HEALTH, ENVIRONMENT, DEVELOPMENT

DIAGNOSTIC AND PROGNOSTIC VALUE OF MEASURING SEROTONIN IN MALIGNANT TUMOR ANEMIA IN PATIENT WITH COLORECTAL CANCER

Artem Andriiaka
Postgraduate Student, Shupyk National Medical Academy of Postgraduate Education, Ukraine
e-mail: aandriiaka0806@gmail.com, orcid.org/0000-0003-4562-5680
Stanislav Vydyborets
M.D., Professor, Shupyk National Medical Academy of Postgraduate Education, Ukraine
e-mail: vydyborets57@gmail.com, orcid.org/0000-0003-0546-4325

Summary
Colorectal cancer is an extremely urgent issue in modern medicine. This disease is often complicated by anemia, which has specific pathogenetic mechanisms of development and forms a mutual burden syndrome of diseases in cancer patients. The anemic syndrome is accompanied by the development of tissue hypoxia, which in turn activates the processes of oxidative stress and leads to increased release of biologically active compounds, in particular, biogenic amines. One of these is serotonin. Moderate concentrations of serotonin cause dilation of arterioles, reduction of myositis in venule walls, accompanied by venous stasis. Its high concentrations cause spasm of the arterioles, which exacerbates tissue hypoxia. We have examined 153 patients with colorectal cancer without anemia, 75 patients with colorectal cancer complicated by malignant tumor anemia, and 53 patients with iron deficiency anemia. The content of plasma free serotonin fractions was determined by the fluorometric method proposed by Mikhailychenko, B. V., Vydyborets, S. V. (1999). The patients with iron deficiency anemia and malignant tumor anemia have shown to have a significant increase in plasma free serotonin, compared with the control group and the group of patients with colorectal cancer without anemia. Plasma free serotonin was increasing together with the severity of anemia. The article discusses the feasibility of using the content of plasma free serotonin, as an option, to assess the state of compensation of secondary metabolic disorders in iron deficiency anemia and malignant tumor anemia during treatment and its possible differential diagnostic value.
Keywords: anemic syndrome, hypoxia, biogenic amines, blood plasma.

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1. Introduction

Every year, more than 6 million people are diagnosed with and more than 4 million people die from cancer all over the world, which is approximately 10% of the total mortality. The incidence of cancer in Ukraine shows a gradual increase, with the number of newly diagnosed

