EJMR
ERA'S JOURNAL OF MEDICAL RESEARCH
p-ISSN: 2348-9839, e-ISSN: 2394-5222 | www.ejmr.org

Volum 12 Issue 2
REVIEW ARTICLE

Organotropism in Breast Cancer: Molecular Mechanisms, Therapeutic Strategies and Future Perspective

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Received on: 30-04-2025 Publish on: 30-08-2025

ABSTRACT

Breast cancer is the most common malignancy in women and leading cause of cancer-related mortality. While significant progress in screening and targeted therapies have improved outcomes in localized disease, but metastatic spread to distant organ remains the major concern. Each organ site exhibits the unique molecular signatures and microenvironmental condition that shape tumor colonization and resistance. Bone metastasis is driven by a vicious cycle of osteoclast activation and tumor growth. Lung metastasis relies on chemokine signaling, EMT plasticity, and immune evasion. Liver metastasis is supported by metabolic reprogramming and stromal interactions, while brain metastasis is limited by the blood–brain barrier, which restricts effective drug delivery. Current therapeutic strategies involve subtype-specific systemic therapy, but tumor heterogeneity, drug resistance, and organ-specific barriers continue to compromise durable responses. Emerging concepts including liquid biopsy-based surveillance, multi-omics integration, and artificial intelligence driven predictive models ensure earlier detection, personalized interventions, and improved clinical trial design. Future research must aim to transform breast cancer metastasis from an incurable complication into a controllable condition, helping to improve the patient survival and quality of life.

Keywords: *Breast cancer metastasis, molecular mechanisms, Organotropism, Therapeutic strategies.*

Era's Journal of Medical Research. 12(2);2025 [doi: 10.24041/ejmr.2025.31]

INTRODUCTION

Breast cancer is one of the most commonly diagnosed cancer worldwide, with approximately 2.3 million new cases and 685,000 deaths reported in 2020. The projected global burden is to rise significantly, reaching over 3 million new cases and about 1 million deaths annually by 2040. According to WHO- IARC report, breast cancer cases may exceed 3.2 million annually in 2050, with deaths surpassing 1.1 million, representing increases of 38% and 68%, respectively. At the time of initial diagnosis, between 3-6% of breast cancer patients reported in high-income countries already have distant metastasis (de novo metastatic breast cancer). However, in low- and middle-income countries, this number can be significantly high as 30%. Even in patients who were first diagnosed with non-metastatic disease, a large number of them eventually have a recurrence at letter stage. A comprehensive review of more than 280,000 patients indicated that the aggregated rate of metastatic recurrence was 12.2% in the initial 1-4 years post-diagnosis, 14.3% between 5–9 years, and 23.3% at 10 years or more. Higher recurrence rate within 1–4 years were found in Africa (26.4%) and South America (22.6%), while Europe (11.0%) and North America (10.2%) had lower rates.[1]

Metastasis accounts for approximately 90% of breast cancer-related deaths worldwide. The most common metastatic site is the bone, affected nearly 70% of women with stage IV breast cancer, followed by the lungs, liver, and brain. Each associated with distinct clinical challenges and poor prognoses.

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How to cite: Singh A. Organotropism in Breast Cancer: Molecular Mechanisms, Therapeutic Strategies and Future Perspective. Era J Med Res. 2025;12(2):71–76.

Once metastasis occurs, survival outcomes drop drastically. Women with localized breast cancer have a 5-year survival rate of ~99%, this figure falls to 31% in case of distant metastasis.[2]

Clinically, metastasis accounts for the majority of cancer-related deaths as compare to the primary tumor development. It disrupts the function of vital organs like bone marrow, lungs, liver, and brain, create life-threatening complications that are rarely treatable with current treatments facility. Another key challenge is that metastatic tumors often change their form and gain new biological properties compared to their primary forms. Additionally, unique organ microenvironments also influence the metastatic behavior of breast cancer cells, making difficult to predict the behaviour and their treatment. While early detection and management of the primary tumor have greatly improved the breast cancer patient's survival, the control of metastatic spread remains the major clinical obstacle.[3]

Although numerous reviews on breast cancer organotropism exist, the present review offers a more comprehensive perspective by examining organ-specific metastatic patterns, underlying molecular mechanisms, diagnostic strategies,

and current therapeutic approaches in an integrated manner. In addition, it also addresses the key clinical challenges and outlines future directions, thereby providing a distinctive and holistic contribution as compared to earlier reviews.

