

Advances in Research on the Mechanisms of Breast Cancer Bone Metastasis

Mu Gao¹, Hongtao Sun^{1*}

¹ Guangdong Second Provincial General Hospital, School of Medicine, Jinan University, Guangdong, Guangzhou, China

Email Address

1026781779@qq.com (Mu Gao), 13808849918@163.com (Hongtao Sun)

*Correspondence: 13808849918@163.com

Received: 16 March 2024; Accepted: 30 March 2024; Published: 22 April 2024

Abstract:

Breast cancer is one of the most common malignancies among women, and its bone metastasis is one of the leading causes of worsened prognosis and decreased quality of life in patients. This article reviews the research progress on breast cancer bone metastasis, including the basic concepts of breast cancer and bone metastasis, clinical significance, molecular mechanisms, and recent research advances. By analyzing cytokines, signaling pathways, and the regulatory network of metastasis and tumor suppressor genes, the mechanisms by which breast cancer cells invade bone tissue and form metastatic lesions are revealed. Furthermore, new treatment strategies for breast cancer bone metastasis have been proposed, providing novel insights for clinical therapy. This review contributes to a deeper understanding of the pathophysiological processes of breast cancer bone metastasis and provides guidance for future research and clinical applications.

Keywords:

Breast Cancer, Bone Metastasis, Pathophysiology, Molecular Mechanisms, Treatment Strategies

1. Introduction

As shown in Figure 1, Breast cancer is one of the most common malignancies among women, with its incidence steadily rising, posing a serious threat to the health and well-being of patients. It is estimated that breast cancer has become one of the leading causes of cancer-related deaths among women worldwide. Despite significant progress in the early screening, diagnosis, and treatment of breast cancer, some patients still experience recurrence and metastasis after treatment, with bone metastasis being the most common form of metastasis. Breast cancer bone metastasis has significant clinical implications, not only leading to a decline in patients' quality of life but also significantly increasing mortality rates. Bone metastasis can cause severe complications such as bone pain, fractures, and hypercalcemia, seriously affecting patients' functional and psychological well-being. Moreover, breast cancer bone metastasis also imposes a significant burden on healthcare resources, increasing the difficulty and cost of treatment. The mechanism of breast cancer bone metastasis

is extremely complex, involving the interaction of multiple factors. Factors such as cytokines, signaling pathways, and the regulatory network of metastasis and tumor suppressor genes all play important roles in this process. In recent years, with the continuous development of molecular biology and biochemistry technologies, new breakthroughs have been made in the study of the mechanisms of breast cancer bone metastasis, providing important experimental evidence for a deeper understanding of the pathophysiological processes of breast cancer bone metastasis. This article aims to systematically review the research progress on breast cancer bone metastasis, including the basic concepts of breast cancer and bone metastasis, clinical significance, molecular mechanisms, and the latest treatment strategies. Through comprehensive analysis of relevant literature and research findings, we hope to provide more effective measures and methods for the prevention and treatment of breast cancer bone metastasis, thereby improving patients' survival rates and quality of life [1].

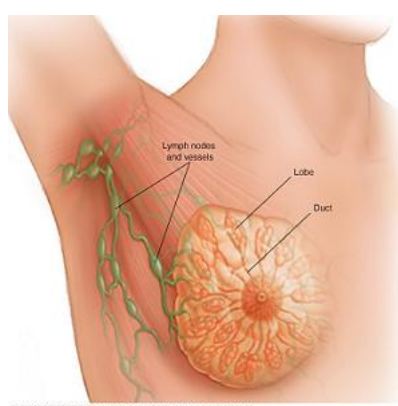


Figure 1. Breast cancer.

2. Breast Cancer: Basic Concepts

2.1. Definition and Classification of Breast Cancer

Breast cancer is one of the common malignancies among women and can also occur in men, although it is relatively rare. It typically originates from epithelial cells within the breast ducts or lobules, presenting as a heterogeneous tumor whose pathogenesis is influenced by various factors, including genetics, environment, and lifestyle [2].

