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ORIGINAL ARTICLE

Luminescent Analysis of Blood Serum for Diagnostics of Pathological and Pre-Pathological States of Cancer Patients

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Abstract

This study is devoted to the development of a methodological approach to mathematical analysis and data interpretation of blood serum phosphorescence intensity in cancer patients for determining the pathological states and differential diagnostics of oncological process stages. The purpose of the study is blood serum phosphorescence research in patients with colorectal cancer (CRC) and stomach adenocarcinoma (SAC) and determination of the ultraweak luminescence role for diagnostics of the disease, determining its stages, control of pathogenetic therapy efficiency and forecast of recovery. The values of phosphorescence intensity of blood serum films in patients with CRC and SAC are significantly higher than the corresponding values for the control group. Contrary to the absolute intensity, the relative intensity increase compared to the control group is much more informative for oncoprocess diagnostics, since it exhibits three times increase even at the first stage of tumoral process. Serum phosphorescence intensity continues to increase with progressing of the disease. As the result of our study, the relative intensity increase compared to the first stage can be recommended as an informative indicator for differential diagnostics of oncological process stages. As a conclusion, determination of blood serum phosphorescence intensity can be considered as a sensitive and specific diagnostic method in oncology. With a correct methodological approach to data processing and interpretation, this method can be used in clinical practice for determining the oncopathological states, differential diagnostics of oncoprocess stages and diagnostics of precancer changes, which precede tumoral process development.

Keywords Oncoprocess · Blood serum phosphorescence · Relative intensity · Mathematical analysis · Methodological approach · Differential diagnostics · Cancer stages

Introduction

The human blood serum phosphorescence method is widely applied in oncological practice because it allows estimation the condition of conformational structure of biological macromolecules, in particular, proteins, and their metabolic activity. It has high specificity and sensitivity, that gives the chance to diagnose proteinopathy, which can act as a pathogenetic factor of carcinogenesis formation, already at early stages of tumoral process development. In the current research we propose a methodological approach to mathematical analysis and data interpretation of the examination of blood serum phosphorescence intensity in cancer patients for determining the pathological states and differential diagnostics of oncoprocess stages. The presented approach can be used also in preventive medical practice, because correct assessment of conformational protein structure and metabolic activity of blood serum is an important predictive pre-nosological diagnostic criterion of precancer states, which precede the tumoral process development.

There are many concepts, hypotheses and theories of carcinogenesis problem in the modern professional world, but meanwhile any of them cannot be considered as exhaustive [1–7].

The analysis of research in the field of oncology [8, 9] demonstrates that, in the conditions of oncoprocess

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development, the protective and compensatory mechanisms, aimed at providing homeostasis, fail due to long-term activation of free radical processes, peroxide oxidation of lipids and oxidizing modification of biological macromolecules (proteins, nucleic acids, etc.) that inevitably leads to violation of nuclear and cytoplasmic interactions and regulation of intracellular metabolism.

Characteristic initial changes in metabolism, structural and functional features of biological macromolecules, which happen at initiation of cell malignization process and development of all types of tumors, are still insufficiently studied and are not always available to experimental determination [10–15]. One of priority problems of preventive and clinical medicine is development of informative diagnostic and predictive methods which would allow to estimate the functional condition of an organism still during the premorbid period.

Studying the pathological conditions of an organism at the molecular level is an important problem of oncology. Adequate knowledge about violations of molecular bases of activity of various systems of the organism in the conditions of oncopathology formation allows the doctor to diagnose a disease correctly and in time, to carry out the pathogenetic treatment, to predict the recovery and to implement rehabilitation actions [8, 9, 16].

Numerous research studies [17–19] demonstrate that at the first stage of carcinogenesis development, the alterations in protein exchange, as well as in structural and functional state of polypeptides are observed. It is generally accepted that change of the spatial organization of protein macromolecules affects their biological activity and represents one of the pathogenetic determinant of oncopathology formation [20–23]. Therefore, studying the integral structural and metabolic activity of blood serum proteins is of great importance in early oncopathology diagnostics, determination of disease severity stage, prevention of tumoral process development, justification of pathogenetic therapy and development of predictive basis of recovery and rehabilitation of cancer patients.

