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Multidimensional Predictors for Neoadjuvant Chemotherapy Efficacy in Breast Cancer

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Abstract: ***Breast cancer is one of the most common malignant tumors in women worldwide, and neoadjuvant chemotherapy (NAC) is an important treatment modality for locally advanced breast cancer. Predicting its efficacy has significant implications for guiding clinical treatment. This review aims to comprehensively explore the clinical applications and future prospects of multidimensional predictors in evaluating NAC efficacy in breast cancer. We will systematically analyze the characteristics, applications, and limitations of various predictors from clinical pathology, imaging, molecular biology, and liquid biopsy perspectives. Additionally, we will explore the combined application of predictors and their potential in individualized treatment, as well as discuss future development trends.***

Keywords: Breast cancer, Neoadjuvant chemotherapy (NAC), Multidimensional predictors**.**

1. Epidemiology and Background

Breast Cancer Epidemiology Breast cancer has become one of the most common cancers globally, with approximately 2.3 million new cases and 685,000 deaths in 2020[1,2]. Global incidence has increased rapidly, rising by 57.8% over the past 30 years[3]. In China, both incidence and mortality rates are increasing, particularly in urban areas[4]. The disease is affecting younger women, with the primary age group now between 40-50 years[5]. Early detection and prevention are crucial, as breast cancer grows relatively slowly and is treatable if detected early[6]. Regular self-examination and professional screening are recommended, especially for high-risk individuals[7].

1.1 Definition, Application, and Importance of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NAC) is an essential component in treating locally advanced breast cancer[8]. It involves systemic chemotherapy administered before local treatments such as surgery or radiotherapy. NAC can effectively eliminate systemic tumor cells, reduce primary tumor volume, increase surgical opportunities for advanced or inoperable patients, achieve downstaging while preserving breast and axilla, and effectively improve patient prognosis. Studies through meta-analysis have shown that breast cancer patients achieving pathological complete response (pCR) have significantly improved survival outcomes, and patients achieving pCR have notably longer event-free survival (EFS) and overall survival (OS) compared to those who do not achieve pCR. Therefore, achieving pCR in post-surgical pathology is generally considered a surrogate indicator for long-term survival[9,10].

2. Significance of NAC Efficacy Prediction and Multidimensional Predictors

Predicting NAC efficacy remains challenging. Recent research has explored various biomarkers and methods to improve NAC response prediction. These include integrating single-cell and bulk RNA sequencing data to identify gene signatures[11], examining tumor microenvironment characteristics such as stromal tumor-infiltrating lymphocytes and cyclin-dependent kinase expression[12], and low lymphocyte-to-monocyte ratio[13]. Significant differences in expression levels of HER2, ER, PR, TOPO II, EGFR, and Ki67 have been found between pCR and non-pCR patients[14]. Furthermore, models based on the expression of AHNAK, CIDEA, ADIPOQ, and AKAP12 have demonstrated good predictive performance[15]. PET/CT radiomics can predict pathological complete response to neoadjuvant chemotherapy in locally advanced breast cancer patients[16]. Next, we will elaborate on the clinical applications and prospects of multidimensional predictors in evaluating NAC efficacy in breast cancer.

2.1 Gene Expression Profiles Gene expression profiling is widely used to predict NAC efficacy.

By analyzing gene expression in breast cancer tissue, patients can be classified into different molecular subtypes, such as hormone receptor-positive, HER2-overexpressing, and triple-negative types. These subtypes show significant differences in neoadjuvant chemotherapy response and survival rates[17,18].

2.1.1 HER2-Overexpressing

Breast Cancer HER2-overexpressing breast cancer typically shows high sensitivity to anti-HER2 targeted drugs such as trastuzumab and pertuzumab. By detecting HER2 gene or protein expression levels, patients can be identified for this subtype, and targeted drugs can be added to the neoadjuvant chemotherapy regimen[19,20].

2.1.2 Hormone Receptor-Positive Breast Cancer

Hormone receptor-positive breast cancer is typically sensitive to hormone therapy. By detecting estrogen receptor (ER) and/or progesterone receptor (PR) expression levels, patients suitable for hormone therapy can be identified. During neoadjuvant therapy, either chemotherapy or endocrine therapy may be used to enhance efficacy.

2.1.3 Triple-Negative Breast Cancer

Triple-negative breast cancer is not sensitive to either

endocrine therapy or anti-HER2 targeted drugs, making chemotherapy the primary treatment option. Gene expression profile analysis can further refine triple-negative breast cancer subtypes, helping predict patient response to different chemotherapy drugs. For example, gene expression-based analysis can determine which patients might benefit from everolimus, bevacizumab, carrelizumab, and other drugs[21].

