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CLINICAL SIGNIFICANCE OF MUCINS AS MARKERS OF COLON CANCER

Aleh E. Kuzniatsou[1*], Vladimir M. Tsyrkunov[1], Ali. Adeeb. Hussein. A[2]

Grodno State Medical University, Grodno, Republic of Belarus[1]
Yanka Kupala State University of Grodno, Grodno, Republic of Belarus[2]
Al-Muthanna Health Department - Al-Hussein Teaching Hospital - Al- Samawa – Iraq[2]
Iraqi Medical Laboratories Association - Iraq[2]

Corresponding Author: 1*

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ABSTRACT

Currently, many biological markers have been described, the determination of which contributes to the detection of a malignant tumor. Membrane-associated mucins (MUC) may be a potential marker for colon cancer. The aim of the study is to evaluate the clinical significance of the expression of high molecular weight glycoproteins MUC-1 and MUC-13 as markers of tumor processes in the large intestine. Samples of tissues and blood serum of 106 patients with a malignant neoplasm of the large intestine were studied. Immunological (enzymatic immunoassay), determination of antibodies to MUC-1 and MUC-13 receptors. The role of antibodies to MUC-1 and MUC-13 receptors as diagnostic markers in the process of clarifying the diagnosis of colon cancer was evaluated. The established limits of fluctuations in serum antibodies to MUC-1 and MUC-13 in healthy individuals differed from those in patients with a tumor (p=0,02). In patients with colon cancer, the levels of antibodies to MUC-1 and MUC-13 receptors in the tumor tissue are higher than in non-tumour-affected intestinal tissue. The level of expression of MUC-1 and MUC-13 in the tumor tissue does not depend on the size of the tumor, lymph node involvement, the presence of distant metastases, age and sex of patients. Thus, mucins MUC-1 and MUC-13 are of practical interest as additional markers for assessing tumor processes in the large intestine and their concentration in the tissue can be used to control the completeness of the volume of resection of the large intestine tumor during surgical interventions.

1. INTRODUCTION

Approximately 1.1 million new cases of colon cancer are diagnosed each year worldwide, causing the death of half of patients. In economically developed countries, colon cancer / colorectal cancer (CC/CRC) are common diseases, in the structure of which the incidence of colon and rectal cancer is 58.7/100 thousand and 28.8/100 thousand of the population, respectively, and the five-year survival rate is 60%. The latter figure in countries with limited resources is less than 40% [1]. Statistical data on the economic losses from this

oncopathology are not available, but in high-income countries they amount to about 6.5 billion dollars per year [2].

In the Republic of Belarus, about 50 thousand patients with newly diagnosed malignant neoplasms are detected annually. The country is included in the group of countries with a relatively low incidence of colon cancer, not much different from neighboring countries. Over the past decade, the incidence of CC/CRC has tripled [3]. About 2.5 thousand new cases of colon tumors and 1.9 thousand cases of rectal cancer are detected annually. 35% of them are diagnosed at stages III and IV. The five-year survival rate of patients, depending on the stage of the disease, varies from 60.6 to 14.5% [4].

To date, many biological markers have been described, the determination of which in cells, tissues, or body fluids can help detect a malignant tumor and serve as an indicator of its biological characteristics or prevalence in the body. The determination of markers, the determination of which will allow assessing the risks of developing the disease, diagnosing a tumor, and serving as a biological indicator of the tumor process, is currently the subject of research [5].

A potential marker of colon tumors can be membrane-bound mucins (MUC), high molecular weight glycoproteins that have attracted the attention of researchers in recent years [6]. Normally, in the human body, MUCs are expressed by cells of a single-layer epithelium, are localized on the apical surface of cells, and are part of a molecular system that contributes to the stability of the epithelial barrier in the event of damage. In their structure, MUCs contain tandem repeats of amino acids such as proline, threonine, and serine; it is on the last two that glycosylation occurs. In humans, up to 21 types of mucoproteins are isolated, which, according to their location, are divided into membrane and secreted [7].

In malignant tumors, one can detect an increased expression of MUC compared to normal epithelium, a change in their intracellular localization, and an increase in the content of hypoglycosylated forms of the glycoprotein, as well as MUC present on the surface membrane of tumor cells, which can be considered an ideal target for targeted therapy [8].