One of the leading pathogenetic mechanisms of oncopathology formation are violations of energetics of biochemical and metabolic processes, membrane cell pathology, which lead to acceleration of organism aging and potentiate activation and induction of carcinogenesis [8, 9, 20, 22].

The primary characteristics of modern analytical tools used for monitoring of the biological tissue and cellular population condition, have to possess high selectivity, relative simplicity, time resolving ability and possibility of integrated assessment of complex pathological processes. Among a big arsenal of the spectroscopic methods available to testing of cellular populations and biological liquid functional conditions, the phosphorescence method ranks high. While light scattering distorts measurements of circular dichroism, Raman spectroscopy is characterized by low sensitivity, and absorption of water damages the infrared spectra, phosphorescence spectroscopy is a fast, easy in use, highly sensitive and highly selective method. The biological implication of phosphorescence research allows to obtain a deep knowledge about structural, functional and metabolic changes in cells, organs, systems which occur at the molecular level. Phosphorescence is considered as one of important instruments of studying molecular energetics of biochemical reactions in the organism, which provides important information for early diagnosis of pathology, in particular of premorbid states, differentiation of diseases, allows to watch the course of pathogenetic therapy [20, 24–28].

The purpose of work is blood serum phosphorescence research in patients with colorectal cancer (CRC) and stomach adenocarcinoma (SAC) and determination of the ability of ultraweak luminescence for diagnostics of the disease, determining its stages, control of pathogenetic therapy efficiency and forecast of recovery.

Materials and Methods

Prospective clinical trials were conducted in Kharkiv City Oncological Center, Kharkiv, Ukraine.

The blood serum proteins phosphorescence was studied and estimated in 209 patients with CRC and in 59 patients with SAC aged from 35 up to 68 years. The diagnosis was confirmed by clinical and histomorphological methods. Groups of patients depending on localization of the tumor were selected from 209 patients with CRC: rectum cancer (RC), sigmoid colon cancer (SCC), cecum cancer (CC) and transverse colon cancer (TCC). The control group consisted of 486 healthy blood donors of a similar age range.

Research of blood serum phosphorescence intensity was performed after its excitation by light source using a spectrofluorimetric method. The source of exciting light was a mercury lamp DRK-120. By means of the DMR-4 monochromator spectral lines with such wavelengths were allocated: $\lambda_{exc} = 297$; 313; 334; 365; 404; 434 nm. Quanta of light were absorbed by a blood serum film with the subsequent radiation of quanta of afterglow (phosphorescence) that was detected using a photoelectric multiplier (PhEM-130). The output slit of the monochromator was 2 mm wide. Maximum spectral sensitivity of the photoelectronic multiplier corresponded to ultra-violet and visible parts of the range. Phosphorescence registration was carried out at room temperature in the photon counting mode by the photon counter SBS-2. All measurement procedures were automated, the error did not exceed 3 % in all cases.

Statistical processing of the obtained data was carried out using the software package Statistica v. 6.0 (Statsoft Inc.). Quantitative parameters in the studied groups are presented in the form of average values M with standard deviations s ($M \pm s$). Testing of distinction reliability was carried out by means of Student and Fischer criteria. For critical significance

Table 1 Distribution of numbers of patients with CRC (various localizations) and SAC taking into account the sex (men (m) and women (w)) and oncological disease stages (I, II, III, IV)

Disease stage	Oncoprocess localization, sex									
	RC, n=54		SCC, n=62		CC, n=27		TCC, n=66		SAC, n=59	
	m n=29	w n=25	m n=33	w n=29	m n=15	w n=12	m n=48	w n=18	m n=33	w n=26
I	6	3	3	4	1	1	5	2	8	6
II	8	5	13	7	1	1	12	4	7	7
III	9	12	11	14	12	9	27	9	9	7
IV	6	5	6	4	1	1	4	3	9	6

Healthy donors: men (m) − 202; women (w) − 284; total n = 486

value, when checking statistical hypotheses, it is accepted $p < 0.05$.

Results and Discussion

Distribution of numbers of patients with CRC by groups depending on oncoprocess localization (RC, SCC, CC, TCC) and with SAC is represented in Table 1 taking into account the sex of the patient and the disease stage (I, II, III, IV).

For the group of healthy blood donors (control group) the normal limits of blood serum phosphorescence intensity levels are provided in Table 2.