Organotropism in breast cancer, molecular signatures and treatment strategy

Bone metastasis

Bone is the primary site of breast cancer metastasis, accounting for approximately 65–75% of cases at advanced stages. It shows a strong propensity for bone, where metastatic growth is sustained by a self-reinforcing "vicious cycle".[4] In case of bone metastasis, tumor and osteoblast signals increase the RANKL expression, activates osteoclasts through RANK. This further leads to accelerates bone resorption, and releases matrix-bound growth factors such as TGF-β, IGF-1, PDGF, FGF, and calcium that, in turn, stimulate further tumor proliferation and more osteoclastogenesis. Although the majority of bone lesions are osteolytic, a proportion present as osteoblastic or mixed.[5] In osteoblastic metastases, endothelin-1 inhibits DKK1 activity, thereby releasing the suppression of Wnt signaling and facilitating osteoblast differentiation. Additional bone-tropic mechanisms involve tumor integrins (notably αvβ3 and α4β1, with RUNX2-driven α5), chemokine axes such as CXCR4/CXCL12, and TGF-β/SMAD signaling that induces osteolytic mediators including IL-11 and CTGF. In parallel, inflammatory and post-transcriptional regulators such as CCL20 under control of HuR enhance MMP-2/9 activity which disrupt the RANKL/OPG balance and move toward the osteolysis, while host components—including platelets, megakaryocytes, and myeloid cells helps in vascular arrest, extravasation, immune evasion, and niche establishment within the bone marrow.[6]

There are different biomarkers are associated with bone metastasis can be categorized into tissue-based, circulating, and pathway-associated indicators. At the tumor level, factors such as integrins (αvβ3 and α5), RUNX2, TGF-β/SMAD signaling components, CXCR4, and CCL20 are frequently associated with the ability of cancer cells to colonize in bone. In addition, multigene signatures linked to bone relapse—such as a reported 15-gene includes, APOPEC3B, ATL2, BBS1, C6orf61, C6orf167, MMS22L, KCNS1, MFAP3L, NIP7, NUP155, PALM2, PH-4, PGD5/PLOD2, SFT2D2 and STEAP3, encoded mainly membrane-bound molecules responsible for protein binding which predict a higher risk of skeletal recurrence. From a clinical perspective, patients with bone metastasis found to be increased levels of CA-15-3, CA-125, and alkaline phosphatase, along with reduced hemoglobin concentrations. Circulating ratios of RANKL to OPG further indicate enhanced osteoclast activity. Together, these markers provide a basis for risk assessment, support patient classification in clinical trials, and reveal potential therapeutic targets within tumor bone interactions.[7]

The treatment of bone metastases typically involved cancer subtype-specific systemic therapy with bone-modifying agents to reduce the skeletal-related events (SREs). Nitrogen-containing bisphosphonates, such as zoledronic acid, which initiates osteoclast apoptosis, to reduce the risk of SREs and provide relief from bone pain. However, they do not consistently enhance the overall survival of patients. Once disease control is attained, administering them on every 12 weeks is equally effective as monthly dosing and reduce the treatment burden. Denosumab, a RANKL inhibitor, has exhibited superior efficacy compared to zoledronic acid in the prevention of skeletal-related events (SREs) and also in pain management, but it fails to improve the patient's survival. New strategies are being tested to more directly target the interaction between the tumor and the bone. These include cathepsin-K inhibitors to stop bone resorption, Src inhibitors to stop osteoclast and tumor signaling, and experimental antagonists against TGF-β, CXCR4, and integrin αvβ3 to stop tumor homing, osteolysis, and niche formation. However, most of these are still in the early stages of clinical trials and are not yet part of standard care.[8]