In a number of clinical and morphological studies, in cancers of various localizations (breast, lung, stomach, intestines, and epithelial malignant neoplasms of other organs), a high level of correlation of MUC expression in tumor cells with an unfavorable disease prognosis has been described. Clinical observations are supported by experimental studies that suggest that MUC overexpression and its abnormal intracellular localization may increase the invasive and metastatic potential of malignant cells [9].

Other studies have shown that the relationship between the MUC level and the clinical characteristics of the tumor is ambiguous: MUC expression is detected in CC and characterized by a high histological stage of the process [10]. An increase in blood MUC, for example, in breast cancer, is associated with the degree of differentiation, tumor size, and relationship to the estrogen receptor [11]. In patients with a tumor process in the intestine, MUC expression may be associated with the stage of the TNM characteristics of the tumor and the presence of metastases. Expression of membrane-bound MUCs in the tumor was detected in 58.5% of living patients with CC with a favorable outcome in the first 5 years [12], [13].

Thus, MUC, as an object of study, is of interest for understanding the biology of malignant neoplasms of the epithelium and the background processes preceding their development, as well as for improving methods of diagnosis and prognosis in cancer [14].

Many aspects of the potential role of MUC in the occurrence and progression of malignant tumors, as well as the possibility of practical application of the accumulated experimental and clinical data, remain insufficiently studied to date.

The aim of the study was to evaluate the clinical significance of the expression of high molecular weight glycoproteins MUC-1 and MUC-13 as markers of tumor processes in the large intestine.

2. Materials and research methods

Materials and research methods. The objects of the study were tissue and blood serum samples of 106 patients with malignant neoplasm of the large intestine (CC): CRC, colon cancer, and cancer of the rectosigmoid junction. The patients were being treated at the Grodno Oncological Dispensary. The age of the subjects at the time of diagnosis was 29-87 years; the median age (Me) - 61.8±13.7 years, lower quartile (Q25) - 52 years; the upper quartile (Q75) - 72 years.

There were 45 women (42.5%) and 61 men (57.5%) among those examined with a tumor process of the intestine. The tumor was more often localized in the rectum (54/50.9%), sigmoid colon (8/7.6%), transverse colon (7/6.6%), cancer of the caecum and hepatic flexure of the colon (37/34, nine%). The diagnosis of cancer in each patient was confirmed morphologically. Distribution of patients in accordance with the International Clinical Classification of TNM: T3 - 52.8% (n = 56); T4 -23.6% (n = 25); T2-16.0% (n = 17), T1 - 7.6% (n = 8). At the time of diagnosis, 31.4% (n = 33) of patients had metastases to regional lymph nodes (N1), 9.4% (n = 10) had distant metastases (M1). The incidence of tumors with a low degree of malignancy (highly differentiated, G1) was 70.8% (75 people), tumors of an average degree of malignancy (poorly differentiated, G2) - 17.9% (19 people), and tumors of a high degree of malignancy (undifferentiated, G3) – 11.3% (12 people).

Tissue samples and paraffin blocks of patients with large intestine cancer (rectosigmoid junction cancer, CRC, CC) from the archives of the Grodno Regional Clinical Pathological Bureau and blood samples of the same patients obtained when applying for advisory and therapeutic assistance to the oncological dispensary (as part of the mandatory medical examinations in accordance with the current diagnostic and treatment protocols). Examination of intestinal tissue extract samples was performed in two zones: in the tumor zone and in the area of "healthy" tissue with morphologically undescribed malignancy criteria (n = 34).

The group of control studies is represented by blood samples from 35 apparently healthy individuals with no malignant neoplasm and no viral infections. The studies were carried out as part of preventive studies in 20 men (57.1%) and 15 women (42.9%), with a mean age 56.5±8.3 years (minimum 42 years, maximum 68 years).

The study of the level of antibodies to mucins (MUC-1, MUC-13, ng/ml) was carried out using the method of enzyme-linked immunosorbent assay (ELISA) in tissue samples and blood serum of patients using a kit of reagents manufactured by Wuhan Fine Biological Technology Co. Ltd" (China) on the enzyme immunoassay analyzer "Mindray 96RA" (China).