Based on histological and molecular characteristics, breast cancer can be classified into different subtypes, which hold significant clinical implications:

- a. **Non-invasive Breast Cancer:** This type of breast cancer is usually confined to the breast ducts or lobules without invading surrounding tissues or blood vessels. Non-invasive breast cancer includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS).
- b. **Invasive Breast Cancer:** This is the most common type of breast cancer, characterized by malignant cells infiltrating surrounding tissues or blood vessels, with the potential for metastasis and spread. Common subtypes of invasive breast cancer include invasive ductal carcinoma and invasive lobular carcinoma.
- c. **Special Histological Types:** These encompass rare subtypes of breast cancer, such as intraductal papillary carcinoma, mucinous carcinoma, and phyllodes tumor. These

subtypes may exhibit different clinical presentations and require tailored diagnostic and treatment approaches [3].

d. **Molecular Subtypes:** Based on the expression of molecular markers in breast cancer cells, breast cancer can be classified into estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative subtypes. These subtypes have significant implications for treatment selection and prognosis assessment. For example, hormonal therapy may be effective for ER and PR-positive breast cancer, while targeted therapy may be more effective for HER2-positive breast cancer. Understanding the different classifications of breast cancer is crucial for developing individualized treatment plans and assessing prognosis. With advancements in the molecular biology of breast cancer, the classification system continues to evolve, providing a more reliable basis for precision medicine and personalized therapy.

2.2. Mechanisms and Clinical Manifestations of Breast Cancer

The pathogenesis of breast cancer is a complex process involving the interaction of multiple factors. Genetic factors play a crucial role in breast cancer pathogenesis, particularly mutations in genes such as BRCA1 and BRCA2, which are closely associated with familial breast cancer risk. These mutations can lead to impaired DNA repair mechanisms, increasing the likelihood of cellular mutations and tumorigenesis. Additionally, hormonal factors also play a significant role in the development and progression of breast cancer. Excessive exposure or imbalance of estrogen and progesterone may result in abnormal proliferation and carcinogenesis of breast tissue. Environmental factors such as dietary patterns, lifestyle, and environmental pollution are also believed to be associated with the pathogenesis of breast cancer. Unhealthy habits such as high-fat diets, lack of exercise, smoking, and alcohol consumption may increase the risk of breast cancer. Abnormal immune system responses may be involved in the pathogenesis of breast cancer, and long-term use of immunosuppressive agents or immunodeficiency states may also increase the risk of breast cancer. In terms of clinical manifestations, symptoms of breast cancer vary among individuals. In addition to common symptoms such as breast lump, nipple discharge, changes in breast skin, alterations in breast size or shape, and enlargement of axillary lymph nodes, clinical manifestations of breast cancer may also include breast pain, tenderness on palpation of breast tissue, breast skin erythema, and nipple retraction. In summary, a comprehensive understanding of the pathogenesis and clinical manifestations of breast cancer is crucial for early diagnosis, treatment, and prognosis assessment [4].

3. Bone Metastasis: Basic Concepts

3.1. Definition and Classification of Bone Metastasis

Bone metastasis, a process where malignant tumor cells disseminate from the primary tumor site via the bloodstream or lymphatic system to bone tissue, giving rise to secondary bone tumors, represents a common complication of various malignant tumors, notably breast cancer, prostate cancer, and lung cancer, among others, with a high incidence rate. The intricate process of bone metastasis involves multifaceted cellular and molecular mechanisms encompassing tumor cell invasion, bone resorption, and bone formation. Bone metastasis, characterized by its pathological features and clinical presentations, can be categorized into distinct types:

a. **Osteolytic Bone Metastasis:** Among the most prevalent forms, malignant tumor cells secrete osteolytic factors like interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF- α), triggering osteoclast activation and subsequent bone resorption. This process leads to bone tissue degradation and osteolysis, culminating in the formation of lytic bone metastatic lesions.

b. **Osteoblastic Bone Metastasis:** This type of bone metastasis is closely associated with enhanced bone formation. Malignant tumor cells release factors such as bone morphogenetic proteins (BMPs), osteoprotegerin (OPG), and transforming growth factor-beta (TGF- β), which stimulate osteoblast proliferation and differentiation, fostering new bone formation and resulting in the development of sclerotic bone metastatic lesions.

c. **Mixed Bone Metastasis:** Exhibiting both osteolytic and osteoblastic characteristics, this type manifests with concurrent bone destruction and new bone formation, giving rise to mixed bone metastatic lesions. Clinically, this type of bone metastasis is also frequently encountered.

Comprehending the diverse manifestations of bone metastasis facilitates the formulation of tailored treatment strategies by healthcare professionals and enables more precise prognosis assessments. With advancements in elucidating bone metastasis mechanisms, the ongoing development of targeted therapies brings renewed optimism for patients confronting this challenging condition[5].

