

## **Abstract**

### **Utilisation of New Biomarkers for the Optimization of Diagnostics and Therapy of Tumors of the Gastrointestinal Tract**

#### **Introduction:**

Tumor markers are standard diagnostic tools. They are mainly used to monitor the course of the disease and to check the efficacy of the treatment. It is important to observe dynamics. Changing the level of the biomarker can prevent clinical manifestation and lead to early diagnosis of relapse, which in turn means improving the quality of life, including prolonging survival. Recently, we have encountered a number of diagnostic algorithms that suggest algorithms for estimating the risk of tumor presence or the risk of progression of cancer, using statistical methods.

#### **Objectives:**

The aim of this work is to verify new biomarkers for the diagnosis of gastric cancer and to develop an optimal algorithm for their use. Further, to evaluate the importance of cytokeratin markers - Tissue Polypeptide Antigen (TPA) and Tissue Polypeptide Specific Antigen (TPS) for the diagnosis of metastatic colorectal carcinoma in the liver. To carry out a pilot study of FGF23 levels in people with colorectal carcinoma and other gastrointestinal tumors.

#### **Methods and patients:**

Patient samples were analyzed using immunoradiometric, chemiluminescence and fluorescence assays. For each solved problem, a specific patient set was selected. Groups of patients with malignant tumors of the stomach (105 persons), colorectal carcinoma at various stages (60 persons) and a group of patients with colorectal cancer with metastatic liver disease (111 persons) were evaluated. Control groups of healthy individuals were evaluated.

#### **Results and Discussion:**

This chapter of the thesis is structured according to the solved problems.

### **Stomach cancer.**

The result of our research is a mathematical model for calculating the risk of stomach cancer, which we called the Gastric Cancer Index - GCI. When using GCI, we achieved the best ROC curve and the highest AUC. In the follow-up study, we will focus on verifying the benefits of the individual parameters of our mathematical model and the overall improvement of the algorithm for calculating the GCI index. From the results, we can state that tumor markers CEA and CA 72-4 remain the best individual markers for the diagnosis of gastric cancer. We have assured that MMP-1, MMP-7, OPN and PIVKA II are promising candidates for new biomarkers for the detection of gastric cancer. We have confirmed lower levels of pepsinogen-I, higher levels of gastrin and the presence of *Helicobacter pylori* as risk factors for gastric cancer. We have created a mathematical algorithm for assessing the risk of gastric cancer in the human population. Further studies need to be carried out to verify our findings in a larger patient population.

### **Metastases of colorectal carcinoma to the liver.**

In evaluating the second set of patients, we focused on changes in tumor marker levels at individual stages and on interpretation of patient results without metastasis and with metastasis. From the above data, each of the markers used was statistically significantly higher in Stage IV compared to Stage I + II + III. CEA is the most commonly used tumor marker in serum and a number of studies show its significant increase in patients with hepatic metastases. Based on the ROC curves and the AUC resulting from our study, it is clear that CEA (AUC = 0.6903) does not achieve such metastatic detection success rates as both cytokeratin - TPS (AUC = 0.9912) and TPA (AUC = 0.9116). Our findings are in line with the findings of other authors who have dealt with the same topic.

### **Use of fibroblast growth factor (FGF23) in the diagnosis of colorectal carcinoma.**

FGF23 values in patients with colorectal cancer are statistically significantly higher than those measured in the healthy population. However, according to the minimal-maximal values, it is evident that FGF23 will not be useful as a marker of capture at early stages. Conversely, when we evaluated only the patients in stage IV, where the measured values were the highest, the comparison with stages I, II and III was very optimistic. The FGF23 values of these groups did not overlap at all. However, it should be noted that this was a very small set. The clinical relevance of this information should be verified in a larger patient population.

## **Conclusions:**

### **Group of patients with gastric cancer:**

- A multivariate regression analysis was designed to calculate the risk of stomach cancer risk in the following form:  $GCI = CEA * 0.6315 + 0.9344 * CA72-4 - Pepsinogen-I * 0.00217 + Helicobacter\ pylori * 0.0362 + MMP-7 * 0.00180$ .
- The CA 72-4 remains the best single tumor marker for the diagnosis of gastric cancer.
- Reduced levels of pepsinogen-I, higher levels of gastrin and the presence of Helicobacter pylori are risk factors for gastric cancer.

### **A group of patients with colorectal carcinoma metastases:**

- Cytokeratin tumor markers TPA and TPS can be recommended for use in the diagnosis of colorectal carcinoma liver metastases
- The combined CEA + cytokeratin test has better sensitivity than CEA alone.
- The highest sensitivity to nearly 100% liver metastasis is achieved with the combination of CEA and TPS. If we choose a cut-off that has been calculated for each test individually, it is necessary to calculate the specificity at 80%.
- Cytokeratin markers, like CEA, cannot distinguish pure liver metastases from multiple metastases at different locations.

### **A group of patients using FGF23 in the diagnosis of colorectal cancer:**

- FGF23 values in colorectal cancer are statistically significantly different from the healthy population.
- Significantly elevated values can be found in metastatic forms of the disease.
- The usefulness of FGF23 to early diagnosis of the metastasis will need to be verified in a larger group of patients.

## **Keywords:**

Tumor markers, soluble cytokeratin fragments, FGF23, immunoradiometric assay, chemiluminescence assay, colorectal carcinoma, gastric cancer, metastatic liver disease, CGI.