Serial sections were prepared from blocks of tissue in paraffin. In accordance with the standard protocol, tissue samples were prepared for analysis with a set of reagents manufactured by MagneSil Genomic, Fixed System (Promega, USA).

Samples of biological material (blood serum) were obtained in a standard way using Vacuette vacuum

systems with a coagulation activator manufactured by Greiner Bio-One, Austria. Preparation of blood samples for the study was carried out in a unified way: centrifugation (Fenox-24M centrifuge, China) at 3000g for 10 minutes. Serum samples were taken into separate systems in which the study was performed.

The results obtained during the study were entered into the original database. Statistical data processing was carried out using the standard package of applied statistical programs, SPSS. The difference between the studied parameters was recognized as significant at $p<0.05$. Among the methods of mathematical processing used are:

- Investigate the type of distribution and obtain numerical data. in the case of a normal distribution, the variable was characterized using the mathematical expectation (mean) – M and the standard deviation (σ). If the distribution of variables did not correspond to Gaussian, then the values of the upper (Q75) and lower quartiles (Q) and median (Me) were used to describe them;
- identifying the response to the impact in a two-sample task: to test the hypothesis of equality of the average values of the two groups of the variable, the Student's test (t) was used. If the distribution of the variable did not correspond to normal, the comparison of two independent groups of the studied variable was carried out using the Mann-Whitney test (U), and dependent groups, the Wilcoxon test (Z).
- the Hill method was used to compare shares (percentages).
- identification of the relationship between two variables with a normal distribution, the Pearson correlation coefficient (r) was used to assess the linearity of the relationship between the variables. If the distribution of the variables did not correspond to the normal distribution, Spearman's nonparametric correlation analysis (R) was used to assess the relationship between them.

3. Results and Discussion

The concentrations of antibodies to MUC-1 and MUC-13 receptors established in blood serum samples of practically healthy individuals in the population and in blood samples from individuals diagnosed with a tumor process of the large intestine are presented in Table 1.

Table 1. The concentration of antibodies in the blood serum to the MUC-1 / MUC-13 receptors in healthy individuals and in patients with colon cancer

Serum group	Indicator	n	M	min	max	m	p
Healthy ($p_к$)	Antibody receptor MUC-1, ng/ml ($p_{1к}$)	35	0,247	0,105	0,477	0,097	$p_{muc1к-о}$=0,02 $p_{muc13к-о}$=0,00001
	Antibody receptor MUC-13, ng/ml ($p_{13к}$)	35	0,325	0,084	0,622	0,131	
Patients ($p_о$)	Antibody receptor MUC-1, ng/ml ($p_{1о}$)	38	0,316	0,220	0,520	0,066	
	Antibody receptor MUC-13, ng/ml ($p_{13о}$)	38	0,806	0,450	1,630	0,287	

As can be seen from Table 1, the reference values of the concentrations of antibodies to mucins in practically healthy individuals to the MUC-1 and MUC-13 receptor were 0.247±0.097 ng/ml and 0.325±0.131 ng/ml, respectively. The results obtained fully coincided with the results of our earlier study of mucin expression in the age groups of 20.1±1.1 years, the concentration of which to the MUC-1 receptor was 0.25±0.04 ng/ml [15].

The concentration of antibodies to MUC-1 and MUC-13 receptors in the blood serum of patients with CC had significant differences from the control group ($p=0.02$ and $p=0.00001$, respectively).

The concentration of the level of MUC-1 and MUC-13 in the tumor tissue extract and at the border with

healthy tissue is presented in Table 2.