3.2. Pathophysiological Processes of Bone Metastasis

Bone metastasis is a complex pathophysiological process involving the regulation of multiple cellular and molecular mechanisms. This process begins with the shedding of malignant cells from the primary tumor, which then travel through the bloodstream or lymphatic system to distant skeletal sites. Upon reaching the skeletal system, malignant tumor cells must adapt to and alter the bone microenvironment to ensure their survival and proliferation. Tumor cells may regulate the bone marrow microenvironment by secreting growth factors and extracellular matrix proteins, promoting tumor cell colonization and growth. Subsequently, malignant tumor cells promote bone resorption by releasing osteolytic factors, leading to osteoporosis, skeletal structure destruction, and fracture occurrence. Meanwhile, certain tumor cells can also stimulate new bone formation in the skeletal system, resulting in bone metastatic lesions characterized by both osteolysis and new bone formation. Additionally, bone metastasis patients typically experience severe bone pain, which may lead to fractures, hypercalcemia, and other serious complications, significantly affecting patients' quality of life and prognosis. Continued spread and growth are another key step in bone metastasis, as malignant tumor cells can proliferate and spread within the bone tissue, forming larger bone metastatic lesions, exacerbating patient symptoms and complications. A deep understanding of the pathophysiological processes of bone metastasis is crucial for developing targeted treatment strategies and improving patient prognosis.

4. Clinical Significance of Breast Cancer Bone Metastasis

4.1. Incidence and Prognosis of Breast Cancer Bone Metastasis

Breast cancer is a highly complex disease, with bone metastasis being one of its most common and severe complications, significantly impacting both patient survival

rates and quality of life. Statistics indicate that approximately 70% to 80% of advanced breast cancer patients will develop bone metastasis during the progression of the disease, making breast cancer one of the primary primary tumors associated with bone metastasis. Compared to patients with localized primary tumors only, those with breast cancer bone metastasis typically face a more dire prognosis. Bone metastasis not only leads to severe clinical symptoms such as bone pain, fractures, and hypercalcemia but also may cause persistent physical discomfort and a decline in quality of life for patients. Additionally, bone metastasis adversely affects the survival rates of breast cancer patients, often marking an advanced stage of the disease and complicating treatment efforts. Therefore, early screening for bone metastasis in breast cancer patients and effective treatment are crucial, as they can significantly improve patient prognosis and quality of life.

4.2. Impact of Bone Metastasis on Patient Quality of Life and Treatment Plans

Breast cancer bone metastasis has a significant impact on patient quality of life and treatment plans. Firstly, bone metastasis often accompanies severe symptoms such as intense bone pain, fractures, and hypercalcemia, severely affecting patients' daily lives and work capacity. These symptoms can lead to decreased physical strength, increased mental stress, and even interference with social and family life. Secondly, bone metastasis poses challenges to the treatment plans for breast cancer patients. Due to the presence of bone metastasis, some traditional treatment methods, such as surgery and radiation therapy, may be limited or ineffective, as the presence of bone metastatic lesions increases the complexity and risks of treatment. Moreover, bone metastasis may also affect patient tolerance and efficacy of systemic treatment options such as chemotherapy, hormone therapy, and targeted therapy. Therefore, treatment strategies for breast cancer bone metastasis typically need to consider the severity of the condition, overall patient status, and the risks and benefits of treatment comprehensively. Personalized treatment plans often include bone protective treatments (such as bisphosphonates, anti-resorptive agents), pain management, and systemic treatments (such as hormone therapy, targeted therapy, chemotherapy), aimed at alleviating symptoms, controlling disease progression, and maintaining patient quality of life as much as possible. In summary, bone metastasis not only directly impacts patient physical health and quality of life but also has significant implications for treatment plan selection and effectiveness, necessitating comprehensive treatment strategies and personalized management plans[6].

