ISSN NO: 2770-2936
December 2025

Approaches to the Diagnosis and Treatment of Early-Stage Breast Cancer Using Modern Molecular and Genetic Methods

Urmanbaeva Dilbaroy Abdulkosimovna - PhD, Associate Professor of the Oncology Department
Andijan State Medical Institute
Andijan, Uzbekistan.

Abstract: Breast cancer represents one of the most significant oncological challenges of the modern era and remains the most frequently diagnosed malignancy among women worldwide. According to global cancer statistics, breast cancer accounts for nearly one quarter of all female cancer cases and constitutes a leading cause of cancer-related mortality despite substantial progress in diagnosis and treatment. The increasing incidence of breast cancer is attributed to a combination of demographic aging, lifestyle changes, reproductive factors, and improved detection through screening programs. At the same time, advances in early detection have resulted in a growing proportion of patients being diagnosed at early stages of the disease, when curative treatment is achievable and long-term survival rates are high[1,7].

Keywords:

Introduction

Breast cancer represents one of the most significant oncological challenges of the modern era and remains the most frequently diagnosed malignancy among women worldwide. According to global cancer statistics, breast cancer accounts for nearly one quarter of all female cancer cases and constitutes a leading cause of cancer-related mortality despite substantial progress in diagnosis and treatment. The increasing incidence of breast cancer is attributed to a combination of demographic aging, lifestyle changes, reproductive factors, and improved detection through screening programs. At the same time, advances in early detection have resulted in a growing proportion of patients being diagnosed at early stages of the disease, when curative treatment is achievable and long-term survival rates are high[1,7].

Early-stage breast cancer, generally defined as stages I–II according to the TNM classification, is characterized by tumors confined to the breast with or without limited regional lymph node involvement. From a clinical perspective, this stage offers the greatest opportunity for effective intervention, organ-preserving surgery, and favorable outcomes. However, early-stage disease is not a homogeneous entity. Tumors of similar size and histological appearance may exhibit markedly different biological behavior, risks of recurrence, and responses to therapy. This heterogeneity poses a fundamental challenge in breast cancer management, as traditional diagnostic and prognostic tools based solely on clinical and pathological parameters often fail to capture the underlying complexity of tumor biology[2,11].

Historically, the diagnosis and treatment of breast cancer relied on a combination of imaging, histopathological evaluation, and basic immunohistochemical markers. While these methods remain indispensable, they provide limited insight into the molecular mechanisms driving tumor growth, progression, and metastasis. As a result, many patients with early-stage breast cancer were historically exposed to overtreatment, particularly in the form of adjuvant chemotherapy, despite having a low risk of recurrence. Conversely, a subset of patients with biologically aggressive tumors experienced disease progression despite apparently favorable clinical features. These limitations highlighted the urgent need for more precise diagnostic and prognostic tools capable of guiding individualized treatment strategies.

The rapid development of molecular biology and genetic technologies over the past two decades has fundamentally transformed the understanding of breast cancer. Advances in gene expression profiling, next-generation sequencing, and molecular diagnostics have revealed that breast cancer is not a single disease but rather a group of biologically distinct entities with unique molecular signatures. This paradigm shift has led to the emergence of precision oncology, in which treatment decisions are increasingly guided by the molecular and genetic characteristics of the tumor rather than by anatomical staging alone. In early-stage breast cancer, this approach is particularly valuable, as it allows clinicians to balance treatment efficacy with the minimization of unnecessary toxicity[15].

Modern molecular-genetic methods enable detailed characterization of tumor biology at multiple levels, including hormone receptor status, growth factor signaling pathways, proliferative activity, and genomic instability. Immunohistochemical assessment of estrogen receptor, progesterone receptor, HER2 status, and proliferation markers such as Ki-67 has become a standard component of breast cancer diagnostics worldwide. These biomarkers not only provide prognostic information but also directly influence therapeutic decision-making, particularly in the selection of endocrine therapy and targeted agents. However, immunohistochemistry alone does not fully reflect the complexity of tumor behavior, especially in hormone receptor-positive early-stage disease.