Table 2. Concentration of MUC-1 and MUC-13 levels in tumor tissue extract

Serum group	Indicator	n	M	min	max	m	p
Tumor tissue (p_o)	Antibody receptor MUC-1, ng/ml (p_{1o})	62	1,345	0,243	2,330	0,617	$p_{muc1o-з}$ =0,0000001 $p_{muc13o-з}$ =0,000001
	Antibody receptor MUC-13, ng/ml (p_{13o})	60	0,986	0,245	1,530	0,318	
healthy tissue ($p_з$)	Antibody receptor MUC-1, ng/ml($p_{1з}$)	33	0,175	0,140	0,210	0,020	
	Antibody receptor MUC-13, ng/ml ($p_{13з}$)	34	0,554	0,250	0,715	0,101	

As can be seen from Table 2, the average concentrations of antibodies to MUC-1 and MUC-13 receptors in the tumor tissue extract and at the border with the tumor-affected tissue had significant differences ($p<0.05$). The concentration of MUC-1 and MUC-13 in the tumor tissue was significantly higher than in the tissue not affected by the tumor (at the border of the surgical incision, Wilcoxon, Z-Test): MUC-1 - Z=5.01, p=10-7; MUC-13 - Z=4.66, p=10-6, Figure 1.

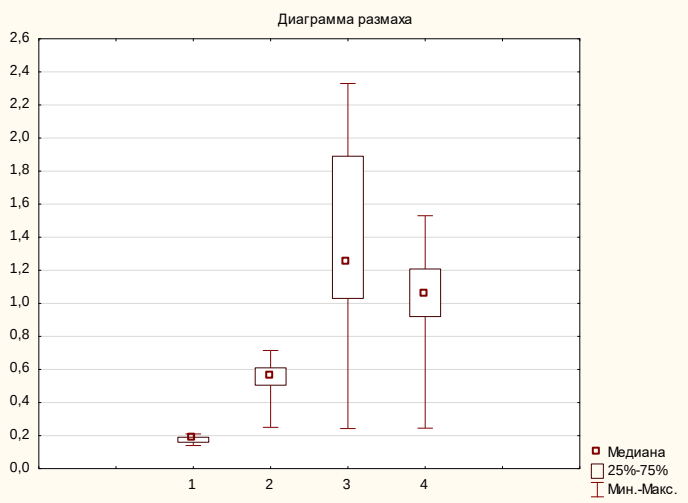


Fig. 1. Expression of MUC-1 and MUC-13 in the extract of tumor tissue and healthy tissue of the large intestine in patients with CC (abscissa axis: 1 - healthy tissue, MUC-1 receptor, 2 - healthy tissue, MUC-13 receptor; 3 - tumor tissue, MUC-1 receptor, 4 – tumor tissue, MUC-13 receptor, y-axis: mucin concentration in ng/ml

