

UDC: 616-006-071.1-08-039.71

**N.T. BALTABEKOV<sup>1</sup>, M. CHESARE<sup>2</sup>, G.K. ALIPOV<sup>3</sup>, S.A. POTANIN<sup>4</sup>, Ye.I. ISHKININ<sup>5</sup>**<sup>1</sup>Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan;<sup>2</sup>Medical University of Brescia, Brescia, Italy;<sup>3</sup>Nagasaki University School of Medicine, Nagasaki, Japan;<sup>4</sup>Military Medical Academy, St. Petersburg, the Russian Federation;<sup>5</sup>Almaty Oncology Center, Almaty, the Republic of Kazakhstan

## New approaches to diagnostics and medical rehabilitation of malignant neoplasms at the Primary Health Care (PHC) level: International project report

**Relevance:** Malignant neoplasms (MN) are one of the major causes of death in the Republic of Kazakhstan [1]. In the treatment of this formidable pathology, the mortality rate is known to be directly dependent on the stage of the oncologic disease [2]. Besides, rehabilitation treatment after toxic courses of antitumor drug and radiation therapy is vital to reduce MN mortality.

The purpose of this study was to improve the quality and accessibility of early detection and medical rehabilitation for cancer patients at the Primary Health Care (PHC) Level.

**Results:** The use of the "Oncotest" software at the level of examination rooms and the district doctors resulted in a significant increase in early detection of visually accessible tumors by more than 2.3 times ( $p < 0.001$ ). The use of the "Oncotest" software did not influence the efficiency of early detection in the case of internally localized tumors (cancer of the esophagus, stomach, lung, etc.) due to the low availability of additional examinations for that group of patients, especially in rural regions.

The use of Adenorin has significantly reduced the number of hematological complications in the form of leukopenia and the number of cardiological complications of anthracyclines during chemotherapy in the AC regimen in patients diagnosed with breast cancer. The use of Adenorin with radiation therapy has also reduced the period of recovery and relief of radiation reactions by almost 2.5 times.

The laboratory analysis of Adenorin efficacy has shown its high protective and preventive potential in increasing the survival of immunocompetent cells exposed to chemo- and radiation therapy effects.

The administration of IGS4000 allowed to complete the entire course of chemotherapy under the AC regimen without interruption in patients diagnosed with breast cancer and to reduce the number of hematological complications in the form of leukopenia.

More comprehensive implementation of medical rehabilitation in pilot regions reduced the one-year mortality by more than 11.8% without significant expenses, proving it as an essential reserve for reducing mortality from malignant neoplasms.

**Conclusion:** The analysis of the obtained data showed the high efficiency of the "Oncotest" software in identifying visually accessible oncology diseases. The use of Adenorin spray and IGS4000 in medical rehabilitation for malignant neoplasms can reduce infectious complications and one-year mortality during chemo- and radiation therapy.

**Keywords:** oncology, diagnostics, chemotherapy, radiation therapy, rehabilitation, Adenorin, IGS4000.

**Relevance:** Malignant neoplasms (MN) are one of the major causes of death in the Republic of Kazakhstan [1]. In the treatment of this formidable pathology, the mortality rate is known to be directly dependent on the stage of the oncologic disease [2]. Besides, rehabilitation treatment after toxic courses of antitumor drug and radiation therapy is vital to reduce MN mortality.

Unfortunately, a complex inspection of the cancer service by the Ministry of Health and the monitoring and evaluation group has shown that early detection of MNs and medical rehabilitation of cancer patients at the level of PHC and oncologic dispensaries remain an unsolved problem of practical medicine in the Republic of Kazakhstan [3, 4].

The implementation of efficient, cost-effective, and affordable methods of medical rehabilitation of cancer patients on the basis of national standards is required to im-

prove this situation. Such standards shall be based on international experience and domestic clinical studies [5-8].

All the above has necessitated this clinical research – international project "New Approaches to Diagnostics and Medical Rehabilitation of Malignant Neoplasms at the Primary Health Care (PHC)." The research protocol was approved at the meeting of the Scientific Council of Kazakh Institute of Oncology and Radiology (KazIOR), minutes № 7 of 12.09.2017.

**The purpose of this study** was to improve the quality and accessibility of early detection and medical rehabilitation for cancer patients at the Primary Health Care (PHC) Level.

