoskeletal metastases.

Most of the cases were registered in women older than 50 years and residing in rural regions (Chart 3). This is also reflective of the fact that Romania belongs to a low breast cancer awareness area.

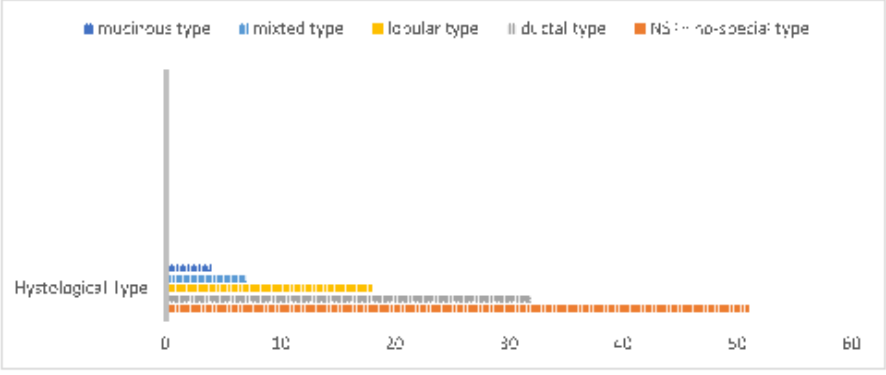


***Chart 1**. Types of breast cancer (histologically aligned) discovered during 78 months in the Department of Obstetrics Gynecology and General Surgery of the University Emergency Hospital Bucharest, Romania*

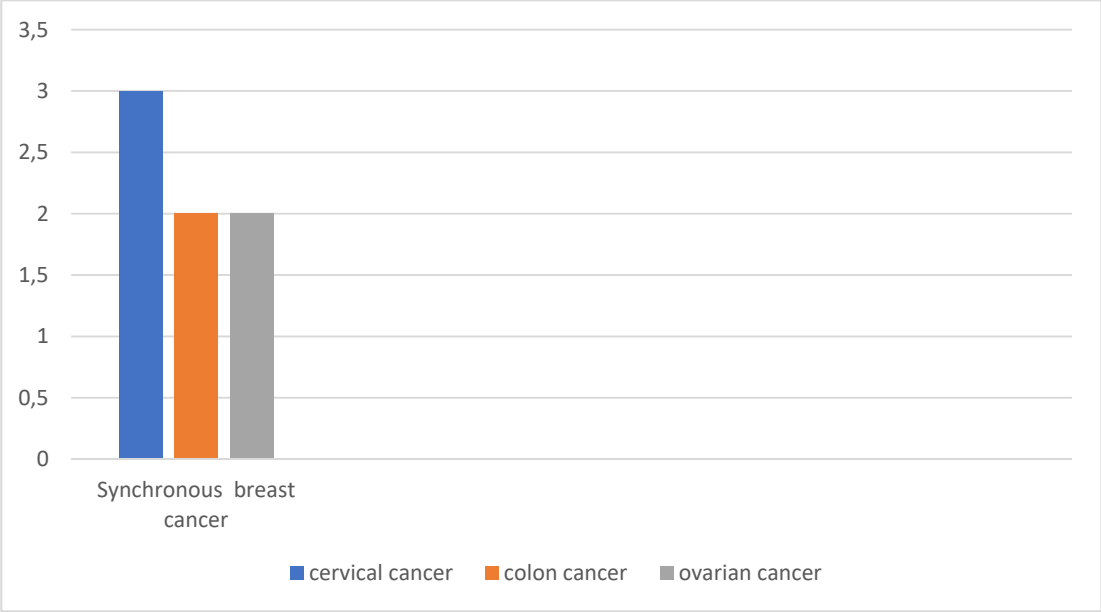


***Chart 2**. Breast cancer associating other types of synchronous neoplasia during 78 months in the Department of Obstetrics Gynecology and General Surgery of the University Emergency Hospital Bucharest, Romania*