Any reliable difference between examined healthy men (202 persons) and healthy women (284 persons) in blood serum phosphorescence intensity on all excitation spectral lines was not revealed. In examined patients (158 men and 110 women) a reliable difference by sex between blood serum phosphorescence levels on all spectral lines was also not revealed.

It should be noted that in general the values of phosphorescence intensity of blood serum films in patients with CRC and SAC were much higher in comparison with the values for the control group, and the highest levels of intensity were noted in ultra-violet (λ = 297 nm) and visible (λ = 404 nm; 434 nm) parts of the wavelength range.

The analysis of blood serum phosphorescence data in patients with CRC depending on tumoral process localization displays the following dynamics of intensity in all groups of observation.

Charts of phosphorescence intensity on the studied excitation wavelengths for different localizations of tumors in patients with CRC are given on Fig. 1.

The highest levels of phosphorescence intensity in patients with CRC were observed with the monochromatic light wavelength λ = 297 nm. However, a much more important parameter for oncopathology diagnostics is not the absolute value of phosphorescence intensity, but its change in comparison with the control group. A convenient indicator of this change is the ratio of phosphorescence intensity in patients with oncopathology to intensity in the control group (relative intensity).

Charts of relative phosphorescence intensity on the studied excitation wavelengths at different tumor localizations in patients with CRC are provided on Fig. 2.

Figure 2 shows that the maximum relative intensity increase is observed at 404 and 434 nm wavelengths. Thus, at λ = 404 nm, the increase in phosphorescence intensity in patients with CRC on average compared with the control group was from 3.58 to 3.59 times, at λ = 434 nm - from 3.01 to 3.27 times. Compare these data to the absolute intensity value on Fig. 1, where, as it has been already noted, the maximum intensity values were observed on the 297 nm wavelength. The increase in this case ranged from 1.87 to 2.10 times.

It can be seen, in the diagnostic aspect, relative values should be considered more informative, i.e. they give a chance of early disease detection or determination of premorbid situation existence in the surveyed person. Thus, in medical practice it is appropriate to recommend using 404 nm and 434 nm wavelengths as the most indicative and informative ones.

It should be noted that substantial increase of blood serum phosphorescence intensity in cancer patients in comparison with healthy donors demonstrates existence of intramolecular processes of macromolecule reorganization which are combined with accumulation of a large number of molecules in the triplet excited state, that is with two uncoupled electrons in

Table 2 Distribution of blood serum phosphorescence intensity levels intervals in healthy donors at the selected wavelengths

Excitation wavelength, λ, nm	297	313	334	365	404	434
Intensity, *I*, imp·s^{-1}	3000… 3320	280… 350	580… 700	1700… 1800	450… 550	550… 650