patients 304 – 308 per 100 thousand people *(Fedorenko et al., 2019)*. According to the official data of the Ministry of Health of Ukraine, 25% of patients are diagnosed with stage IV disease already during the initial visit, which in most cases is the reason for denying specialized care and providing them with symptomatic treatment. Serotonin (SN) as a pain mediator plays an important role in chronic pain syndrome in cancer patients. The accumulation of serotonin is the first link in a long chain of physiological and biochemical processes that accompany anemic hypoxia *(Moore et al., 2020; Shchur, 2014)*. SN is a biologically active compound released by mast cells as a response to hypoxic conditions. According to modern ideas, serotonin influences the functions of various organs and tissues by interacting with specific serotonergic receptors, which refer to the membrane chemoreceptors. Interaction of serotonin with specific receptors is accompanied by activation of adenylate cyclase, which leads to increased formation of cyclic adenosine monophosphate or guanosine monophosphate. SN is quite common in nature: in plants, mollusks and other invertebrates, insects, tissues of all vertebrates. In humans, a significant amount of SN is contained in enterochromaffin cells of the intestine (0,9 – 8,6 μg/g), which is why it is called enteramine *(Cerqueira, Hussni, & Yoshida, 2005)*. Certain amounts of SN are contained in platelets of humans and warm-blooded animals (2,4±0,5 μmol/g protein). The concentration of whole blood SN, according to various authors, ranges from 0,05 to 0,2 mg/l, or 0,28-1,14 μmol/l. SN also accumulates in mast cells of the skin, lung, digestive tract, kidney, spleen tissue, central nervous system (CNS). In the CNS, its concentration differs in different sections: the highest is found in the hypothalamus and midbrain, and the lowest – in the thalamus, hippocampus, cerebellum and gray matter of the spinal cord. A large amount (22,8 μg/g) of SN has been found in the pineal gland, with the highest concentrations during the day and the lowest at night *(Gaidukova, Tkachenko, & Bublij, 2018)*. Cells, which are able to capture and decarboxylate amine precursors synthesize and accumulate SN, belong to the system of APUD (Amine precursor uptake and decarboxylation) cells *(Jang, Kwon, & Chang, 2015; Shchur, 2014)*. One of the biological mechanisms of maintaining the optimal level of physiologically active SN in the body is serotoninopexy. The essence of this phenomenon is the binding of free SN by plasma proteins and some cells. Bound SN loses its physiological activity. The main SF binding plasma proteins are albumins. One molecule of albumin can bind 11 molecules of SN. Mast cells, lung tissue cells, erythrocytes, platelets, hepatocytes also can bind SN, but the nature and mechanisms of this process are different from binding to proteins. The intensity of SN binding is quantified by the value of the serotonin-peptic index (SPI). Normally, according to the spectrophotometric method, it is 30-40%. According to modern ideas, SN influences the functions of various organs and tissues by interacting with specific serotonergic receptors, which refer to the membrane chemoreceptors. Using pharmacological techniques and SN antagonists, three types of SN-sensitive cellular receptors have been identified. They are referred to as D-, M-, and T-serotonin-energy receptors *(Gaidukova, Tkachenko, & Bublij, 2018)*. D-serotonergic receptors, blocked by lysergic acid diethylamide and dibenziline, are localized mainly in the smooth muscles of the internal organs. The interaction of SN with D-receptors is accompanied by a contraction of smooth muscle. M-serotonergic receptors, blockable by morphine and some other substances, are located mainly in the autonomic ganglia. By acting on these receptors, SN has a gangliostimulating effect. T-serotonergic receptors are blocked by tipindole. They are located in the cardiopulmonary reflex zone and serve as conductors for SN induced coronary and pulmonary chemoreflexes. D- and M-receptors are found in the CNS; there is an opinion about the presence of T-serotonic receptors in the brain *(Back et al., 2019, Belagaje, 2017)*. Interaction of SN with specific receptors is accompanied by activation of adenylate cyclase, which leads to increased formation of cyclic adenosine monophosphate or guanosine monophosphate.

Under the influence of various activators, i.e. adenosine diphosphate, platelet activating factor, thrombin, collagen, etc., platelets and chromaffin cells secrete serotonin. Moderate concentrations of serotonin cause dilation of arterioles, reduction of myositis in venule walls, accompanied by venous stasis. Its high concentrations cause spasm of the arterioles, which exacerbates tissue hypoxia. Despite the important role of serotonin in the pathogenesis of numerous pathological processes and diseases, its changes in the content in malignant tumor anemia stayed ignored by researchers, which, in turn, prompted us to the scientific research.

2. Material and methods

The objective of the research was biochemical studies on the content of free serotonin fraction in the peripheral blood plasma of healthy individuals with iron deficiency anemia and malignant tumor anemia in colorectal cancer to identify possible specific changes and use its content index in clinical and differential diagnostic practice.

To solve this problem, we conducted this clinical study at Kyiv Regional Oncology Center. The study involved 392 patients: 186 (47,45 %) women and 206 (52,55 %) men. The material for the study was blood plasma of 392 patients (58 men and 52 women), which included 53 patients (31 women and 22 men) with iron deficiency anemia examined; the latter were the first (I) observation group, and 392 patients (206 men and 186 women) with colorectal cancer, burdened with malignant tumor anemia, were the second (II) observation group. Among the patients of the second (II) observation group, 222 people (119 men and 103 women) had malignant colon tumors (ICD-10 International Classification of Diseases (ICD) – C. 18), 29 people (16 men and 13 women) had malignant rectosigmoid tumors (ICD-10 – C. 19),

138 people (82 men and 56 women) had malignant rectal tumors (ICD-10 – C. 20), and 3 patients (2 men and 1 women) had malignant anal canal tumors (ICD-10 – C. 21). The age of the subjects ranged 22 to 79 years. The mean age of patients was (63,3 ± 1,2) years. The patients on admission had anemic syndrome. The presence of colorectal cancer stage II-IV according to Dukes (1956) and TNM was determined histochemically. All patients were examined before starting any treatment.