2.1.4 Molecular Subtypes and Prognosis

Breast cancer molecular subtypes are closely related to prognosis. Studies have found that patients with hormone receptor-positive breast cancer typically have better prognoses, while triple-negative breast cancer usually has a poorer prognosis[22]. Therefore, through gene expression profile analysis, more accurate prognostic information can be provided to patients, helping doctors select optimal treatment strategies.

2.2 Molecular Markers

2.2.1 HER2 Protein

Human epidermal growth factor receptor 2 (HER2) is one of the important protein markers in breast cancer. HER2 overexpression is typically associated with breast cancer invasiveness and malignancy. For HER2-overexpressing breast cancer patients, targeted anti-HER2 therapy drugs such as trastuzumab and pertuzumab have become important components of neoadjuvant chemotherapy and adjuvant therapy[19,23].

2.2.2 Ki-67 Protein

Ki-67 is a nuclear antigen widely used to evaluate cell proliferation status. Its expression level is typically determined through immunohistochemistry, expressed as a percentage of positively stained cells in the nucleus. In breast cancer, high Ki-67 expression is usually associated with faster tumor growth rates and poorer prognosis[24,25]. Therefore, Ki-67 is widely used to predict breast cancer patients' response to NAC. Studies have found that patients with lower Ki-67 levels often show better survival rates after NAC. For example, a meta-analysis study covering 12,155 breast cancer patients showed that the survival rate was significantly lower in the high Ki-67 expression group, indicating that Ki-67 can be used to predict treatment response and prognosis[24]. Furthermore, studies have found that Ki-67's role may vary among different molecular subtypes of breast cancer. Hormone receptor-positive (ER+) breast cancer typically exhibits lower Ki-67 levels, while triple-negative breast cancer often shows higher Ki-67 expression levels. The clinical application of Ki-67 marker is not limited to predicting treatment response but can also be used to guide post-surgical treatment decisions. For example, after NAC, changes in Ki-67 can be used to assess tumor treatment sensitivity, thereby determining whether further surgery or adjuvant therapy is needed[25].

2.2.3 p53 Protein

p53 is a tumor suppressor gene, and its mutations are common in many cancers, including breast cancer. Abnormal p53 protein expression is associated with treatment resistance and poor prognosis. In neoadjuvant chemotherapy, detecting p53 expression levels and mutation status can help doctors determine whether patients might respond better to certain treatment regimens. Studies have shown that breast cancer patients carrying p53 mutations typically have poorer prognosis, as p53 mutations may lead to tumor cell resistance to treatment[26]. A study found that in neoadjuvant chemotherapy, breast cancer patients with p53 mutations showed significantly poorer response to certain chemotherapy drugs, with lower survival rates compared to p53 wild-type patients[27].

2.2.4 BRCA1 and BRCA2

Proteins BRCA1 and BRCA2 are genes associated with significantly increased risk of hereditary breast and ovarian cancer. Breast cancer patients carrying BRCA1 or BRCA2 gene mutations typically have higher sensitivity to certain treatment drugs, particularly platinum-based drugs. Therefore, detecting BRCA1 and BRCA2 gene mutation status and expression levels can help determine the optimal treatment choice in neoadjuvant chemotherapy strategies. Studies have found that patients carrying BRCA1 or BRCA2 gene mutations respond significantly better to platinum-based drugs[28]. For example, one study found that in neoadjuvant chemotherapy, BRCA1-mutated breast cancer patients showed very significant response to carboplatin, with tumor volume significantly reduced compared to BRCA1 wild-type patients[29].

2.2.5 Bcl-2 Protein

Bcl-2 is an anti-apoptotic protein, and its high expression is typically associated with treatment resistance. In neoadjuvant chemotherapy, detecting Bcl-2 expression levels can help predict patient sensitivity to treatment. Reducing Bcl-2 expression may increase chemotherapy efficacy[30]. Studies have found that breast cancer patients with low Bcl-2 expression typically respond better to certain chemotherapy drugs. For example, one study found that breast cancer patients with low Bcl-2 expression showed significantly better response to combined treatment with cisplatin and fluorouracil, with notably improved survival rates compared to patients with high Bcl-2 expression[31].