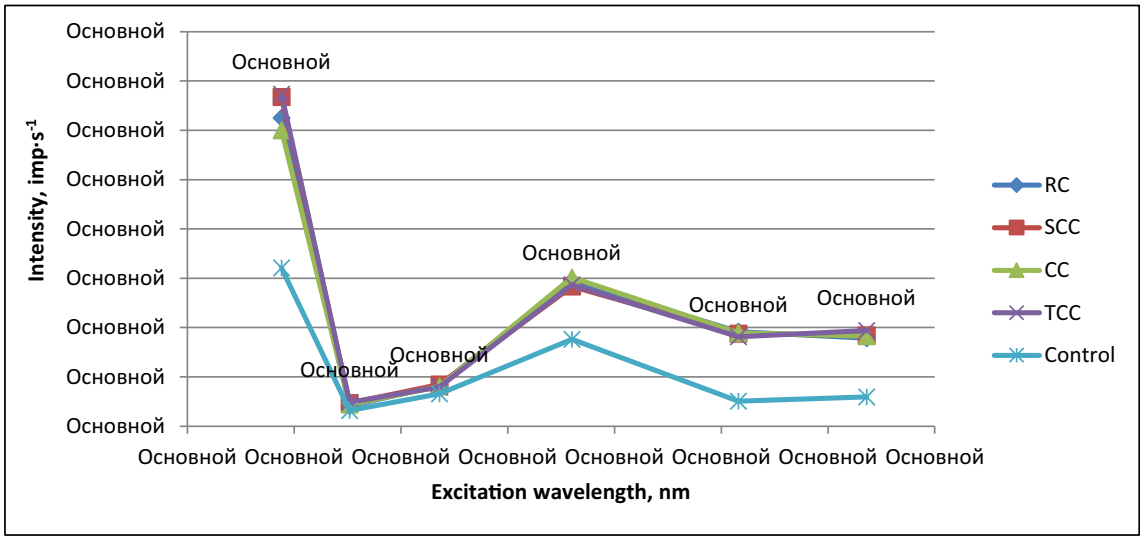

Fig. 1 Blood serum phosphorescence intensity in patients with CRC at the studied wavelengths depending on tumor localization

the external orbital. These molecules emit photons and undergo a transition to the low non-excited singlet level.

Appearance of increased number of molecules in the triplet state can also indicate separation of oxidizing phosphorylation and tissue respiration, that is always followed by dissipation of thermal energy and mitochondrial pathology development. Presence of a significant amount of the electron-excited molecules, capable to activate free radical processes and separate oxidizing phosphorylations, forms energy hunger, tissue hypoxia and membrane molecular pathology.

Long-term oxidizing process activation leads to change of protein molecule conformation, compact structure loss and biological activity decrease. As a result, metabolic possibilities of the organism in cancer patients decrease, as it was observed in patients with CRC and SAC.

Therefore, violation of structural and conformational properties of such biologically important macromolecules, as proteins, are some of pathogenetic factors of carcinogenesis formation.

Assessment of blood serum phosphorescence intensity indicators in patients with CRC found high informational content of this method for studying the dependence on disease severity, that is oncoprocess stage.

Charts of dependence of absolute phosphorescence intensities at studied wavelengths of excitation on the disease stage are provided on Fig. 3.

The chart shows that at all oncoprocess development stages the maximum increase in absolute intensity values is observed at 297 nm wavelength. The increase in phosphorescence intensity relative to the control group at this wavelength ranged from 1.77 (stage I) to 2.13 (stage IV).

Additionally, relative intensity values at different oncoprocess stages in comparison with the control group were estimated (Fig. 4).

From Fig. 4 it can be seen that the relative phosphorescence intensities in patients with CRC considerably exceed 1 even at the first (I) oncological disease stage and continue to grow during pathology progressing course (II, III, IV stages). At

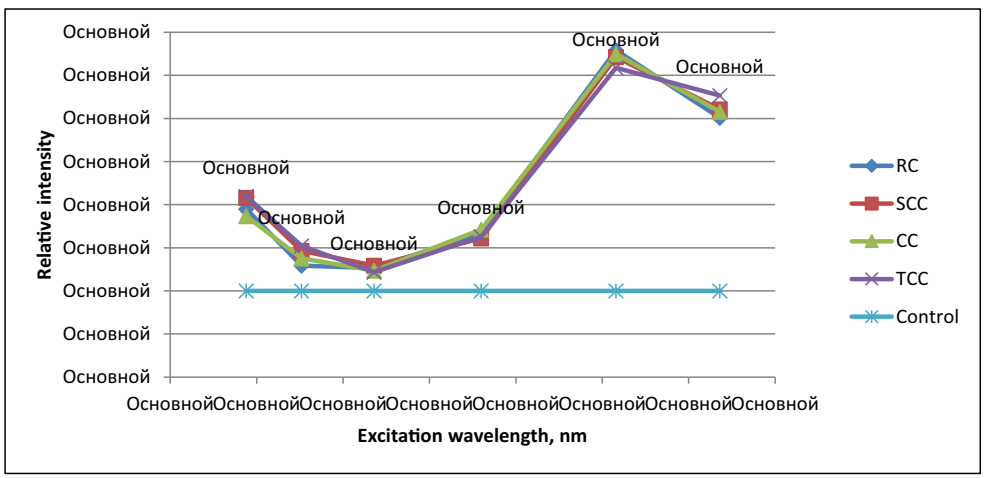

Fig. 2 Relative phosphorescence intensity in patients with CRC with different oncoprocess localization (RC, SCC, CC, TCC) in comparison with the control group