Lung metastasis

Basal-like and luminal B subtypes of breast cancer are more aggressive type and show higher levels of lung specific metastasis. triple negative and HER2 enriched subtypes is highly associated with lung metastasis in invasive ductal breast cancers. CXCR4–CXCL12 chemokine axis is the central driver of pulmonary metastasis. Breast cancer cells that upregulate CXCR4 are chemotactically attracted to CXCL12 rich lung parenchyma, enhancing intravascular arrest, trans endothelial migration, and early survival.[9] This axis works together with a broader lung metastasis gene program including COX 2/PTGS2, EREG, ANGPTL4, and matrix metalloproteinases. These collectively promote the vascular permeability, extravasation, and outgrowth in the pulmonary niche. epithelial–mesenchymal transition (EMT) phenomena promote the Phenotypic plasticity, facilitates escape from the primary tumor and invasion. Partial EMT states often occur alongside stem-like traits and can revert once tumor cells reached at a new site, which helps them colonize more effectively. Exosomes released from the primary tumor help to prepare the lungs for metastasis. These vesicles carry specific integrins proteins (such as α6β4 and α6β1) that guide their deposition in lung tissue. Here, they activate local fibroblasts and epithelial cells and modify the extracellular matrix, ultimately creating a favorable pre-metastatic niche.[10,11]

Immune evasion is the key factor help to colonize the tumor cells. Tumor cells release the cytokines and chemokines which attract the myeloid-derived suppressor cells and tumor-associated macrophages. These are the responsible for the weaken attack of cytotoxic T cells and release pro-metastatic signals that promote new blood vessel growth and reshape tissues, making it easier for cancer to spread.

Breast cancer cells and circulating tumor cell (CTC) clusters frequently express PD L1, leads to T cell exhaustion; this biology underlies the clinical activity of checkpoint blockade in PD L1–positive metastatic triple negative disease. In parallel, neutrophil extracellular traps (NETs) can capture circulating tumor cells and remodel the lung matrix, thereby enhancing seeding or re awakening dormancy. Chemokine-guided trafficking, EMT-driven plasticity, exosome-mediated niche priming, and immune suppression collectively constitute a cooperative network facilitating lung metastasis.[12,13]

Clinically, lung involvement may be asymptomatic and identified through surveillance imaging, or it may manifest as cough, dyspnea, chest pain, hemoptysis, or pleural effusion. Radiologic patterns vary from solitary or multiple nodules to lymphangitic carcinomatosis and malignant pleural disease. In addition to imaging, confirmation at the tissue level is essential (14). Histopathology and immunohistochemistry together give strong proof of a breast origin. This is especially important when trying to tell the difference between metastatic lesions and a new primary lung carcinoma. When pleural effusion is present, cytological analysis of the fluid provides an alternative diagnostic approach. In recent times, molecular techniques like circulating tumor DNA and specific biomarker profiling have come to light as promising, minimally invasive methods that not only help confirm metastasis but also allow for real-time tracking of disease progression and treatment response.[15]

The management of breast cancer lung metastases primarily depends on molecular subtype. In case of hormone receptor, HR+ tumors, endocrine therapy is major available options. Aromatase inhibitors like letrozole and anastrozole, selective estrogen receptor modulators like tamoxifen, and selective estrogen receptor degraders like fulvestrant forming the backbone. In recent years, further progress achieved by using the CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib. In case HER2+ subtype, HER2-targeted combinations have dramatically given significant result. Drugs like trastuzumab and pertuzumab (with taxane backbone) remain frontline, while trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan offer effective options in resistant disease. For triple-negative breast cancer (TNBC), chemotherapy still continues to be the foundation, but recent years immunotherapy has also entered in practice. Drug includes atezolizumab (with nab-paclitaxel) and pembrolizumab (with chemotherapy) are approved for PD-L1 positive advanced TNBC, marking a major step forward in this aggressive subtype.[16] In highly selected oligometastatic cases, stereotactic body radiotherapy or surgery may be added for local control or symptom palliation. Despite of therapeutic advancement, several challenges remain persist in treatment and management of breast cancer metastasis to the lung. Drug resistance in case of both inherent (primary) and acquired type remains a major obstacle. Biological heterogeneity, not only within the same lung lesion (intratumoral) but also between lung deposits and metastases in other organs (interlesional) also complicates treatment process and response. Furthermore, many lung metastases display an "immune-excluded" phenotype, where immune cells are present but unable to effectively penetrate the tumor cell environment, thereby limits the benefit of immunotherapy.[17]

Liver metastasis

The liver is the third most common target site of metastasis in breast cancer. Major subtype is the HER2-positive and triple-negative, which associated with poor prognosis and limited therapeutic options. The hepatic microenvironment plays a pivotal role in facilitating metastatic colonization of breast cancer. The liver has unique architecture, characterized by fenestrated sinusoidal endothelium, which slower the blood flow and also constant to blood from portal venous circulation, favors the arrest and extravasation of circulating tumor cells. By releasing cytokines and growth factors like IL-6, VEGF, and TGF-β, which encourage tumor cell survival and angiogenesis while suppressing anti-tumor immunity, kupffer cells, hepatic stellate cells, and resident immune populations help tumor cells in niche formation.[18]