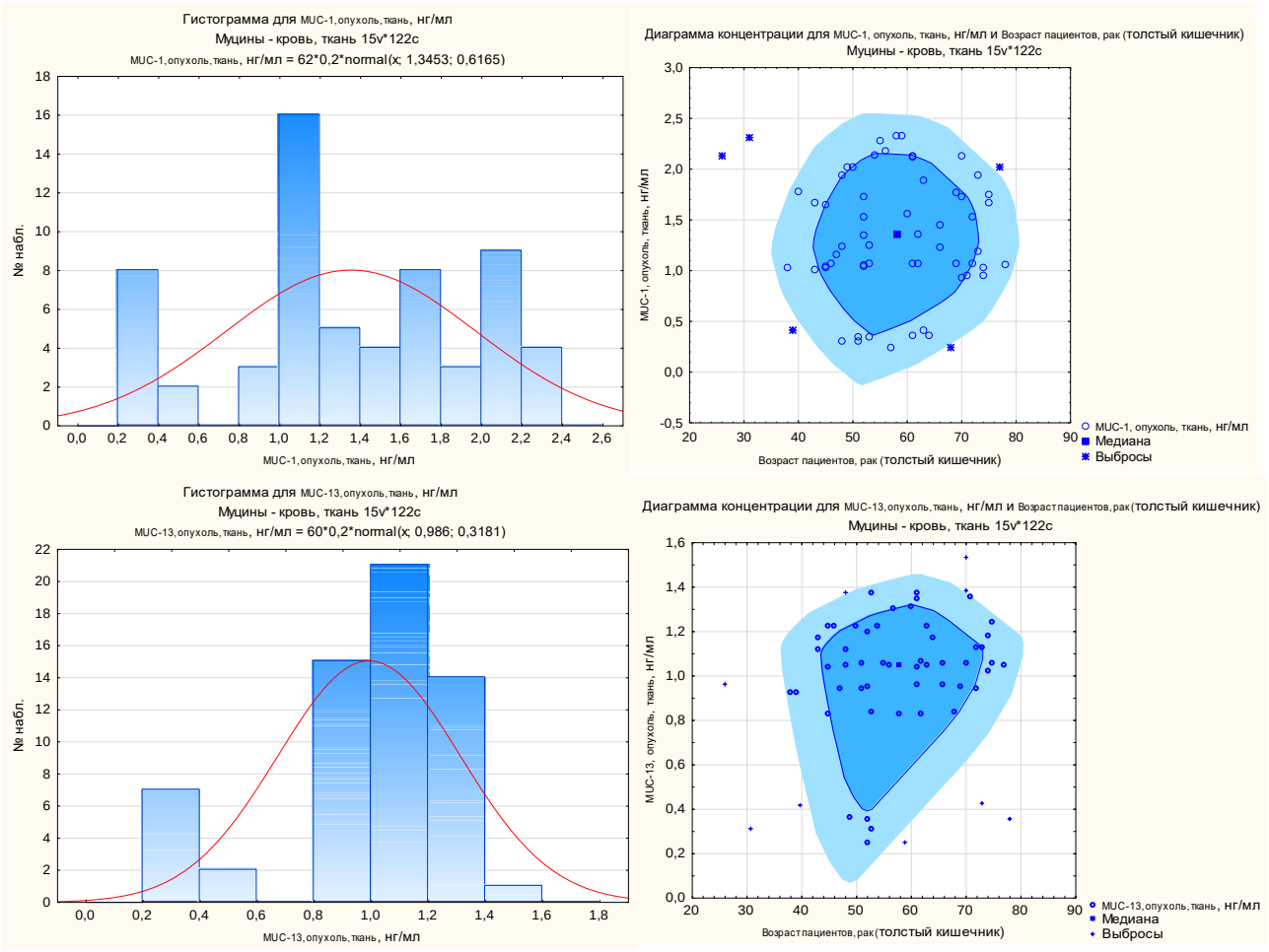
We believe that the overexpression of mucins (MUC-1, MUC-13) in the tumor tissue could be associated with the resistance of the epithelium to apoptosis in CC [16].

Based on the literature data, it should be assumed that when performing surgical interventions for CC, the determination of mucin in the tissue can be considered to control the completeness of the volume of tumor resection [17].

An analysis of the relationship between the level of expression of MUC-1 and MUC-13 in the tumor tissue and the clinical characteristics of the tumor did not establish significant relationships either with the size of the tumor (MUC-1 - p=0.143; MUC-13 - p=0.558), or with the involvement of the lymph nodes. (MUC-1 - p=0.117; MUC-13 - p=0.776), nor with the presence of distant metastases (MUC-1 - p=0.105; MUC-13 -

p=0.78).

Significant correlations between the level of expression of MUC-1 and MUC-13 in the extract of the intestinal tissue affected by the tumor with the age of patients have not been established (MUC-1 - R=0.096, p=0.652; MUC-13 - R=0.18, p =0.121), figure 5 (Spearman), figure 2.



a b

Fig. 2. Dependence of the expression of MUC-1 (a) and MUC-13 (b) from the age of the patient

Analysis of the distribution of concentrations of mucins (variables) MUC-1 and MUC-13 in the tissue extract during CC within age groups is shown in Figure 3.