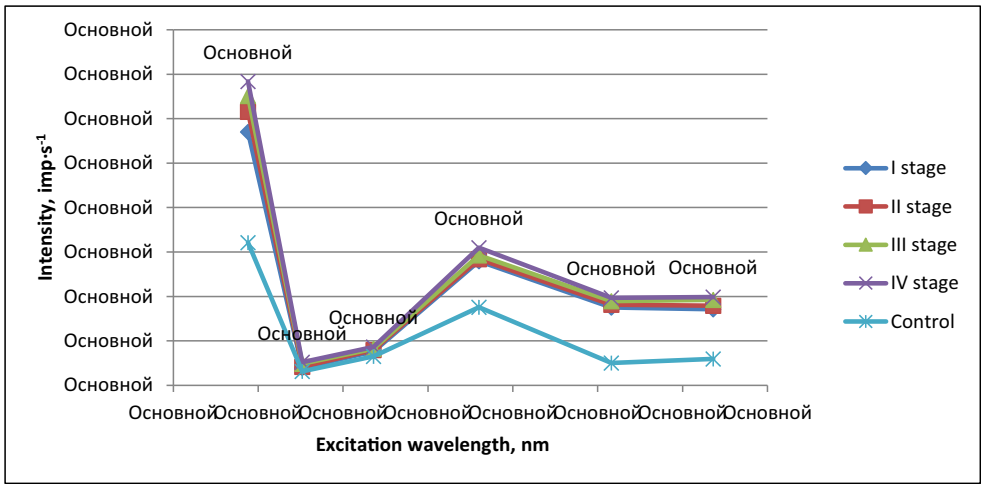

Fig. 3 Phosphorescence intensity in patients with CRC depending on the oncoprocess development stage

the wavelengths studied, the increase in intensity compared with the control group ranged from 1.78 times at $\lambda = 297$ nm to 3.47 times at $\lambda = 404$ nm. During the progression of the pathology (stage II, III, IV), the values of relative intensities continue to increase.

High intensity levels even at the initial carcinogenesis stage testify for rather long term of existence of molecular changes in spatial structure and biological activity of proteins that precede tumoral process development and, therefore, are a predictive factor of oncopathology development and an early diagnostic criterion. Significant increase of phosphorescence intensity at early stages of carcinogenesis development and insignificant, but dynamic its growth in the process of disease course shows that this pathological state develops against the background of long existing protein conformational structure violations and membrane pathology presence which is followed by inhibition of bioenergetic homeostasis.

At 313 nm, 404 nm and 434 nm wavelengths, scatter of relative intensities between stages is noticeable. Therefore, the following stage of research was calculation of intensities for II, III and IV stages relative to the I stage intensity. Relative intensity values are provided as a graph in Fig. 5.

On Fig. 5, in comparison with Fig. 4, the dispersion of relative intensities between stages is seen much more clearly. Therefore, for differential diagnostics of oncoprocess stages the most informative method is comparison of phosphorescence intensities with their values at the I disease stage. At III and IV stages a maximum of relative intensity is observed at 313 nm wavelength. Thus, in stages III, IV of the disease, the increase in the intensity of the glow in comparison with patients with stage I was equal to 1.24 and 1.32, respectively.

The following investigation phase was determination of blood serum phosphorescence intensities in patients with SAC depending on sex, tumor localizations (stomach body, cardial, subcardial part, pre- and pyloric part) and oncoprocess stages.

Investigations revealed that there is no reliable difference ($p > 0.05$) in intensity levels between men and women with SAC as well as depending on the location of the tumor.

Researching the blood serum phosphorescence intensity in patients with SAC depending on oncoprocess stage, the