2.2.6 TOP2A Protein

DNA topoisomerase IIα (TOP2A) is a protein closely related to cell division and DNA repair. In breast cancer, high TOP2A expression has been associated with poor prognosis[32]. Therefore, TOP2A is used to predict patient response to NAC. High TOP2A expression is typically associated with increased tumor malignancy and growth rate. In neoadjuvant chemotherapy, particularly when using platinum drugs (such as cisplatin and carboplatin), TOP2A analysis can help doctors predict patient response to treatment. One study found that in HER2-amplified breast cancer, patients with high TOP2A expression responded well to platinum drugs, indicating that TOP2A markers have important value in guiding treatment selection[33].

2.3 Imaging Predictors

Imaging methods such as MRI and PET-CT can provide detailed tumor information for predicting neoadjuvant chemotherapy response. For example, MRI can assess tumor magnetic sensitivity and provide treatment response information. Imaging evaluation helps determine optimal surgical timing, predict prognosis, estimate survival rates and recurrence risk, thereby developing individualized treatment strategies[34].

Despite progress in applications, challenges and opportunities remain:

1) Multimodal image fusion: Integrating different types of medical imaging data to provide comprehensive information [35].
2) AI-assisted diagnosis: Developing machine learning techniques to improve diagnostic and predictive accuracy.
3) Integration of molecular markers: Combining imaging with molecular data for comprehensive understanding of tumor biological characteristics.
4) Individualized treatment strategies: Developing tailored plans based on patient tumor characteristics[36].
5) Ethics and privacy issues: Attention to medical imaging data's safe collection, storage, and sharing.

2.4 Peripheral Blood Cell Factors in Predicting Breast Cancer Neoadjuvant Chemotherapy

The tumor microenvironment (TME) plays an important role in breast cancer progression and its response to anti-cancer therapy[37]. Peripheral blood immune markers can reflect the composition of local TME, providing clinically important information. Cytokines and chemokines are key factors in systemic immune response and TME activation or suppression. They affect the interactions between immune cells and immune mediators, forming inflammatory TME, which may lead to better response to various treatments[38,39]. However, tumor cells can also produce cytokines that regulate the immune system, creating an immunosuppressive microenvironment favorable for tumor growth [40]. Based on this principle, cytokine levels in patients' plasma before treatment can reflect the current state of the immune system. These factors include IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12P70, IL-17, TNF-α, IFN-α, and IFN-β.

2.4.1 IL-6

Interleukin-6 (IL-6) can be secreted by activated T cells, macrophages, and other immune cells, as well as endothelial cells and fibroblasts, making it one of the most multifunctional cytokines discovered to date[41]. IL-6 is a pro-inflammatory factor that can promote tumor growth by upregulating anti-apoptotic and angiogenic proteins in tumor cells. Studies have found that IL-6 levels are associated with breast cancer fat tissue infiltration, lymph node metastasis, and TNM staging [42]. Therefore, IL-6 can serve as a predictor of NAC efficacy.

2.4.2 IL-10

Interleukin-10 (IL-10), mainly secreted by monocytes and lymphocytes, can be widely expressed in the body. As an anti-inflammatory factor, it was initially recognized as capable of regulating immune cell growth and inhibiting T cell function. Studies have shown that IL-10 can create an immunosuppressive environment by inhibiting the activation of APCs and thereby suppressing T cell biological effects, helping tumor immune escape. IL-10 can also reduce DCs' ability to present tumor cell antigens, hindering T cells from killing tumor cells[43]. IL-10 can also inhibit NK cell and NKT cell activity to suppress CTL-mediated tumor killing effects[44]. Reports have also indicated a trend between increased IL-10 and classical monocyte levels at the end of NAC and reduced pathological complete response rates [45].

2.4.3 IL-1β

Interleukin-1β (IL-1β) mainly originates from monocyte-macrophages and lymphocytes. IL-1β has strong biological activity and can induce inflammatory responses and the expression of other inflammatory factors, promoting fibroblast generation. IL-1β expression can be found in approximately 9/10 of invasive breast cancer tissues[46]. Studies have shown that high levels of IL-1β can inhibit breast cancer cell proliferation, while low levels can stimulate breast cancer cell proliferation and metastasis, indicating that IL-1β can regulate breast cancer cell proliferation and metastasis based on its expression levels in the body[47].

