







## REVIEW PAPER

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# Neoadjuvant therapy in breast cancer – objectives and tasks

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## ABSTRACT

**Introduction.** Neoadjuvant therapy (NCT) in the treatment of breast cancer is employed for patients with early stage disease or with inoperable disease. NCT can decrease the tumor volume. It can facilitate breast conservation therapy. Response to NCT is a strong predictor of outcome breast cancer (BC). Direct target therapies has markedly improved the result of treatment BC.

**Aim.** Therapy for breast cancer continues to improve. The importance of tumor burden on local control rates will be in the future.

**Material and methods.** This analysis was performed using a systematic literature search.

**Results.** The latest scientific reports give hope for greater safety and a better life for patients based on optimized and effective therapy.

**Conclusion.** Currently, improving the effectiveness of breast cancer treatment is mainly related to the optimal use of classic therapeutic strategies. New classes of substances have been approved for treatment or are in advanced stages of clinical development.

**Keywords.** neoadjuvant therapy (NCT), breast cancer (BC), triple negative breast cancer (TNBC)

## Introduction

This work consists of a review of reports from the last 5 years regarding progress in breast cancer (BC) diagnostics and treatment.<sup>1-46</sup> In particular, progress in reference to neoadjuvant therapy (NCT). BC is a heterogeneous disease with morphological and molecular features that influence prognosis and response to treatment. NCT therapy is standard in patients with locally advanced BC and in inflammatory BC.

## The goals of NCT implementation

- Down staging of large, unresectable tumors to sizes that enable surgical resection.
- Reduction in the size of the resected area.
- Ability to perform breast reconstruction or to plan reconstruction.
- Implementation of immediate treatment without convalescence after surgery which is necessary when the first form of therapy is a surgical operation.

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- NCT destroys any micro-metastases which limits the risk of a tumor spreading.
- The ability to monitor response to treatment and individualization of further proceedings.

In the absence of responses to treatment, the inclusion of patients in clinical trials for new drugs is undertaken. The evaluation of the response to treatment with new drugs may serve as a marker (surrogate) of routine therapeutic progress.<sup>9,11</sup> Diagnostic material obtained by core biopsy, mammotomy biopsy (mammotome biopsy MB), stereotactic biopsy (stereotactic biopsy-SBB0), estrogen receptor (ER), progesterone receptor (pr), human epidermal growth factor receptor-2 (HER-2) and proliferation index (Ki67). Depending on the condition of these parameters, the patient receives hormonal trapping, cytostatics or immunotherapy. Currently, the strategy of therapeutic treatment is the assessment of predictive factors which aim to apply optimal treatment, and are prognostic, in order to predict the time frame of the disease and without therapy. The main prognostic factors in BC are: tumor size, number of lymph node metastases, histological grading and status of hormone receptors and HER-2 receptor, and Ki67 proliferative index. Other additional parameters include the presence of DNA ploidy, mutation of the p53 gene, cyclin-E, the presence of tumor cells in the peripheral blood and bone marrow, vascular invasion and perineural spaces. These parameters, including the presence of lymph node metastases, currently determine the type of NCT therapy in BC. The effectiveness of NCT therapy depends on the type of treatment implemented. Despite the implementation of therapy based on these parameters, in some cases resistance to treatment occurs. There is hope in research on predictive and prognostic factors based on disorders at the cellular level.<sup>31,38,43,45</sup> In patients with hormone-dependent cancer (ER +, PR +, HER-2) and without lymph node metastases, molecular profiles may be used (MammaPrint, Oncotype DX, Prosigna, Brest Cancer Index (BCI), Endo Oredict Clin, Pam 50, PEPI, uPA, PAI-1.<sup>2,4,9,24,27,35,40,46,47</sup> They elicit patients with low risk of relapse who do not need a follow-up chemotherapy and patients at risk of relapse. The prognostic and predictive value is associated with the three-dimensional tumor (Tumor volume-Tv), which correlates with the presence of metastases to the lymph nodes. Tv is a better indicator of the presence of metastases than T-assessment.<sup>1</sup> Functional Tumor Volume (FTV), measured using Magnetic Resonance Imaging (MRI), seems to be a strong predictor in the assessment of cancer recurrence after NCT. It can also be used to assess pCR as well as postoperative pathomorphological assessment. The use of MRI (Magnetic Resonance Imaging) can be used as a method of assessing the effectiveness of NCT treatment depending on the cancer subtype. Evaluation is the pattern of shrinkage of tumor mass.