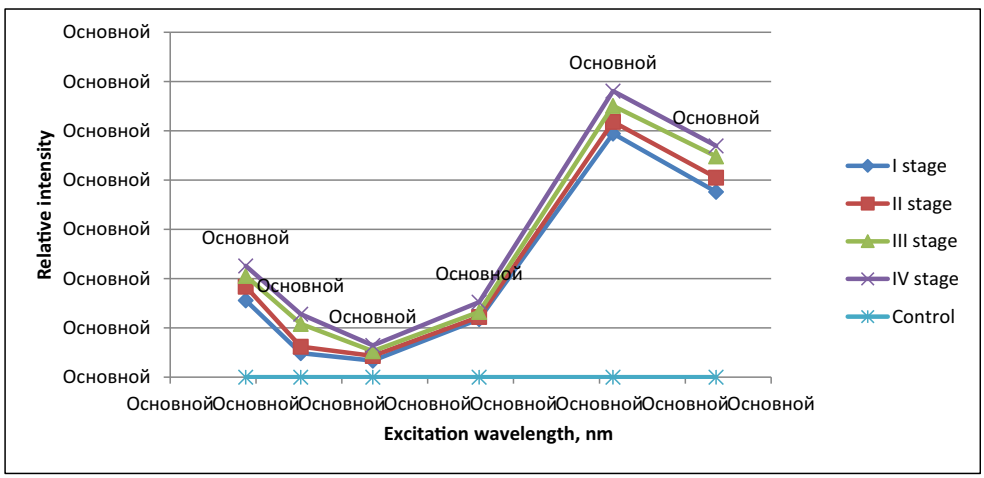

Fig. 4 Relative phosphorescence intensity at different CRC stages in comparison with the control group

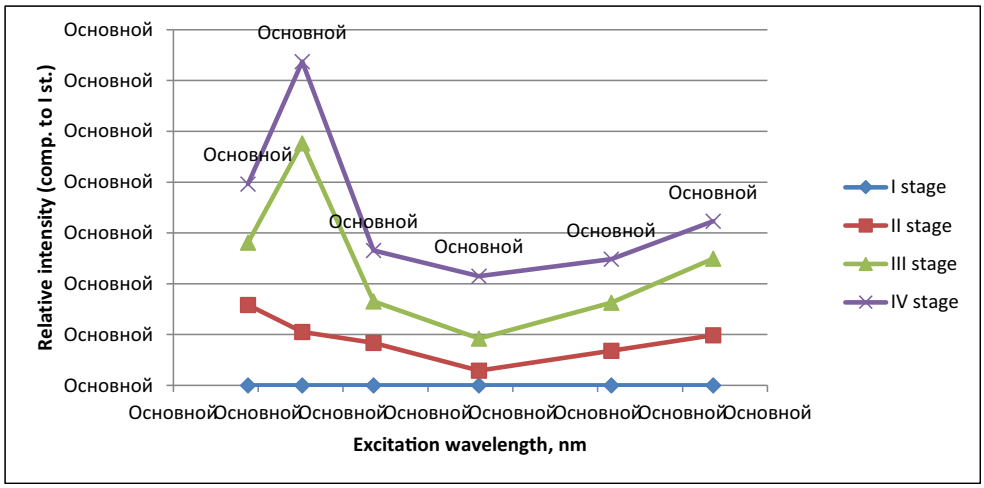

Fig. 5 Relative phosphorescence intensity at II, III, IV CRC stages compared to the I stage

reliable difference in comparison with the control group data was established and reproduced graphically in Fig. 6.

At all wavelengths a direct dependence of phosphorescence intensity on disease course severity was observed.

For identification of the most diagnostically informative wavelengths, values of relative intensity for patients in comparison with the control group were estimated. These data are shown graphically in Fig. 7.

The behavior of relative intensities in patients with SAC demonstrates similar dependence, as well as in the case of patients with CRC. At $\lambda = 297$ nm, the intensity of phosphorescence compared with the intensity of the glow of the blood of the control group at different stages of the disease (I; II; III; IV) was increased 1.67 times; 1.83 times; 2.08 times; 2.12 times respectively.

The maximum relative intensity values are observed at 404 nm and 434 nm wavelengths for all stages. The magnitude of the increase was at $\lambda = 404$ nm − 3.27 times; 3.61 times; 3.85 times; 3.98 times, at $\lambda = 434$ nm − 2.86 times; 3.01 times; 3.12 times; 3.36 times.

For differential diagnostics of SAC stages, it has been calculated relative intensity values for II, III, IV stages compared to the I stage, data are shown graphically in Fig. 8.

As evident from Fig. 8, the most informative wavelength for differential diagnostics of SAC stages, as well as in case of CRC, is 313 nm. The intensity of phosphorescence increased relative to the intensity of serum phosphorescence for patients with stage I, respectively, in stages II, III and IV in 1.19 times; 1.35 times and 1.48 times.

