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Clinical Relevance of Serum Periostin in Breast Cancer Diagnosis and Metastatic Risk Assessment

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ABSTRACT

Background: *Breast cancer remains the most prevalent malignancy among women worldwide and a leading cause of cancer-related mortality. Despite advances in imaging and molecular diagnostics, there remains a need for reliable, minimally invasive biomarkers that can aid in early detection, monitor disease progression, and predict metastasis. Periostin (POSTN), a secreted extracellular matrix protein, has recently emerged as a promising candidate biomarker in breast cancer due to its role in tumor progression, invasion, and metastasis. This review synthesizes current evidence on the diagnostic and prognostic value of serum periostin in breast cancer and explores its mechanistic involvement in tumor biology. Periostin is known to modulate cell adhesion, migration, and angiogenesis through interaction with integrins such as αvβ3 and αvβ5, activating key oncogenic pathways including PI3K/AKT and FAK. Elevated levels of serum periostin have been consistently observed in patients with breast cancer, particularly in aggressive subtypes such as triple-negative breast cancer (TNBC). Importantly, high serum periostin correlates with increased tumor grade, lymph node involvement, and distant metastases, making it a potential marker for risk stratification. Its involvement in epithelial-to-mesenchymal transition (EMT) and bone remodeling also links periostin to early metastatic events, especially in bone metastases. Serum-based periostin detection offers several clinical advantages, including non-invasiveness, repeatability, and the ability to monitor dynamic tumor behavior. Preliminary studies utilizing ELISA-based assays have demonstrated the feasibility of serum periostin quantification with high sensitivity. Moreover, periostin's role in therapy resistance and its expression within the tumor microenvironment further supports its dual utility as both a biomarker and a therapeutic target. However, challenges such as assay standardization, cut-off value determination, and specificity concerns due to periostin's elevation in non-malignant fibrotic conditions need to be addressed. Future research should focus on large-scale, longitudinal studies to validate periostin's clinical utility, potentially in combination with other biomarkers for enhanced diagnostic precision. In conclusion, serum periostin represents a promising, multifaceted biomarker for breast cancer diagnosis, prognostication, and metastasis prediction, with significant potential to impact personalized patient management.*

Keywords: Serum Periostin, Breast Cancer, Metastasis

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1. INTRODUCTION

Breast cancer remains one of the most prevalent and deadly cancers among women worldwide. Early diagnosis significantly improves prognosis and survival rates. Clinical pathology plays a crucial role in identifying and classifying breast cancer, employing various diagnostic tools such as histopathological examination, immunohistochemistry (IHC), and molecular profiling to detect malignancy and assess the tumor characteristics. Pathologists analyze tissue biopsies to determine tumor grade, hormone receptor status, and HER2 expression, all of which inform treatment strategies [1].

The accurate diagnosis of breast cancer involves integrating clinical data with pathological findings. Symptoms such as palpable lumps, nipple discharge, and skin changes prompt further evaluation through imaging and biopsy. Histological assessment distinguishes between in situ and invasive carcinomas and helps grade the tumor based on nuclear atypia and mitotic activity. These pathological features serve as biomarkers for disease progression and help stratify patients for treatment [2].

Tumor grading is a significant prognostic factor in breast cancer pathology. The Nottingham Histologic Score (also known as the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) is widely used to assess tubule formation, nuclear pleomorphism, and mitotic count. Higher scores correlate with more aggressive tumor behavior and poorer outcomes. This grading system allows clinicians to estimate metastatic potential and tailor interventions accordingly [3].

Immunohistochemistry enhances traditional histological methods by identifying specific proteins expressed in tumor cells. Hormone receptors such as estrogen receptor (ER) and progesterone receptor (PR), as well as HER2, are commonly evaluated through IHC. The expression levels of these biomarkers influence the responsiveness to endocrine therapy or HER2-targeted therapy. IHC results are indispensable for both diagnosis and prognosis in clinical practice [4].

In addition to receptor status, proliferation markers like Ki-67 are utilized to predict tumor aggressiveness. High Ki-67 levels indicate rapid cell proliferation and are associated with worse clinical outcomes. By integrating Ki-67 expression with other clinical features, oncologists can better assess the risk of metastasis and recurrence, allowing for more personalized treatment approaches [5].

Advances in genomic technologies have introduced gene expression profiling as a tool to predict breast cancer prognosis and metastatic potential. Tests such as Oncotype DX, MammaPrint, and Prosigna analyze the expression of specific genes involved in tumor progression. These multigene assays classify tumors into low, intermediate, or high-risk categories, aiding in the decision-making process regarding chemotherapy and other systemic treatments [6].

Sentinel lymph node biopsy (SLNB) is another critical aspect of clinical pathology in breast cancer staging. By examining the first lymph node(s) draining the tumor, pathologists can determine whether cancer has started to spread. If metastasis is detected in sentinel nodes, further axillary dissection or

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systemic treatment may be required. SLNB reduces morbidity compared to full lymph node dissection while still providing accurate staging information [7].