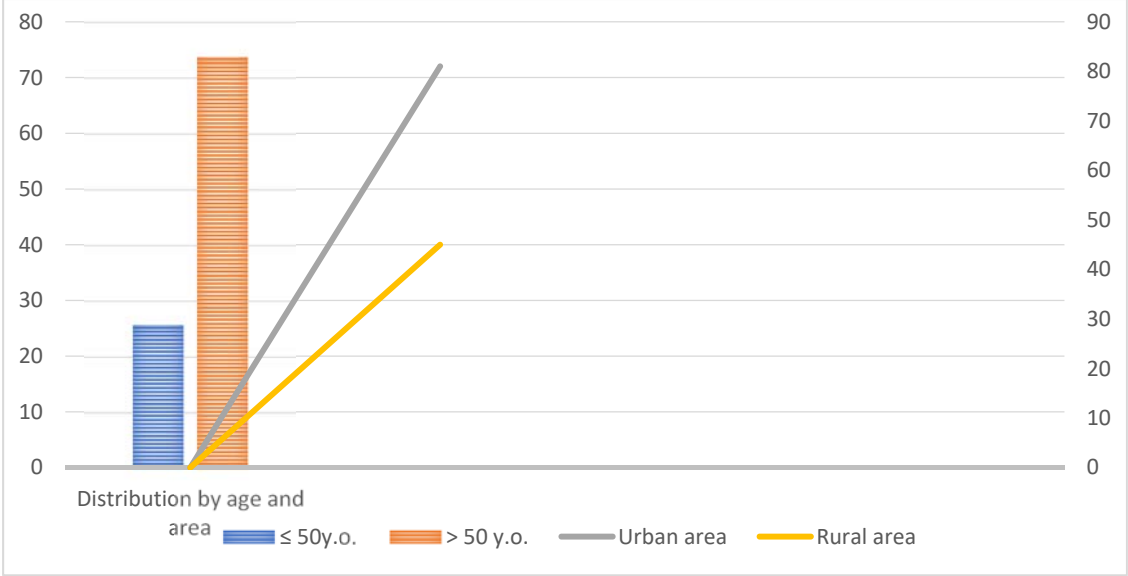


***Chart 3**. Comparison between the rural and urban area of the distribution of breast cancer during 78 months in the Department of Obstetrics Gynecology and General Surgery of the University Emergency Hospital Bucharest, Romania*

Discussions

In our study, 3.57% of the patients included presented bone metastases, which represents a relatively low percent compared to literature data. The main mechanism of dissemination in breast cancer is represented by a hematogenous pathway and there are numerous studies that show the bone as a common organ involved in a majority of cases - almost 70% of all metastatic patients [**10**]. Bone involvement is facilitated by some intrinsic properties of the tumor cells such as specific expression of certain genes that amplify the bone metastatic potential, like CXCR4, fibroblastic growth factor 5 - angiogenesis promoter, interleukin 11 (IL11) - osteoclast stimulating factor. Another important process that emphasizes tumor cell capacity of reaching the bone is represented

by changes regarding the bone microenvironment - increase of TGF β signaling, increased expression of adhesion molecules, increased expression of cytokine receptors and increased expression of ligand receptors. These changes create a homing process at the bone level, which is influenced by the presence of stromal bone marrow cells [**11-13**]. However, we must state the fact that most of the patients included were lost during follow-up, thus the accurate percentage of bone metastases regarding this current study might be difficult to assess.

Regarding other types of gynecological cancers, cervical and ovarian cancers rarely metastasize to the bone, given the fact that the major pathway of dissemination is represented by transcoelomic and lymphatic for ovarian cancer, respectively direct local extension and lymphatic for cervical cancer. Thus, the percentages of bone metastases in ovarian and cervical cancer are relatively low (0.1-0.12% for ovarian neoplasia, 3.8% for cervical neoplasia) compared to breast cancer bone metastatic potential [**14,15**].

Another essential topic is represented by the necessity of including certain screening methods to accurately identify bone metastases, especially when there are no symptoms of actual bone involvement. The advantages of these screening methods consist of adequate disease staging, which is important when it comes to elaborating the right therapeutic approach - diminishing disease complications such as the risk of pathologic bone fractures and perioperative risks. If there are no apparent lesions on standard radiographies, MRI and CT with or without the use of contrast can be useful, with a detection limit of 2 mm for MRI and 5 mm for CT. What should be noted is that the use of contrast-enhanced CT or MRI improves the chance of adequately depicting soft tissue involvement. Also, the differential diagnosis between osteoblastic vs. osteolytic lesions should be established with the help of bone scintigraphy [**16,17**].

The latest NCCN guidelines regarding the management of metastatic disease in breast cancer focus on the use of CT and bone scintigraphy prior to the start of new therapies, but also after 2-4 cycles of chemotherapy or 2-6 cycles of endocrine therapy, meaning a continuous and optimal follow-up protocol. Moreover, restaging using these imagistic studies is mandatory whenever the concern for progression of disease arises. The findings correlated with disease progression might be: aggravating pain or dyspnea, alteration of performance status, unintentional notable weight loss, elevated alkaline phosphatase, ALT, AST, hypercalcemia, radiographic alterations or pre-existing evolving lesions or other anomalies on functional imaging, elevated tumor markers (CEA, CA 15-3, CA 27.29) [**18**].

Conclusions

From the point of diagnosis to treatment, the cancer continuum and survivorship is a very variable process. For certain cancers, therapeutic strategies try to account for musculoskeletal effects. However, for breast cancer, the presence of metastases remains the biggest hurdle. Recent findings have established a conceptual framework of cancer metastasis and provided deeper insights on the molecular basis of metastatic traits, their origins, and their evolution. How to incorporate this knowledge into the design of next-generation therapy is the key to combating breast cancer metastases.

Conflicts of interest

The authors state no conflict of interest.

Informed Consent and Human and Animal Rights statements

An informed consent has been obtained from all individuals included in this study.

Authorization for the use of human subjects

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the review board of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.

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Disclosures
None.

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