Introduction:

Breast cancer still remains the most common malignancy in women and its incidence is slowly increasing. A marked reduction of mortality has been achieved in the last 10 years thanks to modern diagnostic methods, mammary screening, and comprehensive and targeted cancer therapy. Modern diagnostic capabilities not only allow early diagnosis of a primary tumor lesion and precise determination of its biological nature before commencing treatment, but they also enable early diagnosis of local and regional recidives, including diagnosis of metastases in distant organs.

In addition to clinical examination, conventional and complementary imaging examinations and tumor markers our objective was to determine the importance and use of growth factors in relation to the overall prognosis. The growth factors physiologically act already during the ontogenetic period when they control cell growth, proliferation, differentiation and apoptotic processes. It is known that they take part in the tumor growth processes which are characterized by autonomous behavior, increased proliferative activity, distinct differentiation activity and reduced apoptosis. Growth factors work as autoregulation factors in the neoplastic process as well as through their paracrine effects mediated by more or less specific receptors.

Objective of the study:

Our goal was to determine such growth factors that would be useful in the pre-treatment diagnostic phase to determine the risk for a female-patient related to progression of the disease and long-term survival.

Material and methods:

The research project was conducted from January 2008 to December 2011. It was a prospective, non-randomized study that included female-patients with primarily surgically treated breast cancer in the study group, and those who underwent surgery due to a benign lesion in the control group.

The female-patients from the studied cohort were divided into 3 subgroups based on the clinical status: G1 - clinical stage I, G2 - clinical stage IIa, G3 - clinical stage IIb and III. Blood samples were taken immediately before the surgery and on Day 9 following the surgery in all patients. The samples were tested for the levels of the selected growth factors (GF) – IGF-1, IGFBP-3, Leptin, HGF, EGF, TGF, VEGF levels and tumor markers (TM) - CA 15-3, CEA, TK, TPA and MonoTotal. The results were statistically analyzed, differences between the single subgroups were evaluated, and the GF and TM with a predictive value in relation to disease free interval (DFI) and overall survival (OS) were determined. Correlations with anamnestic risk factors and adverse prognostic tumor factors were performed for a selected group of female-patients with a malignant disease. By comparing the

preoperative values in the studied and control group we focused on determination of a value of GF and TM that could help in primary or differential diagnosis.

Results:

The study included 98 patients with a malignant disease, 54 in the G1 subgroup, 25 in the G2 subgroup, and 19 patients in the G3 subgroup. The control group consisted of 25 patients. Overall, 13 patients experienced progression of cancer and 10 patients died.

Testing between the subgroups found statistically significant differences in tumor grading, expression of estrogen receptors and proliferative activity always in favor of the unfavorable factors for the G3 subgroup. Significantly higher frequencies in locally advanced tumors were found in progesterone receptor negativity, amplification of the HER2 gene, oncological positivity including family history of breast cancer, BMI > 30, in nulliparae and female-patients who do not breastfeed and women with menopause after 50 years of age.

A significantly shorter DFI and OS was found in the group testing for the G3 subgroup, in which the pre-operative and early post-operative levels of GF and TM were further evaluated. As for DFI, an increased risk is indicated by elevation of MonoTotal, Leptin, HGF, CA15-3, TK, TPA and CEA, and by elevation of MonoTotal, HGF, VEGF, TK and TPA, preoperatively and postoperatively, respectively. In relation to OS a risk is indicated by elevated MonoTotal, HGF, VEGF, CA 15-3, TK and TPA, and by elevated MonoTotal, HGF, VEGF, TK and TPA, pre-operatively and post-operatively, respectively. Pre-operatively reduced levels of TGF and EGF were found to be adverse prognostic factors of overall survival. We failed to prove any prognostic importance for IGF-1, IGFBP-3, and postoperatively for Leptin, CEA, TGF and EGF as well. Correlations with the prognostic usable GF and TM found association with oncological positive family and personal history, hormone therapy, including hormonal contraception, obesity, smoking and cancer incidence below the 40 years of age, first delivery after 30 years of age and menopause after 50 years of age. With regard to cancer we found a correlation with HER2 gene amplification and estrogen receptor negativity. For early cancers (subgroup G1 and G2) a relation between pre-operative and early the post-operative GF and TM levels and prognosis of patients was not statistically assessable.

By comparing the preoperative values of GF and TM between the studied and control group we failed to find a value that would determine a biological nature of the lesion.

Conclusion:

Pre-operative and early post-operative values of TK, TPA, Monototal, HGF, and pre-operative CA 15-3 value are important prognostic factors for disease progression and overall survival, while a perioperative determination of VEGF is an important prognostic indicator of overall survival in locally

advanced breast cancer. When considering other risk factors they can select a "more risky" group of patients at the time of diagnosis. Therefore, we believe that neoadjuvant personalized oncological therapy and intensification of dispensarization care could provide improvement of prognosis for female-patients.

Keywords:

breast cancer - prognostic factors - growth factors - tumor markers – disease free interval - overall survival - dispensarization