Histopathological subtypes of breast cancer influence the likelihood of metastasis. Invasive ductal carcinoma (IDC) is the most common subtype and tends to metastasize to bones, lungs, liver, and brain. Invasive lobular carcinoma (ILC), while less common, often presents with diffuse infiltration and has a unique metastatic pattern. Recognizing these histological differences helps clinicians monitor for site-specific metastasis [8].

Triple-negative breast cancer (TNBC) lacks ER, PR, and HER2 expression, making it difficult to treat with targeted therapies. TNBC is often high-grade and demonstrates aggressive clinical behavior with early metastasis. Clinical pathology plays a key role in diagnosing TNBC and guiding its management through morphological features and emerging molecular markers [9].

Inflammatory breast cancer (IBC) is a rare but highly aggressive form of breast cancer characterized by rapid onset of symptoms and skin involvement. Pathologically, IBC often shows dermal lymphatic invasion. Due to its aggressive nature, early recognition through clinical pathology is vital for timely treatment initiation and improved outcomes [10].

The tumor microenvironment, including immune cells and stromal components, has gained recognition for its role in breast cancer progression. Tumor-infiltrating lymphocytes (TILs) can be assessed histologically and have prognostic significance, especially in TNBC and HER2-positive subtypes. Higher levels of TILs are associated with better response to immunotherapy and chemotherapy [11].

Liquid biopsy is an emerging non-invasive method that complements traditional pathology. It involves analyzing circulating tumor DNA (ctDNA), RNA, and exosomes in the blood. This technique allows for real-time monitoring of tumor evolution and early detection of metastasis. While still under development, liquid biopsy holds promise for improving metastasis prediction [12].

Artificial intelligence (AI) and machine learning (ML) are being integrated into clinical pathology for enhanced diagnostic accuracy. Algorithms trained on digital pathology slides can identify histological patterns, quantify IHC markers, and predict patient outcomes. AI-powered tools can assist pathologists in detecting subtle changes indicative of metastasis, improving diagnostic precision [13].

Metastasis prediction also benefits from radiologic-pathologic correlation. Radiologists and pathologists work collaboratively to link imaging findings with histopathological features. For instance, suspicious lymph nodes seen on MRI or PET scans can be further evaluated through biopsy and histological examination, ensuring comprehensive staging [14].

Molecular subtyping of breast cancer using PAM50 classification (Luminal A, Luminal B, HER2-enriched, and Basal-like) provides insights into tumor biology and metastatic potential. Each subtype has distinct patterns of recurrence and treatment responses. Clinical pathology facilitates molecular subtyping through RNA expression profiling and supports risk stratification [15].

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Clinical pathology also identifies lymphovascular invasion (LVI), which is a marker of increased risk for metastasis. Presence of tumor cells within blood or lymphatic vessels correlates with a higher likelihood of distant spread. Reporting LVI status is essential for staging and prognosis, especially in early-stage breast cancers [16].

Bone metastasis is particularly common in hormone receptor-positive breast cancers. Pathologists often examine bone biopsies or bone marrow aspirates to confirm metastasis in symptomatic patients. Histological features like osteolytic or osteoblastic changes guide the therapeutic approach, including bisphosphonates or radiation therapy [17].

Lung and liver metastases are frequently associated with HER2-positive and TNBC subtypes. Liver biopsies stained with IHC markers help confirm metastatic origin in cases of hepatic lesions. Accurate identification of metastatic sites through pathology allows oncologists to optimize systemic therapy and monitor treatment response [18].

Brain metastases, although less common, are associated with significant morbidity and often occur in HER2-positive and TNBC patients. Pathologists use neuroimaging-guided biopsy followed by histological analysis to confirm diagnosis. Predictive models integrating clinical and pathological data are under development to better anticipate CNS involvement [19].

The future of breast cancer pathology lies in integrative diagnostics, combining histopathology, molecular biology, imaging, and AI. Such a multidisciplinary approach enhances diagnostic accuracy and enables precise metastasis prediction. Continuous advancements in clinical pathology are key to improving patient outcomes and personalizing breast cancer care [20].

Serum Periostin as a Biomarker for Breast Cancer Diagnosis and Metastasis Prediction

Periostin (POSTN), an extracellular matrix protein, has gained considerable attention for its role in tumor progression and metastasis, especially in epithelial cancers such as breast cancer. It is highly expressed in tissues undergoing remodeling, such as during wound healing and cancer invasion. Recent evidence suggests that periostin levels are significantly elevated in the serum of patients with breast cancer compared to healthy controls, highlighting its potential as a non-invasive diagnostic biomarker [21].

Breast cancer remains the most commonly diagnosed cancer among women worldwide and a leading cause of cancer-related deaths. Despite advances in diagnostic tools, early detection and accurate prediction of metastatic potential remain critical challenges. Biomarkers like serum periostin offer promising avenues to enhance diagnostic sensitivity and specificity while predicting disease progression [22].

