

The Role of Immunotherapy and Gene Therapy in The Treatment of Breast Cancer in Middle-Aged Women: Integration with Pathomorphological Markers and Organ-Preserving Surgery

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Abstract: This article analyses modern, biologically targeted approaches to the treatment of breast cancer in middle-aged women. The main focus is on determining the pathomorphological and molecular characteristics of the tumour, the role of immunotherapy, particularly in triple-negative breast cancer, the current level of clinical research on gene therapy, and the possibilities for reducing the extent of surgery. In breast cancer, the choice of treatment is determined by the histological type and grade of the tumour, lymph node status, estrogen receptor (ER), progesterone receptor (PR) and HER2 status, proliferative activity and other biomarkers. Modern neoadjuvant systemic therapy, including pembrolizumab-based chemoimmunotherapy, increases the likelihood of a pathological complete response in certain early-stage triple-negative tumours and allows surgery to be individualised. Gene therapy encompasses such areas as p53, oncolytic viruses, immunomodulatory genes, siRNA/shRNA, gene editing and genetic vaccines; however, in breast cancer most of these approaches remain at the clinical research stage. The role of the pathologist is not limited to diagnosis but is also essential in assessing response to treatment and selecting subsequent therapy. Organ-preserving and oncoplastic surgery, in turn, makes it possible in suitable patients to reduce surgical trauma and functional and aesthetic losses while maintaining oncological control.

Keywords: Breast Cancer, Middle-Aged Women, Pathological Anatomy, Immunohistochemistry, HER2, ER, PR, Triple-Negative Breast Cancer, Pembrolizumab, Immunotherapy, Gene Therapy, P53, Oncoplastic Surgery, Breast-Conserving Surgery

Introduction

Breast cancer is one of the most common malignant tumours in women: in 2024, approximately 2.4 million new cases were diagnosed among women worldwide and about 694,000 deaths were recorded. [1]. [2] Because of the biological heterogeneity of the disease, the “one treatment fits all patients” principle has lost its relevance in modern oncology. According to the WHO, treatment is based on a combination of surgery, radiotherapy and systemic therapy tailored to the type, extent and biological characteristics of the tumour. [3].[4]

Breast cancer diagnosed in middle age may follow different clinical and biological courses. Therefore, when a treatment plan is drawn up, not only the size of the tumour but also its histological and molecular profile is taken into account. [5]. [6] Pathomorphological examination of biopsy material makes it possible to determine the type of invasive carcinoma, the histological grade, lymphovascular invasion, lymph node metastases, as well as therapeutically significant markers such as ER, PR and HER2.[7][8][9][10]

In recent years, immunotherapy has entered clinical practice for certain biological subgroups of breast cancer. At the same time, gene therapy is developing as a promising but not yet fully standardised direction aimed at destroying tumour cells or enhancing the immune response by exploiting molecular defects in cancer cells. [11][12][13][14]

Aim of The Study

To analyse modern methods of breast cancer treatment, in particular immunotherapy and gene therapy, in relation to pathomorphological and molecular markers, and to describe the possibilities of breast-conserving and oncoplastic surgery following neoadjuvant treatment.

Materials and Methods

The article was prepared as a literature review. Scientific papers, clinical studies and international clinical guidelines published in 2014–2026 were reviewed using bibliographic platforms such as PubMed, Web of Science and Scopus, as well as reliable sources such as the WHO, NCI, ASCO/CAP and the New England Journal of Medicine. The main areas covered were: the pathomorphological classification of breast cancer; biomarkers; immunotherapy; gene therapy; neoadjuvant treatment; breast-conserving surgery and oncoplastic approaches.

1. Pathomorphological and molecular basis: the starting point for treatment selection

Breast carcinomas are morphologically heterogeneous, and even tumours of the same anatomical stage may differ sharply in their biological characteristics and response to treatment. In modern classification, morphological examination is supplemented by molecular data. In practical terms, ER and PR expression, HER2 status, proliferative indices and, where necessary, genetic/molecular tests help in selecting systemic therapy.