Iron deficiency anemia was verified on the basis of the characteristic clinical signs (signs of anemic hypoxia and sideropenic syndrome), the characteristic hematological pattern of peripheral blood and indicators of iron metabolism.

The severity of anemia was determined and distinguished according to the National Cancer Institute (USA) criteria: mild anemia – Hb 10-12 g/dl (Grade 1); moderate – Hb 8-10 g/dl (Grade 2); severe – Hb 6,5-8 g/dl (Grade 3); life-threatening – Hb <6,5 g/dl (Grade 4). Among patients with IDA, 19 people had mild severity, 15 – moderate, 11 – severe, and 8 – lifethreatening. Mild severity of malignant tumor anemia was diagnosed in 75 patients, moderate – in 14, severe – in 10, and life-threatening – in 6.

All studies were in compliance with the main provisions of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research with Human Participation (1964 with subsequent amendments, including version 2000), and Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009. All patients at admission underwent clinical, laboratory, instrumental and special examinations, they were consulted, if necessary, by related specialists. The examination and treatment of patients were in compliance with the World Medical Association Declaration of Helsinki *(Seoul, 2008)*, and the relevant orders of the Ministry of Health of Ukraine (No. 281

from 01.11.2000, No. 355 from 25.09.2002, No. 356 from 22.05.2009 amended with the Order of the Ministry of Health of Ukraine No. 574 of 05.08.2009, No. 1118 of 21.12.2012).

The control group consisted of 50 healthy primary donors who had no history of oncological or chronic inflammatory diseases. All donors were examined at the "Blood Transfusion Station of the Southwestern Railway" State Institution following the requirements of the "Blood and blood components donor screening procedure", approved by the Order of the Ministry of Health of Ukraine No. 385 of 01.08.2005 "On infectious safety of blood and blood components donors".

Patients with colorectal cancer underwent a thorough histological examination; it considered the nature of the tumor margins with surrounding tissues, the severity of infiltration, the presence of tumor cells in blood vessels, the number of mitoses, including atypical. In addition to the above, cell elements of different degrees of maturity (8,9 %) were determined in tumors – low differentiated (LD), moderately differentiated (MD) (66,8 %), and highly differentiated (HD) (24,3 %) cells. The degree of malignancy and histological type of tumor were assessed according to generally accepted criteria.

The content of plasma free serotonin fraction was measured by the fluorimetric method proposed by *(Mikhailichenko & Vydyborets, 1999)*. The study was conducted in the biologically active compound analytical laboratory of the Department of Forensic Medicine, Bogomolets National Medical University (Kyiv). The author and the supervisor sincerely thank the Head of the Department, Professor Mikhailichenko B. V. for methodological assistance in scientific research. The results of the studies were statistically processed by the variation methods with the calculation of the Student's t-test ($p < 0,05$).

3. Results of the study and discussion

The data analysis has found significantly lower hemoglobin concentrations in patients of groups II and III than in the control and group I ($p<0,001$). In the control group, this parameter averaged (143,82±4,60) g/l. At the same time, it was (147,22±4,31) g/l in men, with individual fluctuations from 135 to 164 g/l, and (131,06±3,77) g/l in women, with individual fluctuations from 125 to 147 g/l. Men had higher hemoglobin concentration than women ($p<0,001$), while patients of groups II and III did not have significant differences in hemoglobin concentration by gender ($p>0,05$). The average number of red blood cells in the control group was $(4,76±0,15)×10^{12}$/l: men had on average $(4,86±0,15)×10^{12}$/l, with individual fluctuations from 4,4 to $5,0×10^{12}$/l, and women – $(4,38±0,13)×10^{12}$/l, with individual fluctuations from 4,2 to $4,7×10^{12}$/l. The number of red blood cells in the control group was higher in men than in women ($p<0,001$). At the same time, patients of groups II and III, did not have significant differences in the number of red blood cells by gender ($p>0,05$). The average number of leukocytes in the control group was $(5,85±1,24)×10^{9}$/l in men, with individual fluctuations from 3,9 to $7,3×10^{9}$/l, and $(5,83±1,32)×10^{9}$/l in women, with individual fluctuations from 3,8 to $8,3×10^{9}$/l. This indicator had no significant differences either between the observation and control groups or by gender ($p>0,05$). The average number of platelets in the control group was $(203,40±13,94)×10^{9}$/l. Men had on average $(204,38±15,23)×10^{9}$/l, with individual fluctuations from 180 to $230×10^{9}$/l, and women – $(201,67±11,51)×10^{9}$/l, with individual fluctuations from 190 to $220×10^{9}$/l. The comparative analysis showed higher levels in patients of groups II and III compared with controls ($p<0,001$). This fact may confirm the idea of the presence of overt or covert bleeding in patients of groups II and III with compensatory enhancement of hematopoiesis in the myelocytic lineage, in particular, platelet cytopoiesis.