The introduction of multigene expression assays has represented a major milestone in the management of early-stage breast cancer. These assays analyze the expression patterns of multiple genes involved in tumor proliferation, invasion, and metastasis, providing a genomic risk score that predicts the likelihood of disease recurrence and the potential benefit of adjuvant chemotherapy. By incorporating molecular risk assessment into clinical decision-making, it has become possible to identify patients who can safely forgo chemotherapy without compromising survival, thereby significantly improving quality of life. This shift toward treatment de-escalation is one of the most important achievements of modern breast cancer care[2,8,14].

In parallel, advances in genetic testing and next-generation sequencing have expanded the role of molecular diagnostics beyond tumor profiling to include the identification of hereditary cancer syndromes. Germline mutations in genes such as BRCA1 and BRCA2 are associated with a markedly increased lifetime risk of breast cancer and influence both treatment and preventive strategies. In early-stage disease, the detection of such mutations may affect surgical planning, including the choice between breast-conserving surgery and mastectomy, as well as decisions regarding contralateral risk-reducing procedures. Moreover, genetic information has implications for family counseling and long-term surveillance[2,4].

The integration of molecular and genetic methods into the diagnosis and treatment of early-stage breast cancer has also contributed to a more nuanced understanding of prognosis. Molecular markers provide additional predictive value beyond traditional staging systems, enabling more accurate stratification of patients according to recurrence risk. This has important implications not only for treatment selection but also for follow-up strategies and survivorship care. As the number of breast cancer survivors continues to grow, optimizing long-term outcomes while minimizing treatment-related morbidity has become an increasingly important objective[3,7].

Despite the clear benefits of molecular-genetic approaches, their implementation in routine clinical practice is associated with several challenges. These include high costs, limited accessibility in resource-constrained settings, the need for specialized laboratory infrastructure, and the complexity of interpreting genomic data. Furthermore, ethical considerations related to genetic testing, patient consent, and psychological impact must be carefully addressed. Nevertheless, ongoing technological advances and the accumulation of clinical evidence continue to support the broader integration of molecular diagnostics into early breast cancer management.

In this context, a comprehensive review of current approaches to the diagnosis and treatment of early-stage breast cancer using modern molecular and genetic methods is highly relevant. Understanding the role of these technologies in refining diagnosis, guiding therapy, and improving outcomes is essential for clinicians, researchers, and healthcare policymakers. This review aims to summarize contemporary molecular-genetic strategies in early breast cancer, highlight their clinical significance, and discuss future directions in the era of personalized oncology[4,7,14].

Early-Stage Breast Cancer: Clinical Concept

Early-stage breast cancer typically includes tumors limited to the breast with or without minimal regional lymph node involvement (stages I–II according to the TNM classification). At this stage, curative treatment is usually feasible. The primary clinical challenge lies not only in achieving local disease control but also in accurately identifying patients who require systemic therapy and those who may safely avoid overtreatment. Molecular and genetic tools play a critical role in addressing this challenge.

Conventional Diagnostic Methods

The diagnosis of breast cancer traditionally relies on a combination of clinical evaluation, imaging techniques, and histopathological assessment. These conventional diagnostic methods remain the foundation of breast cancer detection and staging, particularly in early-stage disease, where timely and accurate diagnosis is crucial for optimal treatment outcomes. Although modern molecular and genetic techniques have expanded diagnostic