### **Tasks of the project:**

1. To develop and evaluate the effectiveness of a new digitized approach – the "Oncotest" software in early diagnostics of cancer at the level of examination rooms and

the visiting nurse service of primary health care (PHC) organizations.

2. To develop and evaluate the effectiveness of cancer patients' medical rehabilitation algorithm at the PHC level.

3. To examine the results and develop guidelines for cancer patients' diagnostics and medical rehabilitation at PHC level.

**Materials and methods:** The objects included patients examined and treated for malignant neoplasms in the medical institutions in West Kazakhstan, Kostanay, Almaty, Karaganda, and Mangystau Regions, as well as in the cities of Almaty and Nur-Sultan from January 2018 to December 2019. In total, the study covered 7 regions (Table 1).

Table 1 - Regions and medical institutions included in the project

№	Region	Medical institution	Research section
1	West-Kazakhstan Region	Outpatient clinics No. 1, 5, 6, Uralsk, Rehabilitation Department of the Regional Oncology Center of West Kazakhstan Region Central District Hospital of Burlinsky District of West Kazakhstan Region	Diagnostics of malignant neoplasms Rehabilitation of cancer patients
2	Kostanay Region	Outpatient clinic No.3 of Kostanay, Municipal Outpatient clinic of Rudny, Rehabilitation Department of the Regional Oncology Center of Kostanay	Diagnostics of malignant neoplasms Rehabilitation of cancer patients
3	Almaty Region	Alakol district, Talgar district, Department of Rehabilitation of AROD	Diagnostics of malignant neoplasms, rehabilitation of cancer patients
4	Karaganda Region	Outpatient clinic No. 3 of Karaganda	Diagnostics of malignant neoplasms
5	Mangystau Region	Outpatient clinic No. 2 in Aktau, Central Hospital of Mangystau District	Diagnostics of malignant neoplasms, rehabilitation of cancer patients
6	The city of Nur-Sultan	Outpatient clinic No.5, 9, Nur-Sultan, Day-patient Chemotherapy Department of the Oncological Center of Nur-Sultan	Diagnostics of malignant neoplasms
7	The city of Almaty	Outpatient clinic No. 3, 5, 8 of Almaly district, Almaty, Day-patient Chemotherapy Department of the Almaty Oncological Center, Radiation Therapy Department of the Almaty Oncological Center	Diagnostics of malignant neoplasms, rehabilitation of cancer patients

*Diagnostics of malignant neoplasms.*

Study inclusion criteria: patients allocated to the outpatient clinic; and:

- patients examined in female and male examination rooms;
- patients above 65 years, subject to routine examination, and identified during yard visits.

Study exclusion criteria:

- Patients not attached to the outpatient clinic;

- Patients above 65 years old who independently contacted the outpatient clinic with complaints suspicious of cancer.

Study design:

- During diagnostics, *the experimental group* uses "Oncotest" at the level of examination rooms, visiting nurse service and district oncologists (Figure 1, 2);
- *the control group* does not use "Oncotest" during diagnostics.

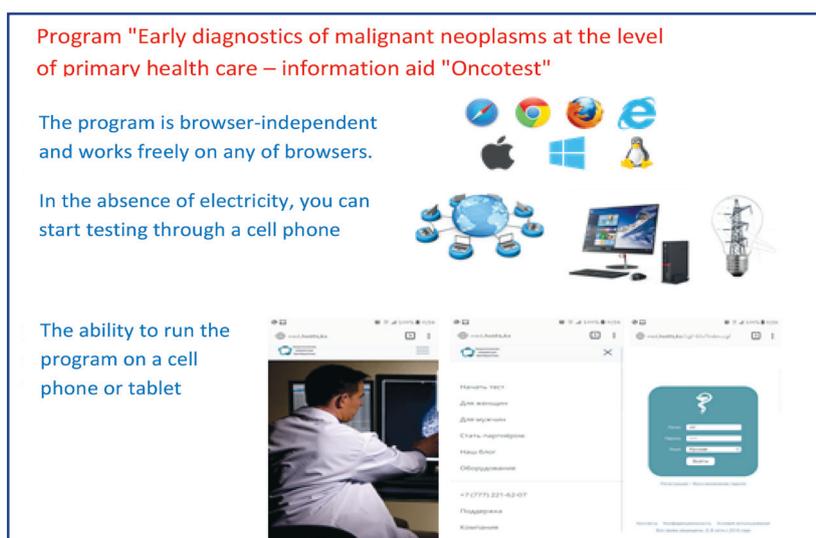


Figure 1 – "Oncotest"

Evaluation of the results.