Conclusions

1. Studying blood serum spectroscopic response intensity dynamics in patients with CRC and SAC showed substantial increase of blood serum phosphorescence intensity in cancer patients in comparison with healthy donors, especially at 297 nm, 404 nm and 434 nm wavelengths.
2. No reliable difference has been revealed in levels of blood serum phosphorescence intensity between men and

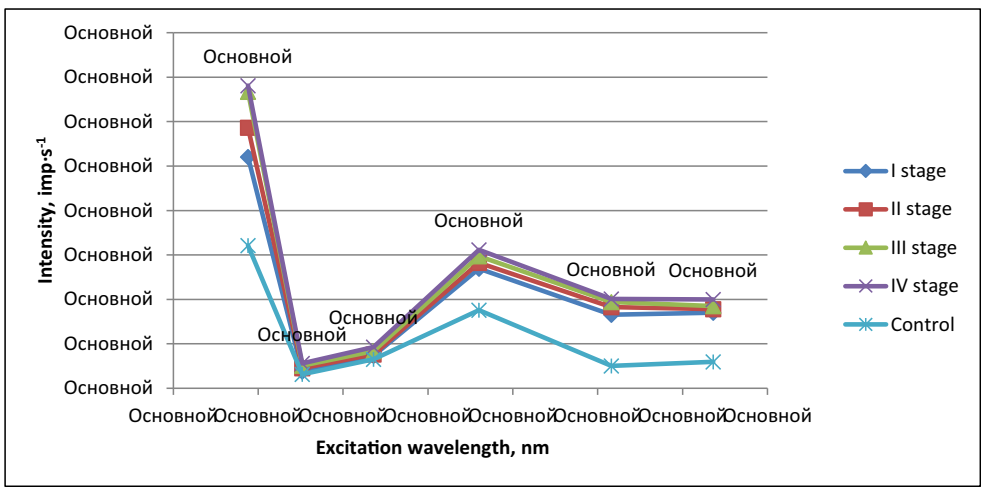

Fig. 6 Blood serum phosphorescence intensity in patients with SAC at the studied wavelengths depending on the oncoprocess stage

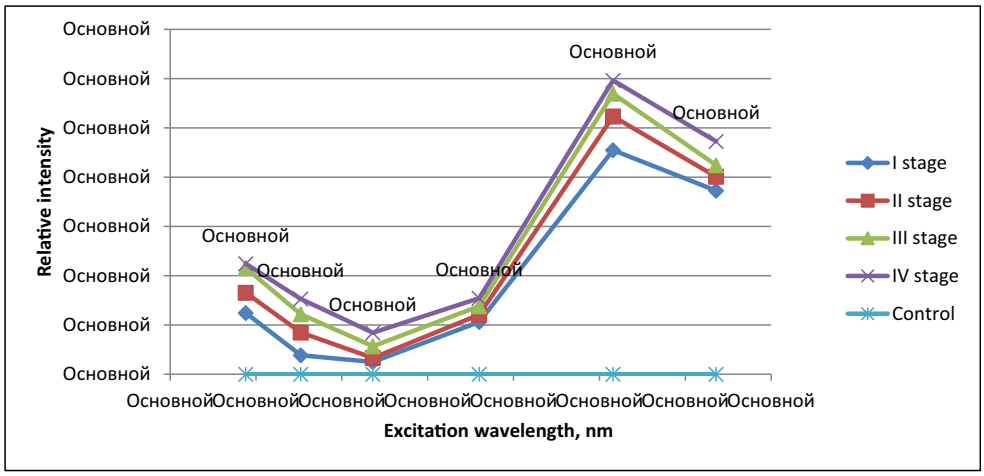

Fig. 7 Relative phosphorescence intensity at different SAC stages in comparison with the control group

women with CRC and SAC. The same conclusion can be drawn also for characteristics of phosphorescence intensity in healthy men and women.

3. Already at the first stage of the disease rather considerable increase of phosphorescence intensity was revealed in patients with CRC and SAC in comparison with group of healthy blood donors.
4. Research revealed that in patients with CRC and SAC in all cases of tumor development stages the serum phosphorescence intensity more than 5000 imp·s^{-1} was observed, reaching 6837.4 ± 162.7 imp·s^{-1} at the fourth carcinogenesis stage. This phosphorescence increase indicates protein conformational structure violation and can demonstrate pre-cancer state formation that is characterized by metabolic activity change of blood serum and its macromolecular polymeric substrates.