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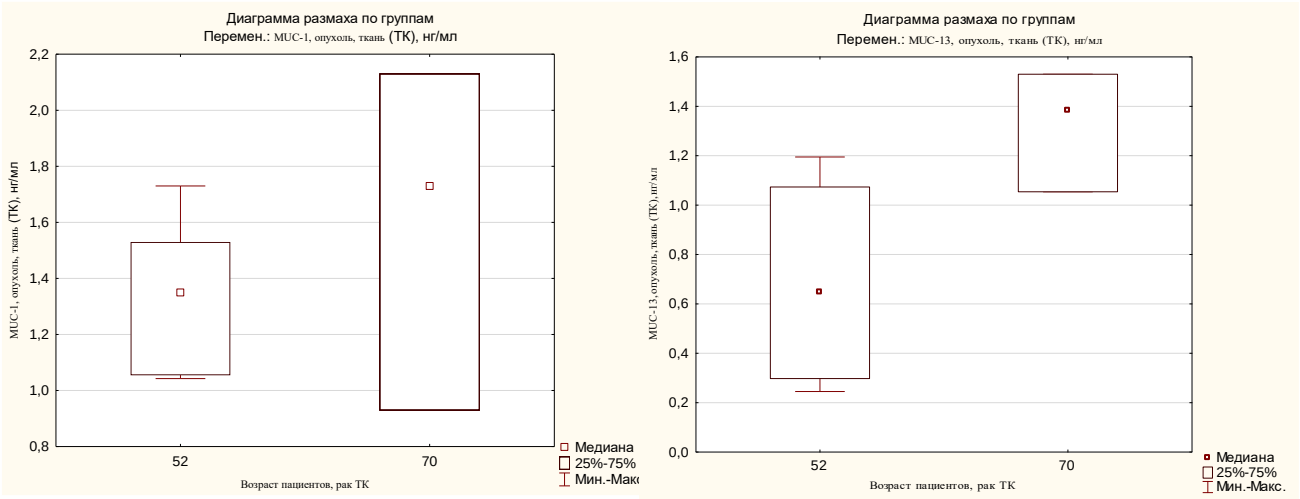
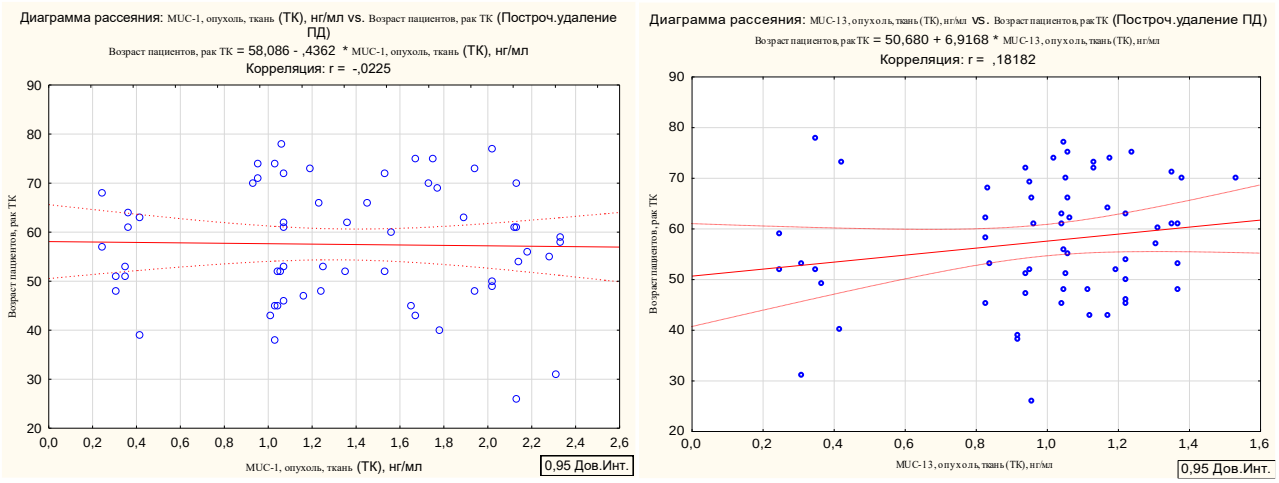


a b

Fig. 3. Diagram of the dependence of the expression of mucins MUC-1 (a) and MUC-13 (b) in the tissue from the age of the patient

As can be seen from Figure 3, the distribution of the minimum range of the concentration of mucins (variable) MUC-1 and MUC-13 in the tissue extract during CC within the age groups was established in the age categories of 52 years and 70 years.

Taking into account the range of variable expression of MUC-1 and MUC-13 mucins in the age groups of persons with an established diagnosis of CC, an assessment of multiple regression of the variables MUC-1 and MUC-13 was carried out (Figure 4).