- The following values are compared during the study:
- The absolute number of patients suspected of having cancer;

- The absolute number of patients diagnosed with cancer;
- The absolute number of patients diagnosed with precancer;

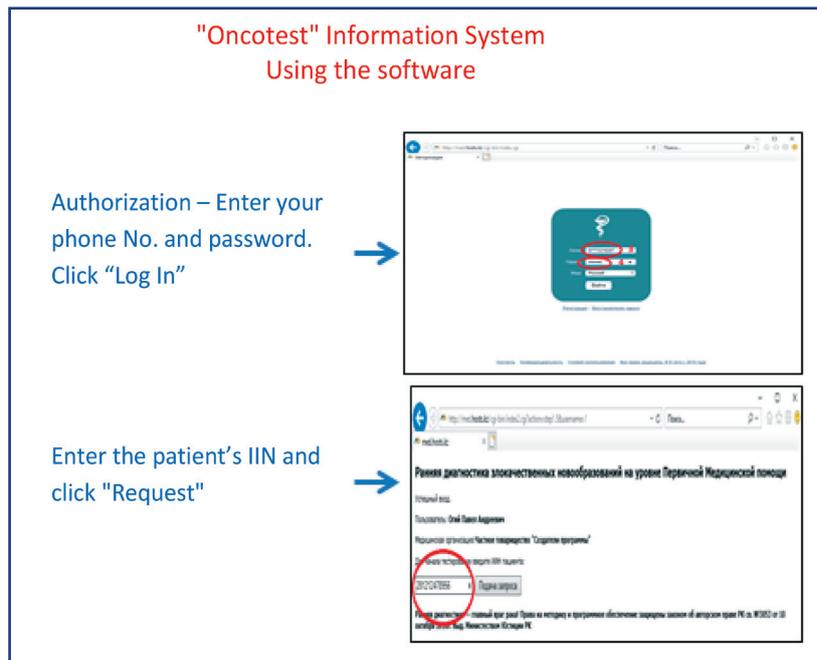


Figure 2 – Using “Oncotest” software

- The average time to identify visually accessible cancer (days);
- The average time to identify cancer of internal localization (days);
- Nosologies, most challenging for diagnostics, and the reasons for the delay in establishing the diagnosis.

Final results in the experimental and control groups were compared, and the statistical significance established. Also, the early detection indicators for every medical institution were compared with the previous year.

*Medical rehabilitation for cancer patients during chemotherapy.*

Study inclusion criteria: patients allocated to the outpatient clinic and having a morphologically verified diagnostics of malignant neoplasms, the histological diagnosis - «breast adenocarcinoma, stage 2-3», receiving chemotherapy according to the AC regimen, 4 courses.

In total, 361 patients were included in this section of the study; of them, 183 - in the experimental group, 178 - in the control group.

The research design for this section is shown in Figure 3.

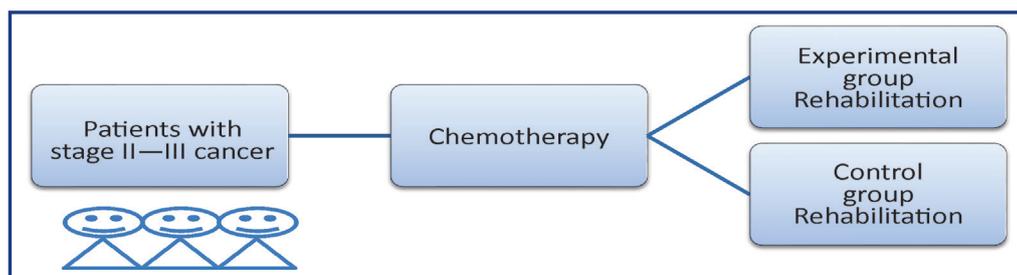


Figure 3 – Design of the study section “Medical Rehabilitation after chemotherapy”

**In the experimental group,** preventive measures were taken to reduce the side effects of antitumor chemotherapeutic treatment according to the following scheme:

The first step at the level of a city or district outpatient clinic, after discharge from the cancer hospital, is the following additional examination is required:

total blood count, blood biochemistry (ALT, AST, urea, creatinine), echocardiography with fractioning the left ventricle output.