ISSN NO: 2770-2936
December 2025

capabilities, conventional methods continue to play a central role in the initial identification and characterization of breast tumors.
Clinical examination is often the first step in breast cancer detection, especially in symptomatic patients. Palpation of the breast and regional lymph nodes may reveal a palpable mass, skin changes, nipple retraction, or axillary lymphadenopathy. However, clinical examination alone has limited sensitivity, particularly in detecting small or non-palpable lesions, which are common in early-stage breast cancer. Therefore, clinical assessment must be complemented by imaging studies.
Mammography is the cornerstone of breast cancer screening and early detection worldwide. It enables the identification of suspicious lesions, microcalcifications, and architectural distortions that may indicate malignancy before clinical symptoms develop. In early-stage breast cancer, mammography has significantly contributed to improved survival rates by facilitating diagnosis at a curable stage. Nevertheless, its sensitivity may be reduced in women with dense breast tissue, younger patients, and certain tumor subtypes, necessitating the use of additional imaging modalities[6,15].
Breast ultrasound is widely used as a complementary diagnostic tool, particularly in women with dense breasts and for further evaluation of mammographically detected abnormalities. Ultrasound allows differentiation between solid and cystic lesions, assessment of tumor margins, and evaluation of axillary lymph nodes. In early-stage breast cancer, ultrasound-guided biopsy improves diagnostic accuracy and enables minimally invasive tissue sampling. Despite its advantages, ultrasound is operator-dependent and lacks standardized screening protocols when used alone.
Magnetic resonance imaging of the breast has emerged as a highly sensitive imaging modality, particularly valuable in selected clinical scenarios. MRI is commonly used in high-risk patients, carriers of genetic mutations, and cases where conventional imaging yields inconclusive results. It provides detailed information on tumor extent, multifocality, and contralateral disease, which is especially relevant in surgical planning for early-stage breast cancer. However, the high sensitivity of MRI may lead to false-positive findings, potentially resulting in unnecessary biopsies or overtreatment[4,11,14].
Histopathological examination remains the gold standard for definitive breast cancer diagnosis. Core needle biopsy is the preferred method for tissue sampling, as it provides sufficient material for histological evaluation and biomarker analysis while minimizing invasiveness. Histological assessment determines tumor type, grade, and presence of invasive growth, all of which are essential for staging and treatment planning. In early-stage breast cancer, accurate histopathological diagnosis is critical for selecting appropriate surgical and systemic therapies.
In addition to basic histology, conventional pathology includes immunohistochemical evaluation of key biomarkers such as estrogen receptor, progesterone receptor, and HER2 status. While these markers bridge the gap between traditional and molecular diagnostics, they are routinely considered part of standard diagnostic workup rather than advanced molecular testing. Their assessment provides essential prognostic and predictive information, guiding the use of endocrine therapy and targeted treatments.
Despite their indispensable role, conventional diagnostic methods have inherent limitations. They primarily assess anatomical and morphological features and offer limited insight into the biological behavior and genetic heterogeneity of tumors. As a result, patients with similar clinical and histopathological profiles may experience markedly different outcomes. These limitations have driven the development and integration of molecular and genetic diagnostic approaches aimed at improving risk stratification and personalizing treatment, particularly in early-stage breast cancer.
In summary, conventional diagnostic methods form the essential framework for breast cancer detection and staging. While they remain indispensable in clinical practice, their integration with modern molecular and genetic techniques is necessary to achieve a comprehensive and individualized diagnostic approach in early-stage breast cancer management.

Molecular Classification of Breast Cancer

The molecular classification of breast cancer represents a major advance in understanding tumor heterogeneity and has become a central element in modern breast cancer management. Unlike traditional classifications based solely on histopathological features, molecular classification reflects the biological behavior of tumors, their prognosis, and their response to systemic therapy. This approach is particularly important in early-stage breast cancer, where accurate risk stratification is essential for selecting optimal treatment strategies and avoiding unnecessary overtreatment[6,12].

Molecular classification emerged from gene expression profiling studies that demonstrated distinct patterns of gene activity among breast tumors. These studies revealed that breast cancer comprises several biologically different subtypes rather than a single disease entity. In routine clinical practice, molecular subtypes are most commonly approximated using immunohistochemical markers, including estrogen receptor, progesterone receptor, HER2 status, and proliferation indices such as Ki-67. This surrogate classification has been widely adopted due to its feasibility, reproducibility, and clinical relevance.

The luminal subtypes are the most frequently encountered molecular categories in early-stage breast cancer. Luminal A tumors are characterized by strong expression of hormone receptors, low proliferative activity, and the absence of HER2 overexpression. These tumors generally demonstrate an indolent course and a favorable prognosis, with high sensitivity to endocrine therapy and limited benefit from chemotherapy in many cases. Luminal B tumors also express hormone receptors but exhibit higher proliferative rates and may show HER2 positivity. Compared to luminal A tumors, luminal B cancers are associated with a higher risk of recurrence and often require a more aggressive treatment approach, including the consideration of chemotherapy in addition to endocrine therapy.