5. Molecular Mechanisms of Breast Cancer Bone Metastasis

5.1. Role of Cytokines and Signaling Pathways in Breast Cancer Bone Metastasis

The occurrence and progression of breast cancer bone metastasis involve a complex process regulated by various cytokines and signaling pathways. Cytokines play crucial roles in bone metastasis by modulating the activities of tumor cells, bone cells, and immune cells, affecting the occurrence, growth, and progression of breast cancer bone metastasis. Some important cytokines and signaling pathways include:

a. TGF- β (Transforming Growth Factor- β) Pathway: TGF- β is a critical growth factor playing a dual role in breast cancer bone metastasis. On one hand, TGF- β can promote epithelial-mesenchymal transition (EMT) of breast cancer cells, enhancing their invasive and migratory capabilities. On the other hand, TGF- β can stimulate

osteoblast differentiation and bone matrix synthesis, promoting the formation of bone metastatic lesions.

b. **RANK/RANKL/OPG System:** RANKL (Receptor Activator of Nuclear Factor κ B Ligand) and its receptor RANK play essential roles in breast cancer bone metastasis. RANKL is a crucial cytokine that can stimulate osteoclast activation and bone resorption. In breast cancer bone metastasis, breast cancer cells can secrete RANKL to promote bone resorption, thereby increasing the occurrence and progression of bone metastasis. OPG (Osteoprotegerin) is a natural antagonist of RANKL, which can inhibit the action of RANKL, reducing bone resorption and suppressing the occurrence of breast cancer bone metastasis.

c. **Wnt/ β -catenin Pathway:** The Wnt/ β -catenin pathway plays a key role in regulating cell proliferation, differentiation, and stem cell fate and also has significant implications for the occurrence of breast cancer bone metastasis. Aberrant activation of the Wnt/ β -catenin pathway may promote the proliferation and invasion of breast cancer cells and also affect bone matrix synthesis and the formation of bone metastatic lesions [7].

Cytokines and signaling pathways play crucial roles in the occurrence and progression of breast cancer bone metastasis. In-depth research into these mechanisms helps uncover the molecular mechanisms of breast cancer bone metastasis and provides a theoretical basis for the development of relevant treatment strategies.

5.2. Regulation Network of Metastasis Genes and Tumor Suppressor Genes

Breast cancer bone metastasis involves a complex regulation network comprising multiple metastasis genes and tumor suppressor genes, pivotal in governing tumor cell proliferation, invasion, and metastasis. Among these genes, HER2 stands out as a significant metastasis gene, with its overexpression linked to heightened invasiveness and metastatic potential in breast cancer. Dysregulated HER2 activation promotes breast cancer cell proliferation, invasion, and metastasis, thereby facilitating bone metastasis progression. Similarly, TWIST1, another crucial metastasis gene, drives epithelial-mesenchymal transition (EMT) and enhances breast cancer cell metastatic capabilities. TWIST1's involvement in regulating breast cancer bone metastasis is underscored by its modulation of key signaling pathways like TGF- β and Wnt/ β -catenin. On the other hand, tumor suppressor genes like BRCA1/2 and PTEN play pivotal roles in restraining tumor metastasis. BRCA1/2 mutations, associated with familial breast cancer, not only heighten breast cancer risk but also correlate with breast cancer bone metastasis progression. BRCA1/2 proteins inhibit tumor metastasis by engaging in DNA repair and cell cycle regulation. PTEN, when inactivated, contributes to various tumor types' occurrence and progression, including breast cancer bone metastasis, by regulating signaling pathways like PI3K/Akt. Together, these metastasis genes and tumor suppressor genes weave a complex regulatory network crucial for breast cancer bone metastasis's onset and progression. Understanding these mechanisms deeply is paramount for elucidating breast cancer bone metastasis's molecular underpinnings and laying the groundwork for relevant treatment strategy development.

6. Research Methods and Techniques

6.1. Establishment and Application of Breast Cancer Bone Metastasis Models

Establishing breast cancer bone metastasis models is a critical step in studying this disease. In order to gain a deeper understanding of the pathogenesis of breast cancer bone metastasis and evaluate the effectiveness of treatment strategies, researchers typically employ various models to simulate this complex process. Animal models are one of the most commonly used methods, with mice being a common model organism due to their ease of accessibility and manipulation. By injecting human breast cancer cell lines into mice, the process of breast cancer bone metastasis can be simulated, allowing observation of tumor growth, formation of bone metastatic lesions, and bone destruction. Additionally, cell line models and primary cell models are widely used. These models, established through in vitro cell culture or using patient-derived tissues, can evaluate the tendency and potential of different breast cancer cell lines to metastasize to bone, providing closer approximation to clinical reality. Moreover, genetically modified models, established through techniques such as gene knockout and transgenesis, elucidate the relationship between specific gene mutations and breast cancer bone metastasis, aiding in a deeper understanding of the mechanisms underlying the role of specific genes in this process. Each of these models has its advantages and limitations, and researchers can choose the appropriate model based on their research objectives and experimental requirements. By establishing breast cancer bone metastasis models, theoretical foundations for the development of relevant treatment strategies can be provided, offering more effective strategies and methods for clinical treatment.