HER2 status is determined by immunohistochemistry (IHC) and, where necessary, by in situ hybridisation (ISH). The ASCO/CAP recommendations emphasise the importance of accurately determining HER2 status in invasive breast cancer for therapeutic decision-making. The clinical significance of HER2-low cases is also expanding, as certain antibody–drug conjugates can be used even in patients without strong HER2 expression or gene amplification. [15]

Pathomorphological assessment is also important for immunotherapy. In triple-negative breast cancer (ER–/PR–/HER2–), features of the tumour microenvironment such as PD-L1 and tumour-infiltrating lymphocytes (TILs) may be associated with response to treatment. In studies based on KEYNOTE-522, high TIL levels showed a significant association with pathological complete response to neoadjuvant chemoimmunotherapy.

2. Immunotherapy: a modern approach that has entered clinical practice

Immunotherapy acts by weakening the mechanisms by which tumour cells evade the immune system or by enhancing the immune response. In breast cancer, checkpoint inhibitors, especially agents targeting the PD-1/PD-L1 pathway, have been most extensively studied in the triple-negative subtype.

According to the NCI, pembrolizumab is the main immunotherapeutic agent used in breast cancer. In certain triple-negative tumours it may be given with chemotherapy in the neoadjuvant setting and then continued in the adjuvant setting after surgery. The KEYNOTE-522 trial showed that pembrolizumab-based perioperative treatment improved pathological complete response and event-free survival rates in early-stage triple-negative breast cancer.

Here, pathological anatomy is at the centre of clinical decision-making: in the postoperative specimen, the residual volume of invasive tumour, the status of the lymph nodes and the pathological response to treatment are determined. Pathological complete response (pCR) has prognostic significance in certain biological subgroups and helps determine the subsequent adjuvant strategy.

Immunotherapy is not applied uniformly to all patients with breast cancer. The molecular subtype of the tumour, its stage, biomarkers, the goal of treatment and the risk of adverse effects are assessed by a multidisciplinary team.

3. Gene therapy: possibilities and current limitations

Gene therapy in breast cancer involves exploiting genetic alterations in tumour cells for therapeutic purposes. The main strategies include delivery of functional genes, restoration of tumour suppressor genes, oncolytic viruses, “suicide gene” approaches, suppression of gene expression via siRNA/shRNA, delivery of immunomodulatory genes and genetic vaccines.

Results

The p53 approach is one of the most extensively studied strategies: theoretically, restoring wild-type TP53 function may lead to cell cycle arrest or apoptosis in tumour cells. However, achieving clinical efficacy is hampered by problems such as gene delivery to tumour cells, ensuring sufficient expression, tumour heterogeneity and immune safety.

Oncolytic viruses represent another direction, aimed at selective replication in tumour cells or at enhancing the immune response through tumour antigens. In current research, gene therapy is also being studied in combination with immunotherapy and radiotherapy. An important scientific point, however, is that most gene therapy approaches in breast cancer are still at the stage of clinical trials; presenting gene therapy as routine standard treatment would therefore be scientifically incorrect.

For this reason, it is appropriate to regard gene therapy in this article not as a “therapy of the future” but as a direction of experimental and translational medicine targeting specific molecular targets.

1. The relationship of immunotherapy and gene therapy with pathological anatomy

Pathological anatomy is one of the key components of modern precision oncology. The histological type and grade of the tumour are determined in biopsy and resection material, while immunohistochemical studies make it possible to assess ER, PR, HER2 and other markers. From the standpoint of immunotherapy, the assessment of immune microenvironment features such as PD-L1 and TILs is gaining particular importance in scientific research.

Pathomorphological examination after neoadjuvant treatment shows the actual effect of therapy on tumour tissue. In this respect, the pathologist answers not only the question “is cancer present or not?” but also the clinical question “how did the tumour respond to treatment?” This information serves to individualise the subsequent surgical and systemic treatment strategy.