Once seeded in the liver, it undergoes significant metabolic adaptations which helps to exploit the nutrient availability and oxidative stress conditions. Enhanced glycolysis and upregulation of lipid metabolism genes make metastatic cells to develop in the glucose and lipid-rich Hepatic microenvironment. Furthermore, tumor cells adapt to hypoxic conditions by inducing the hypoxia-inducible factors (HIFs), which direct the angiogenic response and metabolic reprogramming, promoting resistance to apoptosis and sustained proliferation.[19] These adaptations help to contribute not only colonization but also to the persistence of dormant micrometastases that can escape to systemic therapy.

liver metastases from breast cancer are often clinically silent at early stage, and many cases are diagnosed during routine surveillance imaging. As the disease advances, patients may develop right upper quadrant pain, hepatomegaly, anorexia, nausea, and progressive weight loss. In more advanced stages, severe complications are arising such as jaundice, ascites, and hepatic failure may emerge due to extensive parenchymal infiltration or biliary obstruction.[20]

Diagnosis requires a multimodal approach. Liver function tests can show abnormalities, including elevated alkaline phosphatase, γ-glutamyl transferase, or transaminases, but these changes are nonspecific and often unable to confirm metastatic disease. Imaging remains central to diagnosis system, contrast-enhanced CT and MRI provide detailed anatomical mapping, while PET/CT offers additional functional and metabolic information for accurate staging. In many cases, further confirmation is needed by liver biopsy with immunohistochemical profiling of ER, PR, HER2, GATA3, to establish the breast origin and differentiate metastasis from primary hepatic tumors. More recently, liquid biopsy approaches,

particularly the analysis of circulating tumor DNA (ctDNA), have shown promise as minimally invasive tools for real-time disease monitoring and assessment of treatment response.[21,22]

Clinically, liver metastases possess substantial challenges due to chemoresistance and limited efficacy of targeted therapies. The hepatic microenvironment facilitates the drug resistance through stromal-tumor interactions, activation PI3K/AKT and STAT3 survival pathways, and the expression of efflux transporters that restrict intracellular drug accumulation.[23] HER2-directed therapies like trastuzumab and pertuzumab improve the outcomes in HER2-positive breast cancer, their benefits are often less pronounced in cases of liver metastasis. This is due to inadequate drug penetration, hepatotoxicity concerns, and cross-talk between hepatocytes and tumor cells that helps to facilitate the survival signaling. Same situations also happened with hormone receptor–positive disease, exhibits reduced efficacy in the liver due to ligand-independent ER signaling and stromal reprogramming. Local treatments like surgical resection, radiofrequency ablation, and stereotactic body radiation therapy are options for some oligometastatic cases, although broad hepatic involvement often calls for systemic therapy.[24]

Brain metastasis

There are 10–30% of patients with metastatic breast cancer develop brain or CNS metastases. Brain metastasis is typically viewed as a late complication of disease, after metastases have appeared systemically in the lung, liver, and bone for which limited treatment options exist. Brain metastasis originating from breast cancer exhibit patterns of parenchymal brain metastasis or leptomeningeal metastasis. Parenchymal brain metastasis account for approximately 80% of all brain metastases. Metastases to the brain parenchyma are thought to be hematogenous in origin.[25] Clinically, the risk of brain metastases is highest in HER2-positive and triple-negative disease. Pooled analyses estimate that roughly one-third of patients in these subtypes will develop brain involvement over the disease course, a rate markedly higher than in $HR^+/HER2^-$ cancers. Improved extracranial control with modern systemic therapies likely unmasks the CNS as a site of relapse in $HER2^+$ disease, consistent with intrinsic brain-tropic programs observed in preclinical and translational studies.[26]

The diagnosis strategy for breast cancer brain metastases uses combined approach of imaging and molecular tools, each one deal with the unique challenges posed by the central nervous system. Gadolinium-enhanced MRI remains the clinical cornerstone, due to its sensitivity for both parenchymal deposits and leptomeningeal involvement. In addition, standard T1 post-contrast and T2/FLAIR scans, newer techniques add layers of accuracy. Diffusion-weighted imaging and perfusion MRI (rCBV) can help to distinguish the recurrent tumor from treatment-related injury, while MR spectroscopy, marked by elevated choline and reduced N-acetylaspartate level denotes metabolic changes.[27]