6.2. Application of Molecular Biology and Biochemical Techniques in Research

In the investigation of breast cancer bone metastasis, molecular biology and biochemical techniques are indispensable for uncovering the underlying molecular mechanisms, discovering novel therapeutic targets, and evaluating treatment effectiveness. Various methodologies are commonly employed, including genomics and transcriptomics, which systematically analyze gene expression changes throughout the progression of breast cancer bone metastasis. By comparing the gene expression profiles of normal tissue, primary tumor tissue, and metastatic lesions, potential targets and biomarkers associated with bone metastasis can be identified, laying the groundwork for treatment strategies. Additionally, proteomics technology identifies alterations in protein expression during bone metastasis, facilitating the discovery of biomarkers and therapeutic targets. Techniques such as immunoblotting, immunohistochemistry, and fluorescence microscopy allow for the study of signaling pathway activation and regulation in breast cancer cells during bone metastasis, aiding in understanding their behavior and biological characteristics. Furthermore, cell culture techniques establish breast cancer cell lines to assess their invasive abilities and metastatic potential to bone, while in vitro functional experiments evaluate the effects of potential therapeutic drugs on breast cancer bone metastasis through assays like cell proliferation, migration, and invasion. Molecular imaging techniques such as PET, SPECT, and MRI provide insights into the biological processes of breast cancer bone metastasis, aiding in treatment evaluation and disease progression monitoring. The integration of these molecular biology and biochemical techniques furnishes robust tools and methodologies for studying breast cancer bone metastasis, contributing to a deeper understanding of its pathogenesis, identification of diagnostic biomarkers and therapeutic targets, and providing essential support for personalized and precise clinical treatment strategies.

7. Latest Research Advances

7.1. New Discoveries and Perspectives on Breast Cancer Bone Metastasis

In recent years, significant progress has been made in the research on breast cancer bone metastasis, leading to numerous new discoveries and perspectives that offer fresh insights into the understanding of this disease. Firstly, it has been found that breast cancer bone metastasis is not simply a mechanical process but rather a highly regulated and complex biological phenomenon. Besides the intrinsic characteristics of tumor cells, factors such as cytokines, signaling molecules, and extracellular matrix components within the bone microenvironment also play crucial roles in regulating the occurrence and development of bone metastasis. For instance, the interaction between tumor cells and bone cells is considered pivotal in breast cancer bone metastasis, and this interaction may be mediated through mechanisms such as intercellular signaling pathways and extracellular vesicle release. Secondly, an increasing body of research suggests the critical role of the immune system in breast cancer bone metastasis. The activation and regulation of immune cells may have significant effects on shaping the tumor microenvironment and influencing the occurrence of bone metastasis. Particularly, immune checkpoint inhibitors targeting tumor-associated immune suppressive factors such as PD-L1 and CTLA-4 have emerged as a research focus in breast cancer treatment due to their close association with patient prognosis in bone metastasis. Furthermore, novel therapeutic strategies like molecular targeted therapy and immunotherapy have brought new hope for the treatment of breast cancer bone metastasis. Drugs targeting key signaling pathways involved in breast cancer bone metastasis, such as RANKL inhibitors and PD-1/PD-L1 inhibitors, have demonstrated significant anti-tumor activity and promising clinical outcomes. Additionally, immune checkpoint inhibitors-based immunotherapy has gradually become an important therapeutic strategy for breast cancer bone metastasis. The field of research on breast cancer bone metastasis continues to yield new discoveries and perspectives, offering novel insights into the pathogenesis and treatment of this disease. These advancements hold the potential to make significant breakthroughs in clinical treatments for breast cancer bone metastasis, ultimately improving patient outcomes and quality of life [8].