MUC-1, number of observations – 60 MUC-13, number of observations - 60

a b

Fig. 4. Multiple expression regression for variables MUC-1 (a) and MUC-13 (b) in tissue extract depending from the age of the patient

As can be seen from Figure 4, in the model of relationships between age and the concentration of mucins MUC-1 and MUC-13 in the tissue of individuals with an established diagnosis of CC, concentrations were found to depend on age: MUC-1 - p=0.0005 (R=0.03386413; F=0.0688858, free term 1.445408403, standard error 0.3895034, t(60)=3.7109, MUC-13 – p=0.0007 (R=0.18181942; F=1.982934; free term 0.711223623, standard error 0.1993622, t(58) = 3.5675).

Based on the results of multiple regression of MUC-1 and MUC-13, taking into account the age groups of persons with an established diagnosis of CC (range of variable: 52 years, 70 years), the predicted value of the concentration of MUC-1 and MUC-13 mucins for persons with malignant processes of CC (cancer rectosigmoid junction, colorectal cancer, colon cancer), Table 3.

Table 3. Predicted value of MUC-1 and MUC-13 concentrations for individuals with malignant processes colon cancer (tumor, tissue extract, ng/ml)

MUC-1			CC, tumor tissue
	B-Weights	Age, years	B-weights - value
	-0,001738	52	-0,090382
	free member		1,445408 ng/ml
	predicted value		*1,355026* ng/ml
	-95,0%		1,180654 ng/ml
	+95,0%		1,529398 ng/ml
MUC-1			CC, tumor tissue
	B-Weights	Age, years	B-weights - value
	-0,001738	70	-0,121668
	free member		1,445408 ng/ml
	predicted value		*1,323740* ng/ml
	-95,0%		1,095915 ng/ml
	+95,0%		1,551565 ng/ml
MUC-13			CC, tumor tissue
	B-Weights	Age, years	B-weights - value
	0,004779	52	0,248528
	free member		0,711224 ng/ml
	predicted value		*0,959752* ng/ml
	-95,0%		0,870074 ng/ml
	+95,0%		1,049430 ng/ml
MUC-13			CC, tumor tissue
	B-Weights	Age, years	B-weights - value
	0,004779	70	0,334557
	free member		0,711224 ng/ml
	predicted value		*1,045781* ng/ml
	-95,0%		0,928061 ng/ml
	+95,0%		1,163501 ng/ml

As the analysis showed, the predicted value of the concentration of mucins MUC-1 and MUC-13 in the tissue in the presence of CC was: MUC-1 at 52 years old - 1.36 ng / ml, MUC-1 at 70 years old - 1.32 ng / ml, MUC-13 at 52 years old - 0.96 ng / ml, MUC-13 at 70 years old - 1.05 ng / ml.

The estimated predicted value of the concentration of mucins MUC-1 and MUC-13 in the blood serum for individuals with CC is presented in table 4.

Table 4. Predicted values of MUC-1 and MUC-13 concentrations for individuals with colon cancer (tumor, serum, ng/ml)

MUC-1			CC, serum
	B-Weights	Age, years	B-weights - value
	0,001050	52	0,054577
	free member		0,255509 ng/ml
	predicted value		*0,310087* ng/ml
	-95,0%		0,286348 ng/ml
	+95,0%		0,333825 ng/ml
MUC-1			CC, serum

	B-Weights	Age, years	B-weights - value
	0,001050	70	0,073470
	free member		0,255509 ng/ml
	predicted value		*0,328979* ng/ml
	-95,0%		0,298475 ng/ml
	+95,0%		0,359482 ng/ml
MUC-13			CC, serum
	B-Weights	Age, years	B-weights - value
	0,000268	52	0,013922
	free member		0,790082 ng/ml
	predicted value		*0,804004* ng/ml
	-95,0%		0,698709 ng/ml
	+95,0%		0,909300 ng/ml
MUC-13			CC, serum
	B-Weights	Age, years	B-weights - value
	0,000268	70	0,018741
	free member		0,790082 ng/ml
	predicted value		*0,808824* ng/ml
	-95,0%		0,673522 ng/ml
	+95,0%		0,944125 ng/ml

The value of the concentration of mucins MUC-1 and MUC-13 in the blood serum in the presence of CC was: MUC-1 at 52 years old, - 0.32 ng/ml, MUC-1 at 70 years old, - 0.33 ng/ml, MUC-13 at 52 years old - 0.80 ng / ml, MUC-13 at 70 years old - 0.81 ng/ml.