In cases of leptomeningeal disease (LMD), MRI findings need integration with cerebrospinal fluid (CSF) analysis. Traditional cytology method is still the reference standard. What has changed the way doctors look for brain metastases is the use of liquid biopsies from cerebrospinal fluid (CSF). These tests often work better than blood-based ones because the blood–brain barrier acts like a filter, reducing the amount of tumor DNA or cells that can be detected in blood. In these techniques, CSF circulating tumor DNA (ctDNA) has become especially informative. In HER2-positive breast cancer, CSF ctDNA show important genetic changes such as extra copies of the ERBB2 gene or new mutations like PIK3CA. Finding these changes helps to select the right HER2-targeted treatments and can also point out which patients might benefit from clinical trials. CSF circulating tumor cells (CTCs) provide another layer of information.[28] They not only make easier compared with standard cytology but can also be analysed for specific markers, giving clues about the biology of the disease and helping to predict how it may behave.

One major treatment challenge is that drugs don't always penetrate well into brain metastases due to presence of blood brain barrier (BBB). Even if the BBB becomes leaky near tumors (forming a blood–tumor barrier), drug-efflux pumps are still active. As a result, drug levels inside the brain are inconsistent and often too low to work effectively. Large drugs such as antibodies, antibody–drug conjugates, and many tyrosine kinase inhibitors are especially affected, since they are pumped out by transporters like ABCB1 and ABCG2, leading to poor brain exposure and drug resistance. Although some newer HER2-targeted therapies (like tucatinib + trastuzumab + capecitabine, or trastuzumab deruxtecan) show real activity against brain lesions, drug distribution across all tumor sites in the brain is still incomplete. This highlights the importance of designing drugs that can cross the BBB, combining systemic therapies with stereotactic radiotherapy, and developing strategies to block efflux pumps or use drugs with bystander effects.[29,30]

Challenges and future perspectives

Even though systemic and targeted therapies have come a long way, there are still a number of problems that make it hard to effectively treat breast cancer metastasis. Tumor heterogeneity and drug resistance continue to be significant concern needs to be address. Metastatic lesions often exhibit genetic and phenotypic divergence from the primary tumor, with alterations including ESR1 mutations, PI3K/AKT pathway activation, and drug-efflux transporter overexpression, which contribute to therapeutic resistance and relapse.[31]

Another challenge is the modelling of organ-specific metastasis. Traditional in vitro assays and xenograft models frequently do not accurately reflect the intricacies of bone resorption dynamics, the immune-excluded phenotype of lung metastases, the metabolic reprogramming in hepatic lesions, or the restrictive characteristics of the blood-brain barrier. The lack of reliable preclinical systems obstructs the conversion of experimental therapies into clinically significant results.[32]

Emerging technologies such as artificial intelligence (AI) and precision medicine may hold promise in predicting metastatic spread and therapeutic response. AI-driven integration of imaging, genomic, and liquid biopsy data could facilitate early detection of relapse and guide adaptive treatment strategies.[33]

Finally, we need better preclinical and clinical models, like improvements in organoids, organ-on-a-chip platforms, and patient-derived xenografts that maintain the stromal and immune interactions and may enhance translational precision.

CONCLUSIONS

The most frequent and clinically difficult sites of spread for breast cancer are the brain, liver, lung, and bone. Breast cancer metastasis continues to be the primary cause of the death. Different molecular programs and microenvironmental interactions influence each metastatic niche, promoting both colonization and resistance to treatment. Although survival has increased with subtype directed systemic therapies and targeted agents, tumor heterogeneity, organ-specific barriers like the blood–brain barrier, often compromise their effectiveness. Emerging techniques like precision oncology, multi-omics integration, and artificial intelligence promise more personalized and predictive care. Apart from that, improvement in liquid biopsy technologies, molecular imaging, and biomarker-guided strategies may revolutionize diagnosis and monitoring strategy. Future strategies should include designing new drugs, developing better preclinical and clinical models, and creating trial plans that similar to the complexity of metastatic disease. These steps are needed to overcome drug resistance and improve treatment delivery.

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