7.2. Novel Treatment Strategies for Breast Cancer Bone Metastasis

The treatment of breast cancer bone metastasis has been a significant focus of clinical research. In recent years, novel treatment strategies for breast cancer bone metastasis have emerged, offering new hope for improving patient survival and quality of life. Molecular targeted therapy represents one of the key directions in the current treatment of breast cancer bone metastasis. Drugs targeting critical molecular pathways in breast cancer cells and the bone microenvironment, such as RANK/RANKL, PI3K-AKT-mTOR, and HER2 signaling pathways, have shown promising clinical efficacy. These drugs can inhibit tumor cell growth, metastasis, and drug resistance while also modulating the bone microenvironment to alleviate complications such as bone pain and fractures. Immunotherapy, as an emerging treatment strategy, has garnered considerable attention. Immunotherapy can activate the patient's own immune system to enhance its attack against tumors. Currently, immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors and CTLA-4 inhibitors have shown certain efficacy in clinical trials for breast cancer bone metastasis, offering new hope for treatment. Local treatment strategies are also evolving. Local treatments targeting bone metastases, such as radiation therapy, interventional therapy, and surgical treatment, can effectively alleviate complications such as bone pain,

prevent fractures, and spinal cord compression, thereby improving patients' quality of life. The novel treatment strategies for breast cancer bone metastasis encompass various aspects, including targeted therapy, immunotherapy, and local treatment. The continuous development and refinement of these strategies are expected to provide more effective and personalized treatment options for patients with breast cancer bone metastasis, making further contributions to improving patient prognosis and quality of life.

8. Conclusions

In the research and treatment of breast cancer bone metastasis, we have witnessed many significant advances. From a deeper understanding of the tumor microenvironment to the emergence of novel treatment strategies, these advances have brought about a qualitative leap in our understanding of breast cancer bone metastasis. However, it is essential to recognize that challenges still exist in the treatment of breast cancer bone metastasis, including issues related to personalized and precision medicine, drug resistance, and treatment-related complications. Future research needs to continue exploring the complex regulatory mechanisms of the tumor microenvironment, discovering new therapeutic targets, and effectively combining various treatment strategies to enhance treatment efficacy and patient survival. With the continuous progress of scientific technology and the refinement of treatment strategies, we are confident that significant achievements can be made in the future, bringing more hope and good news to patients with breast cancer bone metastasis.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

- [1] Micha, P.J.; Rettenmaier, A.M.; Bohart, D.R, et al.Cyclin-dependent kinase 4/6 inhibitors in the treatment of advanced or metastatic breast cancer. *Journal of oncology pharmacy practice: official publication of the International Society of Oncology Pharmacy Practitioners*, 2024, 10781552241232701-10781552241232701.
- [2] Young, E.A.S.; Heller, D.A.; Garske, S.D, et al.From breast cancer cell homing to the onset of early bone metastasis: The role of bone (re)modeling in early lesion formation. *Science advances*, 2024, 10(8), eadj0975-eadj0975.
- [3] Chen, Z.; Lu, P.; Li, M, et al.Curcumin suppresses metastasis of triple-negative breast cancer cells by modulating EMT signaling pathways: An integrated study of bioinformatics analysis. *Medicine*, 2024, 103(8), e37264-e37264.
- [4] Panm K.; Li, X.; He, J. et al.Value of the NF- κ B signalling pathway and the DNA repair gene PARP1 in predicting distant metastasis after breast cancer surgery. *Scientific reports*, 2024, 14(1), 4402-4402.

- [5] Sun, J.; Tian, T.; Wang, N. et al. Pretreatment level of serum sialic acid predicts both qualitative and quantitative bone metastases of prostate cancer. *Frontiers in Endocrinology*, 2024, 151338420-1338420.
- [6] Kojundzic, I.; Chehade, R.; Gonzalez, C.A.C. et al. Brain Metastases in the Setting of Stable Versus Progressing Extracranial Disease Among Patients With Metastatic Breast Cancer. *Clinical breast cancer*, 2024, 24(2), 156-161.
- [7] Torto, L.F.; Kaciulyte, J.; Meglio, D.F. et al. Orthotopic vascularized lymph node transfer in breast cancer-related lymphedema treatment: Functional and life quality outcomes. *Microsurgery*, 2024, 44(2), e31147-e31147.
- [8] Akshaya, L.R.; Saranya, I.; Salomi, M.G. et al. In vivo validation of the functional role of MicroRNA-4638-3p in breast cancer bone metastasis. *Journal of cancer research and clinical oncology*, 2024, 150(2), 63-63.



© 2024 by the author(s); licensee International Technology and Science Publications (ITS), this work for open access publication is under the Creative Commons Attribution International License (CC BY 4.0). (<http://creativecommons.org/licenses/by/4.0/>)