No relationship was found between the concentration of MUC-1 and MUC-13 in the tissue and the gender of patients with CC: MUC-1 - p=0.757, MUC-13 - p=0.916 (Mann-Whitney U Test).

According to the results of the studies, based on the analysis of the dependence of the level of expression of MUC-1 and MUC-13 mucins in tissue samples of a tumor nature and healthy tissue, it was concluded that the concentration of MUC-1 and MUC-13 in the tissue does not depend on the clinical and anatomical tumor localization, age, and sex of patients.

Since the content of MUC-1 and MUC-13 in the tissue does not correlate with the clinical characteristics of the tumor or the sex and age of the patient, it seems appropriate to determine MUC-1 and MUC-13 in the tumor and in non-tumor tissue in patients with any form of CC, regardless of gender and age.

Conclusion

The results of the study confirmed the role of antibodies to MUC-1 and MUC-13 receptors as diagnostic markers in the process of clarifying the diagnosis of CC in various histological and clinical-anatomical forms of the tumor. The established limits of fluctuations in serum antibodies to MUC-1 and MUC-13 in healthy individuals (MUC-1 - 0.247 ± 0.097 ng / ml and MUC-13 - 0.325 ± 0.131 ng/ml) had significant differences from similar indicators in patients with CC (MUC-1, p = 0.02, MUC-13, p=0.00001).

In patients diagnosed with CC, the levels of antibodies to the MUC-1 and MUC-13 receptors in the tumor tissue are significantly higher than in the intestinal tissue not affected by the tumor (MUC-1- p=10-7; MUC-13- p = 10-6).

The level of expression of MUC-1 and MUC-13 in the tumor tissue does not depend on the size of the tumor (MUC-1 - p=0.143; MUC-13-p=0.558), lesions of the lymph nodes (MUC-1 - p=0.117; MUC-13 – p=0.776),

presence of distant metastases (MUC-1-p=0.105; MUC-13-p=0.78), age (MUC-1-p=0.652; MUC-13, p=0.121) and sex of patients (MUC-1, p=0.757; MUC-13, p=0.916).

The established overexpression of mucin glycoproteins (MUC-1, MUC-13) in tumor tissue may be associated with resistance to apoptosis of the epithelium in colon cancer.

The determination of the concentration of antibodies to MUC-1 and MUC-13 in the tumor tissue can be used to control the completeness of the volume of colon tumor resection during surgical interventions.

In the presence of CC, the detection of the concentration of antibodies to MUC-1 and MUC-13 is higher than the predicted concentrations in the tumor tissue, which is 1.36 ng/ml for MUC-1 and 0.96 ng/ml for MUC-13 in patients at 52 years of age, and levels of 1.32 ng/ml for MUC-1 and 1.05 ng/ml for MUC-13 in patients 70 years of age indicate a high probability of a latent metastatic process when clinical examination methods do not reveal signs of regional or distant metastasis.

The concentration of antibodies to MUC-1 and MUC-13 in the blood serum, exceeding 0.32 ng/ml for MUC-1 and 0.80 ng/ml for MUC-13, may indicate the risk of a tumor process, in which clinical methods of examination show no signs of neoplasm.

In the final clinical interpretation of the results of determining the concentration of antibodies to MUC-1 and MUC-13 in patients, it is necessary to take into account not only the histological type of the neoplasm, but also other clinical and anatomical characteristics of the tumor. The different levels of circulating mucin that we noted in CC may be the result of a combination of several factors associated with both the biological properties of neoplasms and the development of the pathological process. These factors may include the level of expression of MUC-1 and MUC-13 in tumor cells, the nature of the tumor blood supply, the degree of involvement of lymphatic vessels in the tumor process, the structure of lymphatic collectors, and the severity of reactive changes in surrounding tissues [18].

Thus, high molecular weight glycoproteins MUC-1 and MUC-13 are of not only theoretical but also practical interest to specialists as additional markers for assessing tumor processes in the large intestine.

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