The average number of reticulocytes in the control group was (0,88±0,05) ‰: (0,87±0,05) in men, and (0,88±0,04) ‰ in women. Their level was significantly lower in patients of group II than in the control group and groups I and III ($p<0,001$), which, in our opinion, can be due to suppression of erythropoiesis in patients with MTA by humoral factors and intoxication syndrome.

General MTA in the control group was (30,63 ± 0,25) pg, with fluctuations from 27 to 33 pg. Women had on average (29,40±0,42) pg, with individual fluctuations from 27 to 31 pg, and men – (31,13±0,24) pg, with individual fluctuations from 28 to 33 pg. This group did not have significant differences in MSN levels by gender ($p>0,05$). The comparative analysis showed lower levels in patients of groups II and III compared with the control ($p<0,001$). This fact indicates the disorders of hemoglobin synthesis and iron deficiency in patients of groups II and III. It can be assumed that it develops in patients of group III due to chronic blood loss, while in patients of group II, apparently, due to high pro-inflammatory interleukins and hepcidin.

General MCV in the control group was (93,41±0,91) fl, with fluctuations from 84 to 97 fl. Women had on average (94,22±1,69) fl, with individual fluctuations from 89 to 97 fl, and men – (92,29±1,01) fl, with individual fluctuations from 84 up to 96 fl. Group I had no significant differences in MCV, compared with the control ($p>0,05$), while groups II and III showed a decrease in MCV ($p<0,001$). General MCHC in the control group was (34,38±0,23) %, with fluctuations from 33 to 35 %. Women had on average (34,35±0,31) %, with individual fluctuations from 33 to 35 %, and men – (34,41±0,41) %, with individual fluctuations from 33 up to 35 %. Group I had no significant differences in MCHC, compared with the control ($p>0,05$). However, groups II and III showed a decrease in MCHC ($p<0,001$), which indicates disorders of iron metabolism and the processes of erythropoiesis and hemoglobin synthesis. Shows that the content of serum iron (SI) in the control group, on average, was (20,04±2,03) μmol/l. Men had on average (20,75±1,94) μmol/l, with individual fluctuations from 17,30 to 24,60 μmol/l, and women – (18,77±1,53) μmol/l, with individual fluctuations from 16,40 to 21,30 μmol/l. The SI content in the control group was higher in men than in women ($p<0,01$). The results of our study show a significant decrease in the content of SI in groups II and III ($p<0,001$). The average total iron-binding capacity (TIBC) in the control group was (57,25±2,49) μmol/l: men had on average (56,52±2,37) μmol/l, with individual fluctuations from 52,05 to 61,03 μmol/l, and women – (58,55±2,20) μmol/l, with individual fluctuations from 54,87 to 62,05 μmol/l. TIIBC in the control group was higher in women than in men ($p<0,01$). Patients of groups II and III were found to have a significantly lower TIBC, which indicates iron metabolic disorders ($p<0,001$). The average unsaturated iron-binding capacity (UIBC) in the control group was (35,77±4,07) μmol/l in men, with individual fluctuations from 28,05 to 43,37 μmol/l, and (39,78±3,53) μmol/l in women, with individual fluctuations from 34,18 to 45,65 μmol/l. In general, in the control group, the UIBC was (37,21±4,31) μmol/l: women had higher levels than men ($p<0,01$). Patients of groups II and III were found to have a significantly higher UIBC, which indicates iron metabolic disorders ($p<0,001$). The average transferrin saturation (TS) in the control group was (35,18±4,90) %: men had on average (36,88±4,74) %, with individual fluctuations from 28,60 to 46,10 %, and women – (32,17±3,63) %, with individual fluctuations from 26,40 to 38,30 %. TS in the control group was higher in men than in women ($p<0,01$). Patients of groups II and III were found to have a significantly lower TS, which indicates iron metabolic disorders ($p<0,001$).