This procedure is necessary for early detection of complications of antitumor treatment from the side of vital organs after discharge from the hospital (i.e., presence of cardiological, hematological, hepatic, and renal complications).

*Rehabilitation scheme No. 1 (experimental group, n = 153):*

- Decreased intoxication after antitumor treatment (hydration): physiological saline – 400 mL per 1 m<sup>2</sup> iv for 3 days,
- Adenorin spray 18 mg – 2 injections under the tongue

3 times with an interval of 10 minutes daily for 10 days after each chemotherapy course (4 courses in total).

*Rehabilitation scheme No. 2 (experimental group, n = 30):*

– Decreased intoxication after antitumor treatment (hydration): physiological saline – 400 mL per 1 m<sup>2</sup> iv for 3 days,

– *prevention of infectious complications:* IGS4000 – 10 capsules per day throughout the course of chemotherapy.

Adenorin and IGS4000 are not registered as anticancer drugs in the Republic of Kazakhstan. Their main goal is the restoration of functions of vital organs.

**Control group (n = 178):**

– Saline 400 mL iv for 3 days immediately after chemotherapy.

*Medical rehabilitation for malignant neoplasms during radiation therapy.*

Inclusion criteria: Patients with morphologically verified malignant neoplasm of the oral mucosa, tongue, or larynx, the histological diagnosis - “squamous cell carcinoma,” receiving remote radiation therapy in the single dose of 2 Gy, total boost dose of 40 Gy.

In total, 120 patients were included in this section of the study; of them, 61 - in the experimental group, 59 - in the control group.

The research design for this section is shown in Figure 4.

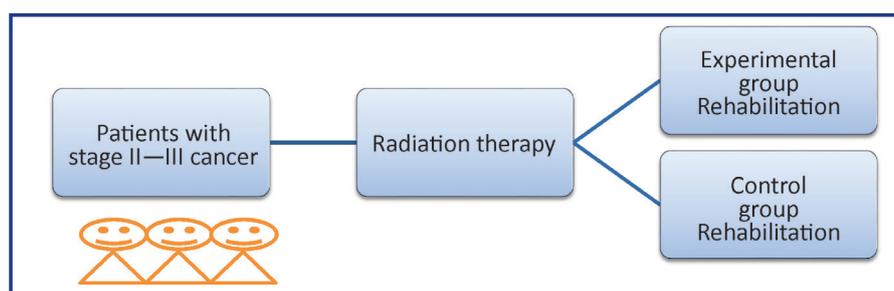


Figure 4 – Design of the study section “Medical Rehabilitation after radiation therapy”

**In the experimental group**, the following preventive measures were taken to reduce the side effects of antitumor treatment:

First, after discharge from the cancer hospital, the patients underwent an additional examination at the city or district outpatient clinic. The examination included total blood count, blood biochemistry (ALT, AST, urea, creatinine), echocardiography with fractioning the left ventricle output.

This procedure was necessary for early detection of complications of antitumor treatment from the side of vital organs after discharge from the hospital (the presence of cardiological, hematological, hepatic, and renal complications).

The following treatment was administered based on laboratory and instrumental tests:

– *For the prevention of mucosal lesions* and toxic myocardial damage - Adenorin spray on the skin in the irradiation zone and under the tongue 9.0 mg daily throughout the course of chemotherapy;

– in the control group – observation (placebo).

**Results:**

*Diagnostics.*

In the regions of the study, the experimental and control groups were identified to compare the results. The “Oncotest” software was installed in examination rooms of outpatient clinics and district doctors’ offices to improve early diagnostics at the PHC level. This software offered the Algorithm for an additional examination of patients with tumors of visually accessible localizations and tumors of internal organs.

A total of 6156 patients were examined; the largest enrollment was reported in municipal outpatient clinic No. 9 in Nur-Sultan (1632), outpatient clinic No. 3 in Almaty (1442), and outpatient clinic No. 3 in Karaganda (749).

The implementation of “Oncotest” resulted in increased efficiency of early detection in all outpatient clinics in comparison to control groups, by almost 2.3 times for breast cancer and 3.1 times for skin melanoma. However, an improvement in the detection of cancer of internal localizations (lung cancer, esophagus, stomach) was noted only in Karaganda, Kostanay, and West Kazakhstan regions.