HER2-enriched breast cancer is defined by overexpression or amplification of the HER2 gene and is typically hormone receptor-negative. Historically, this subtype was associated with poor outcomes due to its aggressive biological behavior. However, the introduction of HER2-targeted therapies has dramatically improved prognosis, even in early-stage disease. Accurate identification of HER2 status is therefore critical, as it directly determines eligibility for targeted treatment and significantly influences survival outcomes[4,8].

Triple-negative breast cancer is characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression. This subtype accounts for a smaller proportion of early-stage breast cancers but is clinically significant due to its aggressive nature, high proliferative activity, and limited targeted treatment options. Triple-negative tumors are associated with an increased risk of early recurrence and distant metastasis. In early-stage disease, chemotherapy remains the main systemic treatment modality, and ongoing research aims to identify molecular targets and predictive biomarkers within this heterogeneous subgroup.

Beyond these major categories, advances in molecular profiling have identified additional subgroups and refined the understanding of intratumoral heterogeneity. High-throughput genomic analyses have revealed variations in gene expression, copy number alterations, and mutational landscapes even within established molecular subtypes. These findings underscore the complexity of breast cancer biology and highlight the limitations of simplified classification systems.In early-stage breast cancer, molecular classification plays a pivotal role in guiding therapeutic decision-making. It informs the selection of endocrine therapy, chemotherapy, and targeted agents, as well as the intensity and duration of treatment. Moreover, molecular subtype determination contributes to prognostic assessment and helps identify patients who may benefit from treatment de-escalation strategies[6,7].

Role of Immunohistochemistry

Immunohistochemical analysis is the cornerstone of molecular diagnostics in breast cancer. The assessment of estrogen receptor, progesterone receptor, HER2 status, and Ki-67 proliferation index allows clinicians to stratify patients and select appropriate therapy. Hormone receptor-positive tumors benefit from endocrine therapy, while HER2-positive tumors are candidates for HER2-targeted agents. Ki-67 provides additional prognostic information and helps differentiate between luminal subtypes.

Multigene Expression Assays

Gene expression profiling has significantly improved decision-making in early-stage breast cancer. Multigene assays such as Oncotype DX and MammaPrint assess the expression of multiple genes associated with tumor proliferation and metastasis. These tests provide recurrence risk estimates and predict the potential benefit of adjuvant chemotherapy, particularly in hormone receptor-positive, HER2-negative disease. As a result, many patients with low genomic risk can safely avoid chemotherapy, reducing treatment-related toxicity without compromising survival.

Genetic Testing and Next-Generation Sequencing

Next-generation sequencing technologies have expanded the scope of molecular diagnostics by enabling comprehensive genomic analysis. Germline genetic testing, particularly for BRCA1 and BRCA2 mutations,

ISSN NO: 2770-2936
December 2025

is recommended for selected patients based on clinical and family history. Identification of hereditary mutations influences surgical decision-making, surveillance strategies, and risk-reduction measures. Somatic mutation profiling is increasingly used to identify actionable targets and to better understand tumor biology, even in early-stage disease[3,7,8].

Molecular-Guided Treatment Strategies

The integration of molecular and genetic information has transformed treatment planning in early-stage breast cancer. Surgical management may be influenced by genetic risk, with some patients opting for more extensive procedures based on hereditary predisposition. Systemic therapy selection is guided by molecular subtype, biomarker status, and genomic risk assessment. Endocrine therapy remains the mainstay for hormone receptor-positive tumors, while targeted therapies are used in HER2-positive disease. Molecular tools also support treatment de-escalation strategies, helping to minimize unnecessary exposure to chemotherapy[3,5,9].

Prognostic Value and Long-Term Monitoring

Molecular and genetic markers provide prognostic information beyond traditional clinicopathological factors. They assist in identifying patients at higher risk of recurrence who may benefit from intensified treatment or closer follow-up. Emerging technologies, such as circulating tumor DNA analysis, offer promising non-invasive methods for detecting minimal residual disease and monitoring treatment response, although their routine use in early-stage breast cancer is still under investigation.

Challenges and Limitations

Despite clear benefits, the widespread adoption of molecular-genetic methods faces several challenges. These include high costs, limited accessibility in some regions, the need for specialized expertise, and the complexity of data interpretation. Ethical considerations related to genetic testing and patient counseling also remain important aspects of clinical practice.