Average serum transferrin (TF) in the control group was (3,23±0,10) g/l. Men had (3,20±0,09) g/l, with individual fluctuations from 2,23 to 3,38 g/l, and women had

(3,28±0,09) g/l, with individual fluctuations from 2,24 to 3,42 g/l. The content of serum TF in the control group was higher in women than in men (p<0,01). Patients of groups II and III showed to have multidirectional changes in TF, compared with the control, while its level was significantly lower in patients of group II, and significantly higher in patients of group III (p<0,001). This nature of the changes indicates the TF synthesis and metabolic disorders due to tumor intoxication. Average serum ferritin (FN) in the control group was (24,91±2,14) µg/l in men, with individual fluctuations from 20,64 to 30,12 µg/l, and (19,19±1,41) µg/l, with individual fluctuations from 17,15 to 21,82 µg/l. Serum FN in the control group was higher in women than in men (p<0,01). Patients of groups II and III also showed to have multidirectional changes in FN, compared with the control, while its level was significantly higher in patients of group II, and significantly lower in patients of group III (p<0,001). This nature of the changes is due to the fact that FN is an acute phase protein, which level increases in response to tumor intoxication.

Table 1 shows data on the results of studies on plasma free serotonin in the subjects.

Table 1

Plasma free serotonin in the subjects (M±m), µg/l

Indicator	Groups			Level of significance (p)
	Control (n=50)	I (first), (n=53)	II (second), (n=392)	
Free serotonin, µg/l	0,47±0,21	0,53±0,27	0,57±0,24	p_1< 0,05 p_2<0,05 p_3< 0,05

Notes: p1 – level of significance of the difference in patients of group I compared with the control group; p2 – level of significance of the difference in patients of group II compared with the control group; p3 – level of significance of the difference in patients of groups I and II.

As the above data show, serum free serotonin in groups I and II was significantly higher than in the control group (p<0,05). This indicator was significantly higher in patients of group II, which may indicate its synthesis, release, and inactivation disorders as a response to tumor intoxication and anemic hypoxia (p<0,05). It was quite natural for us to investigate the way the level of serum free serotonin changes in patients with malignant colon tumor with concomitant MTA, based on the severity of the anemic syndrome. Table 2 presents our data.

As Table 2 shows, patients with malignant colon tumors with concomitant MTA had an increase in their serum free serotonin in proportion to the severity of anemia. That is, the severity of life-threatening anemia in patients with malignant colon tumors with concomitant MTA is accompanied by the most significant increase in plasma free serotonin, which obviously reflects its metabolic peculiarities as a response to tumor intoxication and anemic hypoxia, and may indicate its synthesis, release, and inactivation disorders.

Adaptation and survival of the body depends on the integrity and preservation of regulatory systems within the whole organism and auto-regulatory mechanisms of individual organs. The whole organism has metabolic, humoral, and neurogenic auto-regulatory mechanisms of metabolic protection of each of the functioning organs *(Back, 2019)*.

Table 2

Serum free serotonin in patients with malignant colon tumor with concomitant MTA, based on the severity of the anemic syndrome (M±m), µg/l

Groups (n)		Level of significance (p)
Control (n=50)	**Malignant colon tumor with concomitant MTA (n=75)**	
0,47±0,21	mild anemia (n=45) 0,48±0,28	$p_1 < 0,05$ $p_2 > 0,05$ $p_4 > 0,05$ $p_5 < 0,05$ $p_6 < 0,001$
	moderate anemia (n=14) 0,51±0,24	$p_1 < 0,05$ $p_2 < 0,05$ $p_3 > 0,05$ $p_5 < 0,05$ $p_6 < 0,01$
	severe anemia (n=10) 0,53±0,27	$p_1 < 0,05$ $p_2 < 0,05$ $p_3 < 0,05$ $p_4 < 0,05$ $p_6 < 0,01$
	life-threatening anemia (n=6) 0,59±0,21	$p_1 < 0,01$ $p_2 < 0,01$ $p_3 < 0,05$ $p_4 < 0,01$ $p_5 < 0,01$

Notes: p1 – level of significance of the difference compared with the control group; p2 – level of significance of the difference in patients of group II; p3 – level of significance of the difference in patients with mild anemia; p4 – level of significance of the difference in patients with moderate anemia; p5 – level of significance of the difference in patients with severe anemia; p6 – level of significance of the difference in patients with life-threatening anemia.