Periostin functions by interacting with integrins such as αvβ3 and αvβ5, promoting cell survival, invasion, and angiogenesis, all of which are key hallmarks of cancer. These interactions stimulate downstream pathways such as PI3K/AKT and FAK, which are vital for the survival and migration of

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cancer cells. Elevated serum periostin levels may reflect the dynamic tumor microenvironment and metastatic readiness [23].

Several clinical studies have documented a correlation between high periostin expression and poor prognosis in breast cancer patients. Notably, periostin levels are often higher in triple-negative breast cancer (TNBC), an aggressive subtype with limited treatment options. Therefore, quantifying periostin levels could stratify patients based on risk and guide therapeutic strategies [24].

Serum periostin also plays a role in the epithelial-to-mesenchymal transition (EMT), a process essential for cancer metastasis. Through EMT, cancer cells acquire enhanced migratory and invasive capabilities, facilitated in part by periostin's remodeling of the extracellular matrix. Monitoring periostin levels may thus provide early insights into metastatic transformation [25].

Animal models have provided valuable insights into the mechanistic role of periostin. In xenograft models, periostin-overexpressing tumors showed increased metastatic burden and vascularization compared to controls. These findings support the hypothesis that periostin not only marks aggressive disease but actively contributes to metastatic dissemination [26].

Serum-based biomarkers like periostin are advantageous because they are minimally invasive and can be measured repeatedly over time. This makes them suitable for disease monitoring, early recurrence detection, and assessing treatment response. ELISA-based assays have shown promise in accurately quantifying serum periostin levels in breast cancer patients [27].

Emerging data suggests that periostin may also be involved in resistance to conventional therapies. For instance, periostin can protect tumor cells from apoptosis induced by chemotherapeutic agents, possibly through activation of pro-survival pathways. Elevated periostin levels may thus signal a need for alternative or adjunctive therapies [28].

A meta-analysis evaluating periostin in various cancers identified it as a consistent marker of poor prognosis. Specifically, in breast cancer, elevated serum periostin was associated with increased tumor grade, lymph node involvement, and distant metastases, reinforcing its role as a marker for aggressive disease [29].

Additionally, periostin's association with the tumor stroma provides a unique advantage. Unlike tumor-specific markers that may vary with genetic heterogeneity, stromal markers like periostin reflect broader tumor-host interactions, offering a more stable biomarker landscape across patients [30].

The predictive potential of periostin has also been explored in the context of bone metastases, a common site for breast cancer dissemination. Since periostin is involved in bone remodeling, its elevated levels may herald the onset of skeletal metastases, which are often asymptomatic in early stages [31].

Combination of periostin with other biomarkers, such as CA15-3 or circulating tumor cells (CTCs), may further enhance diagnostic accuracy. Multi-marker panels incorporating periostin have

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demonstrated improved sensitivity and specificity compared to single-marker assays in preliminary studies [32].

Genetic and epigenetic regulation of POSTN expression in breast tumors is another area of active research. Methylation status and transcriptional activators like TGF-β can modulate periostin expression, influencing tumor aggressiveness and metastatic potential. Understanding these regulatory networks could unlock targeted therapeutic interventions [33].

Immunohistochemical analysis of tumor tissues has shown concordance with serum periostin levels, suggesting that circulating periostin reliably mirrors intratumoral expression. This correlation supports its utility not just in diagnosis but also in monitoring disease dynamics over time [34].

Technological advancements in liquid biopsy platforms are expected to facilitate wider clinical adoption of serum periostin testing. High-throughput, cost-effective assays with standardized protocols will be critical in translating periostin from bench to bedside [35].

Interestingly, periostin is not exclusive to cancer and is also elevated in fibrotic diseases such as asthma and idiopathic pulmonary fibrosis. Thus, differential diagnosis and clinical context must be considered when interpreting serum periostin levels to avoid false positives [36].

Despite promising evidence, there remain challenges in establishing periostin as a routine clinical biomarker. These include variability in assay sensitivity, lack of standardized cut-off values, and limited prospective validation studies. Addressing these issues through multicenter trials is essential for clinical integration [37].

Periostin also holds promise as a therapeutic target. Inhibitors targeting periostin-integrin interactions or periostin-neutralizing antibodies have shown efficacy in preclinical models. These therapies could potentially inhibit tumor progression and metastasis, offering dual benefits of biomarker and therapeutic target [38].

In summary, serum periostin is a promising biomarker for breast cancer diagnosis and metastasis prediction. Its multifaceted role in tumor biology, accessibility in blood samples, and association with aggressive disease phenotypes underscore its clinical potential. Further validation is warranted to confirm its utility across diverse patient populations [39].

Future directions should focus on longitudinal studies evaluating periostin's role in treatment monitoring, recurrence prediction, and response to targeted therapies. Integration with genomic and proteomic data may also enhance its predictive power, paving the way for personalized oncology approaches [40].

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