Thus, the use of “Oncotest” in examination rooms and district doctors’ offices allowed increasing the level of early detection in visually accessible localizations by more than 2 times (breast cancer, skin melanoma).

As for tumors of internal localization, an increase in efficiency was noted only in municipal outpatient clinics. No improvement in the diagnostics of internal localization was obtained in the central district hospitals, except for West Kazakhstan Region, where the Regional Oncology Center had a diagnostic and treatment department with the possibility of free follow-up examination of patients with suspected cancer of the lungs, esophagus, stomach, colon or rectum.

At that, the low availability of endoscopic, radiological and morphological studies in remote district centers of Almaty, Mangystau Regions leveled down the activities of examination rooms and district doctors in using “Oncotest” (Table 2).

Table 2 – Results of using “Oncotest” software

Name of the medical institution	No. of tests made	Of them, no. of tests completed	Age above 65				
			Breast examination	Esophagus and stomach examination	Colon and rectum examination	Lung examination	Skin examination
MTsZh LLP, Balkhash	54	54	6	8	9	12	3
Burlinsky Central District Hospital, the town of Aksay	883	544	14	57	81	49	36
Outpatient clinic No. 1, Uralsk	48	8	0	1	1	1	0
Outpatient clinic No. 6, Uralsk	36	13	4	2	1	1	1
Outpatient clinic No. 5, Uralsk	21	13	0	0	0	0	1
Outpatient clinic No. 3, Karaganda	749	717	1	34	30	30	32
PSE Outpatient clinic No. 9, Nur-Sultan	1632	1364	158	238	236	225	203
PSE Outpatient clinic No. 3, Almaty	1442	1233	45	101	95	95	56
PSE Outpatient clinic No. 3, the settlement of Kabanbay, Almaty Region	41	32	0	0	0	0	1
PSE Outpatient clinic No. 1, Balkhash	598	526	64	115	101	121	83
PSE Outpatient clinic No. 2, Balkhash	652	593	72	143	93	113	120
Total	6156	5097	364	699	647	647	536

#### *Rehabilitation after chemotherapy.*

Medical rehabilitation in the first experimental group (n = 153) was conducted during the first line of chemotherapy for breast cancer according to the AC scheme using Adenorin Spray, sodium nucleonate. This allowed to significantly reduce the number of hematological complications in the form of leukopenia from 39.02% to 14.7% compared with placebo (p < 0.001), the number of cardiac complications of anthracyclides (according to Echo-KG) – from 25.1% to 6.0 % (p < 0.001), the percentage of immunosuppression – from 93% to 32% (p < 0.001).

The quality of life of patients in the experimental group receiving Adenorin spray during breast cancer chemotherapy has significantly improved compared to the control group. That allowed all patients to complete all 4 courses of chemotherapy without interruption. In the control group, 39.02% of patients had to terminate chemotherapy and required colony-stimulating factors. Mortality after chemotherapy in the control group was 2.43%.

In the second experimental group, the use of 10 capsules of GS4000 per day during the first-line chemotherapy for breast cancer in the AC regimen allowed to finish all 4 chemotherapy courses without interruption and reduce the number of hematological complications in the form of leukopenia from 39.02% to 30.4% compared to placebo group (p > 0.05).

#### *Rehabilitation after radiation therapy.*

Immediately upon completion of radiation therapy for squamous malignant neoplasms, medical rehabilitation with Adenorin spray (6.0 mg on the skin in the irradiation zone and 9.0 mg under the tongue daily during the entire course of radiation therapy) did not reduce the frequency and severity of radiation reactions in the irradiation zone compared with the placebo group. However, the use of Adenorin Spray allowed an almost 2.5-fold reduction in the duration of recovery and relief of radiation reactions, from 7.4 days to 3.3 days (p < 0.001).

Besides, the cosmetic effect and skin repair occurred already on the 2nd day in the experimental group and only on the 5.3th day (p < 0.001) in the control group.

#### *Laboratory results and discussion.*

In modern oncology, chemotherapy is one of the most important components of treatment, along with surgical aids and radiation exposure. Its improvement follows the path of both increasing efficiency and reducing toxicity, that is, the damaging effect of cytostatics on healthy tissues and physiological functions of the body. Cytostatic damage to hematopoietic cells of the bone marrow leads to a decrease in the number of leukocytes, platelets, and erythrocytes.

In this case, the development of neutropenia is most dangerous since neutrophils are one of the main components of the body's natural defense against infection.