   It should be noted that the maximum absolute intensity values were observed at the 297 nm wavelength, but the maximum relative intensity increase (compared to the control group) was revealed at wavelengths λ = 404 nm and λ = 434 nm. It means that relative values should be considered more informative for diagnosis, thus, they give a chance of early disease detection, that is determination of premorbid state existence. Therefore, in medical practice it is possible to recommend relative fluorescence intensity determination at 404 nm and 434 nm wavelengths as the most indicative and informative for early diagnosis of tumoral pathology.
5. Assessment of blood serum phosphorescence relative intensity indicators (compared to the first stage of the disease) in patients with CRC and SAC found high informational content of the phosphorescence method for determination of disease severity, that is the oncoprocess stage. The 313 nm wavelength was the most informative for differential diagnostics of CRC and SAC stages. For SAC the relative intensity maximum on this wavelength was observed not only at III and IV stages (as for CRC), but already at the II stage of the disease.

Thus, the analysis of results allows to draw a conclusion that in patients with CRC and SAC we observe profound

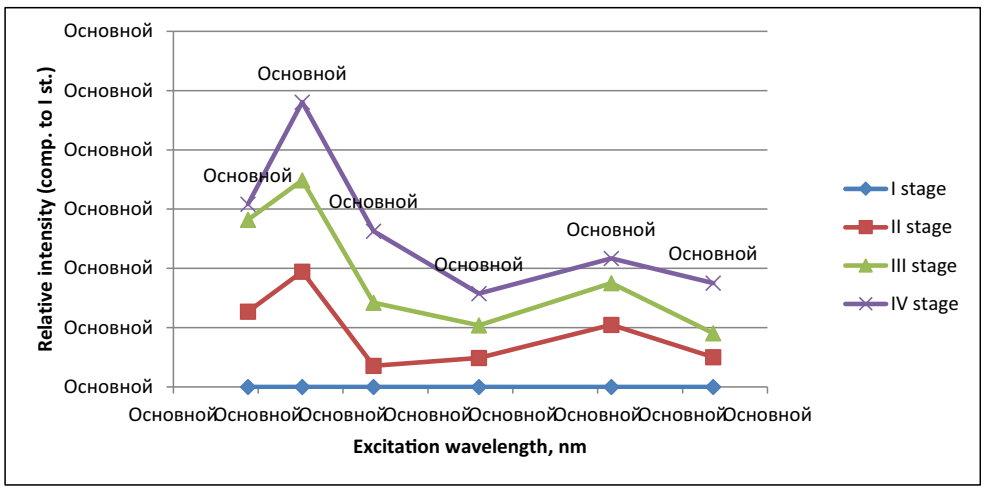

Fig. 8 Relative phosphorescence intensity at II, III, IV SAC stages in comparison with the I stage

structural, conformational and metabolic changes in large polymeric molecules and their monomeric components.

Blood serum phosphorescence intensity increase in cancer patients can indicate development of free radical membrane pathology. Research demonstrates that emergence of excitations of significant amount of molecules in the triplet state in such spectral area can point to separation of oxidizing phosphorylation and tissue respiration, slowing down of bioenergetic processes, accompanied by inefficient use of energy, its dispersion in the form of heat, decrease in ATP production, that is characteristic of mitochondrial pathology. Presence of high energy levels of excited electronic states caused by existence of non-coupled electrons in active molecules indicates a change of conformational properties and reaction ability of proteins. Therefore, the change of the tertiary structural and functional organization of proteins has an important role in the pathogenesis of oncological disease development.

The method of determination of human blood serum phosphorescence intensity can be considered a sensitive and specific method of research of blood serum protein conformational structure and metabolic activity. With a correct methodological approach to data processing and interpretation it gives the chance to diagnose a proteinopathy existence, which can be a pathogenetic factor of carcinogenesis formation, already at early tumoral process development stages. This method can be used in clinical practice for determining pathological states, differential diagnostics of oncoprocess stages and diagnostics of precancer changes of biomacromolecules which precede tumoral process development.

Author Contributions The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors contribute equally to this paper.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Conflicts of Interest/Competing Interests Not applicable.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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