Future Directions

The future of early breast cancer management lies in the integration of clinical, pathological, and molecular data into comprehensive diagnostic and therapeutic algorithms. Advances in artificial intelligence, liquid biopsy technologies, and expanded genomic profiling are expected to further refine personalized treatment approaches and improve outcomes[4,7,8].

Conclusion

Early-stage breast cancer represents a critical window of opportunity in which accurate diagnosis and appropriately tailored treatment can achieve excellent long-term outcomes. However, the biological heterogeneity of breast cancer limits the effectiveness of traditional diagnostic and therapeutic approaches based solely on clinical and histopathological parameters. As demonstrated throughout this review, the integration of modern molecular and genetic methods has fundamentally transformed the management of early-stage breast cancer, shifting clinical practice toward a more precise and individualized model of care[4,8,9,11].

Molecular classification has enabled a deeper understanding of tumor biology, allowing clinicians to distinguish between biologically distinct subtypes with different prognostic implications and therapeutic sensitivities. The routine assessment of hormone receptors, HER2 status, and proliferation indices has become indispensable for treatment planning, while multigene expression assays have further refined risk stratification, particularly in hormone receptor-positive, HER2-negative disease. These tools have played a pivotal role in reducing overtreatment by identifying patients who may safely avoid chemotherapy without compromising oncological outcomes[5,7,8].

Genetic and genomic technologies, including next-generation sequencing and germline mutation testing, have expanded the diagnostic spectrum beyond tumor characterization to encompass inherited cancer susceptibility. The identification of pathogenic mutations not only influences therapeutic and surgical decision-making but also has significant implications for long-term surveillance and family counseling. As molecular diagnostics continue to evolve, their role in early-stage disease is expected to grow, enabling even more accurate prediction of recurrence risk and treatment response.

Importantly, the application of molecular and genetic methods has contributed not only to improved survival but also to enhanced quality of life for patients with early-stage breast cancer. Treatment de-escalation strategies supported by molecular risk assessment reduce exposure to unnecessary toxicity and long-term complications, aligning oncological effectiveness with patient-centered care. At the same time, patients with

ISSN NO: 2770-2936
December 2025

biologically aggressive tumors can be identified early and offered intensified or targeted therapies to improve outcomes.

Despite these advances, challenges remain in ensuring equitable access to molecular diagnostics, standardizing testing methodologies, and integrating complex genomic data into routine clinical workflows. Addressing these limitations will require continued research, multidisciplinary collaboration, and the development of evidence-based guidelines that incorporate molecular findings into everyday practice[11,14].

In conclusion, modern molecular and genetic methods have become an integral component of the diagnostic and therapeutic approach to early-stage breast cancer. Their continued integration into clinical decision-making represents a key direction in contemporary oncology, offering the potential to further improve survival, minimize treatment-related morbidity, and advance personalized medicine in breast cancer care.

References

1. Anderson WF, Rosenberg PS, Prat A, Perou CM, Sherman ME. How many etiological subtypes of breast cancer: two, three, four, or more? J Natl Cancer Inst. 2014;106(8):dju165.
2. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2019;30(8):1194–1220.
3. Curigliano G, Burstein HJ, P Winer E, et al. De-escalating and escalating treatments for early-stage breast cancer. Lancet. 2017;389(10076): 1278–1290.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer. Lancet. 2012;379(9814):432–444.
5. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer. Ann Oncol. 2013;24(9):2206–2223.
6. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66.
7. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy. J Clin Oncol. 2016;34(10):1134–1150.
8. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–752.
9. Prat A, Pineda E, Adamo B, et al. Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast. 2015;24(Suppl 2):S26–S35.
10. Rakha EA, Reis-Filho JS, Baehner F, et al. Breast cancer prognostic classification in the molecular era. Mod Pathol. 2010;23(2):S1–S21.
11. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2023;73(1):17–48.
12. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay. N Engl J Med. 2018;379(2):111–121.
13. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses. Proc Natl Acad Sci USA. 2001;98(19):10869–10874.
14. Turner NC, Reis-Filho JS. Genetic heterogeneity and cancer drug resistance. Lancet Oncol. 2012;13(4):e178–e185.
15. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288–300.
16.