It can be concentric, nodular, or mixed all of which can be seen in MRI. The pattern and intensity of tumor reduction can serve as an indicator of early response after NCT. There is a correlation with the BC biological subtype.<sup>3,35,37,44</sup> Breast MRI and Molecular Breast Imaging (MBI) are imaging methods that allow for non-invasive assessment of BC construction, pathophysiology and biology. BC cells, in order to obtain energy, reprogram cell metabolism. These processes can become the target of therapy. It can become a source of biomarkers used in prognosing and monitoring treatment. Based on the use of these imaging methods, early response to the NCT used can be identified. This allows one to modify the treatment. Research is still ongoing.<sup>3,11,13,29,32</sup> There is a locally advanced BC relationship with type of vascularization, which can be assessed in MRI. Asymmetric crayfish (AIBV-Increase In Breast vascularity) is more aggressive but more susceptible to NCT than BC with symmetrical vascularity.

Persistent AIBV after NCT, even if the tumor decreases, is worse and requires more intensive NCT.<sup>28</sup> Recent research has uncovered new therapeutic strategies based on the evaluation of the androgen receptor (AR). In triple-negative carcinomas (TNBC), despite obtaining a pCR after NCT therapy, the presence of AR makes them prognosticate better than AR negative cancers.<sup>31,38</sup> Tumor Infiltrating Lymphocytes-TIL have a predictive and prognostic value in BC TNBC or HER2+. In studies, patients with higher levels of TIL had better therapeutic effects. The survival time of patients with NCT trastuzumab and derivatives also increased. It may also herald extensive research into BC immunotherapy.<sup>11,14,22,36,41</sup> The course of TNBC is aggressive compared to other cancers. There is also no correlation of tumor size with the presence of lymph node metastases. TNBC is considered a cancer belonging to the BRCAness group. It is characterized by profiles as in cancer with the BRCA-1,2 mutation.<sup>30,36</sup> Research is under way on predictive and predictive factors that may play a role in the treatment of PARP inhibitors (platinum derivatives). Mainly in the treatment of NCT TNCA BRCAness and BRC-1,2 mutations.<sup>7,21,23,24,26</sup> Recent reports speak about the expression of mRNA in BRCA-1,2 negative carcinomas. It can be a predictor of NCT with anthracyclines.<sup>10,18</sup> There are reports of changes in the primary-immunohistochemical profile. This applies to the ER, PR and HER-2 receptors. Therefore, it is recommended to evaluate receptors in a tumor that has undergone NCT and to evaluate receptors in lymph node metastases. This is to check the actual state of the receptors. The patients who had a PIK3CA mutation after NCT had less chance of survival than those that have lost the mutation.<sup>39</sup> Some reports indicate that there is a relationship between the high values of KI-67 in patients who are to receive NCT. These patients have TNBC and BC Her-2+ and receive

anthracyclines and taxanes. The higher the KI-67 value, the more likely the pCR is after using these chemotherapeutics. This also applies to hormone-dependent cancers with high KI-67. The inclusion of chemotherapy in these patients results in a higher percentage of pCR.<sup>19,20</sup>

## Conclusion

Currently, improving the effectiveness of breast cancer treatment is mainly related to the optimal use of classic therapeutic strategies. New classes of substances have been approved for treatment or are in advanced stages of clinical development. It is very important to establish molecular predictors for these substances. It will help physicians to find the best therapeutic option

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