Neurohormones are essential for the regulation of adequate blood supply to vital organs. One of them is serotonin. Serotonin is phylogenetically the oldest biogenic amine, which plays a unique role in ensuring energy metabolism *(Yabut et al., 2019)*. By the way, serotonin induces the first fetal heart contraction. Unlike classical hormones, serotonin is synthesized in various anatomical locations. Brain-synthesized serotonin is only near total serotonin in the human body, and 95 % is synthesized in peripheral organs, with the bulk of serotonin being produced by enterochromaffin cells in the gut *(El-Merahbi et al., 2015)*. Interestingly, brain-synthesized serotonin acts as a neurotransmitter, while in the periphery it can act as a hormone, auto- and/or paracrine factor, and as a cellular signaling molecule. Peripheral serotonin does not cross the blood-brain barrier *(Watanabe et al., 2010)*. The content of serotonin in peripheral tissues depends on both its local production and its free fraction in the blood. In peripheral blood, serotonin is absorbed and stored by platelets. In humans, brain-synthesized serotonin affects behavior, suppresses appetite, increases energy utilization by increasing the effect of the sympathetic nervous system on brown adipose tissue *(Oh et al., 2015)*. Peripheral serotonin improves the absorption and storage of nutrients such as glucose and fatty acids, stimulates insulin secretion,

lithogenesis in liver and white adipose tissue, has a direct bearing on diseases such as metabolic syndrome, obesity, diabetes *(Martin et al., 2017)*. Serotonin as a neurotransmitter causes contraction of smooth muscles of the bronchi, intestines, arteries, increases the functional activity of platelets. By increasing vascular permeability, serotonin enhances the granulation of mast cells, and thus causes the release of histamine, which is central to stimulating the formation of new atherosclerotic plaques *(Xu et al., 2017)*.

Literature reports an increase in serotonin levels during tissue regeneration after myocardial infarction or ischemic stroke *(Mauler, Bode, & Chang, 2015)*. There is evidence of genetic determinism regarding serotonin levels and the risk of myocardial infarction, ischemic stroke, or transient ischemic attack at high levels *(Mortensen et al., 2018)*. Many clinical studies and metaanalyzes have confirmed the association of serotonin with the improvement of patients after ischemic stroke *(Belagaje, 2017)*. As for ischemic changes in the arteries of the intestine, serotonin again comes to the fore. This biogenic amine, most of which is produced in the intestine, regulates motility, increases peristalsis and secretory activity. However, in atherosclerotic vascular lesions, vasoconstrictive responses in the mesenteric bloodstream are enhanced by stimulation of serotonergic and alpha-adrenergic receptors *(Lopez et al., 1989)*.

A number of studies on intestinal ischemia have reported a significant increase in plasma serotonin due to its high release by damaged intestinal cells *(Cerqueira, Hussni, & Yoshida, 2005)*. Ischemic changes in the intestine due to an increase in the number of serotonin-producing cells and their proliferation significantly activate serotonin synthesis *(Toth et al., 2012)*. This process is accompanied by an increase in the synthesis and release of histamine from mast cells, which enhances the processes of atherogenesis. High concentrations of serotonin and histamine lead to the progression of existing pathological changes.

4. Conclusions

1. Patients with IDA and colorectal cancer, accompanied by malignant tumor anemia, have serotonin metabolic disorders manifested as a significant increase in its blood plasma content.

2. Considering to the initial increase in plasma serotonin due to malignant tumor anemia in patients with colorectal cancer at the stage of diagnosis there is, a promising area of scientific and clinical research is to study the changes in this biologically active compound in the treatment process to use its content as an additional assessment criterion for the degree of compensation of metabolic processes in the treatment of patients.

3. Plasma serotonin in patients with malignant anemia in colorectal cancer is significantly higher than in patients with iron deficiency anemia, which, obviously, makes it possible to use it as an additional differential diagnostic criterion for these diseases.

4. In our opinion, a promising area of research in patients with colorectal cancer with concomitant malignant tumor anemia is the follow-up control of plasma serotonin based on changes in anemia and the further treatment of the underlying disease.

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