2.4.4 TNF-α

Tumor Necrosis Factor-α (TNF-α), primarily secreted by monocytes and macrophages, was one of the earliest discovered cytokines. It has been found to participate in inflammatory responses and induce the expression of other inflammatory factors and chemokines, causing inflammatory cell aggregation. In breast cancer, serum TNF-α expression in breast cancer patients is often related to lymph node metastasis and TNM staging. TNF-α expression levels in serum are typically higher in patients with later stages than those with earlier stages, higher in patients with bone metastasis than those with other distant metastasis sites, and higher in patients with lymph node metastasis than those without[48,49].

2.4.5 IL-2

Interleukin-2 (IL-2) is primarily produced by antigen-activated Th1 CD4+ Th1 cells, and partially by CD8+ T cells, NK cells, and NK T cells. IL-2 not only acts as a T cell growth factor during immune response initiation but also plays a crucial role in maintaining self-tolerance by inducing cell death (AICD) in overactive T cells[50]. IL-2 promotes antigen-activated CD8+ T cells and serves as a growth factor for CD4+ T cells and NK cells[51].

2.4.6 IL-12

Interleukin-12 (IL-12) participates in naive helper T cell differentiation into Th1 cells and stimulates IFNγ production by plasmacytoid DCs and T cells. IL-12 enhances cytotoxic T cell activity and increases B cell survival rates. IL-12 induces the production of IP-10 (or CXCL10), which mediates its anti-angiogenic effects [52]. While IL-12 has shown efficacy in a series of preclinical studies in mouse experimental models, the loss of peripheral blood Th1 has been associated with lack of

complete response to neoadjuvant therapy and reduced disease-free survival [53]. Therefore, IL-2, IL-12, and IFN-γ play important roles in favorable breast cancer prognosis.

3. Advantages of Peripheral Blood Cell Factors in Predicting Breast Cancer Neoadjuvant Chemotherapy Efficacy

Compared to traditional pathological and imaging indicators, peripheral blood cell factors demonstrate multiple advantages in predicting breast cancer neoadjuvant chemotherapy efficacy. These advantages improve prediction accuracy and convenience while providing important basis for individualized treatment plans.

3.1 Non-invasiveness Complete Through Simple Blood Collection with Significant Non-invasive Advantages:

- Reduces patient suffering and complication risks
- Improves compliance and facilitates long-term follow-up

3.2 Real-time Nature Can Reflect Tumor Microenvironment Dynamic Changes in Real-time:

- Early detection of treatment response
- Dynamic monitoring with intuitive reflection of effects
- Timely adjustment of plans to optimize effects

3.3 Individualization Provides Important Basis for Achieving Individualized Treatment:

- Assists in precise molecular typing
- Predicts drug sensitivity and guides medication
- Assesses prognosis and develops personalized follow-up

3.4 Multidimensional Assessment Simultaneously Obtains Multiple Indicators, Providing Multidimensional Evaluation:

- Reflects immune function and inflammatory status

3.5 Economic Efficiency Demonstrates Good Economic Efficiency:

- Low detection costs and equipment requirements
- Strong reproducibility without significant additional burden

4. Conclusion

In summary, peripheral blood cell factors have certain clinical significance in breast cancer prognosis. It can be predicted that they are related to neoadjuvant chemotherapy efficacy prediction. However, current research still has some limitations, such as small sample sizes and inconsistent research methods. Future research could seek potential cell factors that can predict NAC efficacy and further explore the possibility of combined application of peripheral blood cell factors to improve the accuracy and reliability of breast cancer neoadjuvant chemotherapy efficacy prediction.

5. Future Prospects

Molecular markers in breast cancer neoadjuvant chemotherapy clinical applications face unprecedented opportunities and challenges. With continuous development in medical science technology and detection methods, future prospects are highly anticipated. The following aspects deserve detailed exploration:

1) Molecular subtype-specific markers: Different molecular subtypes of breast cancer show large differences in treatment response, necessitating specific markers to guide treatment selection.

2) Dynamic monitoring: Marker expression levels may change during treatment. Therefore, dynamic monitoring of marker changes can help doctors better adjust treatment strategies to maximize treatment effects.

3) Machine learning and artificial intelligence: With the development of big data and artificial intelligence technology, machine learning algorithms can be used to analyze large-scale molecular data, discover new markers, and predict patient treatment response.

4) Clinical trials and validation: After discovering potential markers, large-scale clinical trials are needed to validate their predictive value. Only through large-scale validation can the reliability and clinical practicality of markers be ensured.

5) Multiple marker combinations: While significant progress has been made with single markers, breast cancer heterogeneity means that single markers may not fully reflect tumor status. Therefore, one future trend will be developing multiple marker combinations to improve treatment response prediction accuracy.

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