2. Reducing the extent of surgery: from neoadjuvant treatment to an organ-preserving approach

Historically, the surgical treatment of breast cancer has evolved from radical mastectomy towards breast-

conserving operations. In the current approach, the goal is not merely to remove the tumour but to reduce the loss of healthy tissue while maintaining oncological safety.

Breast-conserving surgery is usually considered in patients in whom the tumour can be completely resected and, where necessary, combined with radiotherapy. A 2024 meta-analysis compared the outcomes of breast-conserving surgery and mastectomy based on data from more than 34,000 patients. The results indicate that clinical decisions need to be made taking into account the patient's stage, tumour biology and the feasibility of radiotherapy.

Neoadjuvant systemic therapy can reduce tumour size and make breast-conserving surgery possible in some patients who might initially have required mastectomy. Oncoplastic surgery combines the principles of oncological resection with simultaneous restoration of breast shape. A 2024 meta-analysis analysed numerous studies on oncoplastic breast-conserving surgery and reported favourable results in terms of resection quality and re-operation rates.

Principles of surgical de-escalation are also developing with regard to the lymph nodes. The WHO describes sentinel lymph node biopsy as a method with fewer complications than complete axillary dissection in certain invasive cancers. However, this approach should be selected according to the patient's clinical and pathological status.

3. An algorithm for a comprehensive approach in middle-aged women

1) Clinical assessment and imaging → 2) biopsy → 3) pathomorphological diagnosis and IHC (ER/PR/HER2, required biomarkers) → 4) TNM staging and multidisciplinary discussion → 5) neoadjuvant or adjuvant systemic therapy appropriate to the biological subtype → 6) assessment of pathological response to treatment → 7) breast-conserving/oncoplastic surgery in suitable patients → 8) radiotherapy and adjuvant systemic therapy where necessary.

In this algorithm, immunotherapy and gene therapy do not have the same status: whereas pembrolizumab-based immunotherapy has become part of clinical practice in certain triple-negative breast cancers, gene therapy remains largely within the framework of clinical trials and translational research.

Discussion

The main direction in the development of breast cancer treatment is a shift not towards “more treatment” but towards the principle of “biologically appropriate treatment”. Pathological anatomy and molecular diagnostics help determine which therapy is likely to be most beneficial for which patient. The development of immunotherapy has brought the immune microenvironment into treatment decisions, while gene therapy is expanding the possibilities of targeting the genetic vulnerabilities of tumour cells.

At the same time, reducing surgery does not mean making the operation smaller in every patient. De-escalation should be carried out only without compromising oncological control. Pathomorphological parameters after neoadjuvant treatment, such as pCR, residual tumour, resection margins and lymph node status, are important in determining surgical strategy.

As for gene therapy, scientific caution is required: although the available literature points to many promising platforms, its broad clinical application is limited by challenges in effective delivery, intratumoural heterogeneity, immune response, safety and the lack of large randomised trials.

Conclusion

The modern approach to the treatment of breast cancer in middle-aged women is based on integrating pathomorphological diagnosis, molecular biomarkers, systemic therapy and, wherever possible, organ-preserving surgery into a single multidisciplinary system. Immunotherapy is gaining clinical significance, particularly through pembrolizumab-based treatment in certain stages of triple-negative breast cancer. Gene therapy, meanwhile, is a promising but largely experimental platform developing in such areas as p53, oncolytic viruses, immunomodulatory genes, RNA interference and gene editing.

The role of pathological anatomy is maintained at all stages of treatment: initial diagnosis, identification of biomarkers, assessment of response to neoadjuvant therapy and determination of prognostic indicators after resection. Consequently, the future approach will rely increasingly not on “surgery or drugs” but on the principle of “precise systemic therapy + minimally sufficient surgery + pathological control” matched to the biological characteristics of the tumour.

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