The degree and duration of neutropenia, which develops after chemotherapy, largely determine the quantity of life-threatening infectious complications.

The assessment of human immune status indicates the status and predict complications after chemotherapy. This assessment includes a set of laboratory indicators that characterize the quantitative and functional activity of immune cells.

Functional sensing of neutrophils is of great clinical importance. First, neutrophil tests can be used to determine immunity reserves, i.e., in the traditional aspect. Second, the

obtained data is useful to understand the depth and dynamics of general homeostatic disorders, regardless of the nature of the disease or external exposure. In the first case, the neutrophil effector resources are determined, while in the second case, neutrophils (their reactive shifts) are used as indicators and reflect the viability of immune cells.

The state of leukocyte membranes is assessed instrumentally by luminescent micro spectral analysis of cells and two-wave microfluorimetry and visually by luminescent microscopy (Fig. 5-9).



Figure 5 – Analysis of neutrophils under a luminescent microscope: ethidium bromide, Patient J., 33 years old, a 40-fold increase

Patients with more than 50% of non-viable cells developed acute infectious diseases during the next 2 days (Fig. 6).

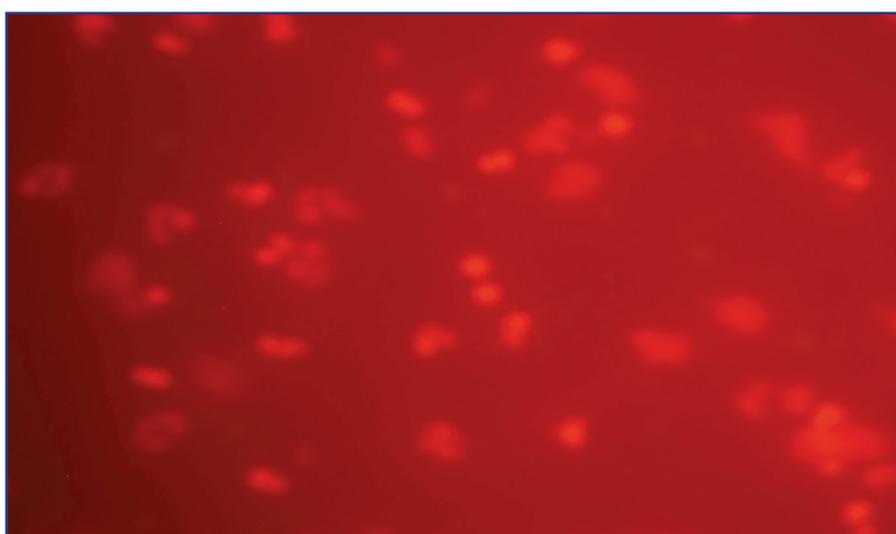


Figure 6 – The state of immune cells just before a respiratory disease: ethidium bromide, a 40-fold increase

At that, the number of mitochondria in immunocompetent cells (ICC) did not exceed 33% in all studied blood samples in the group of patients not receiving Adenorin.

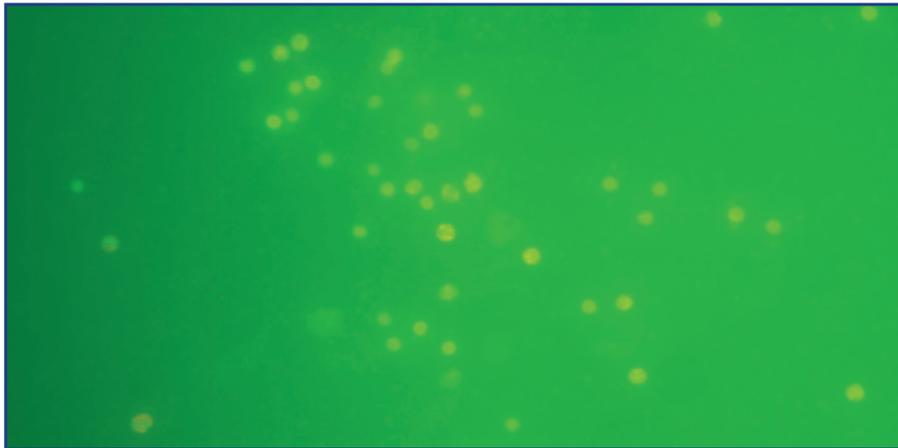


Figure 7 – Control: Adenorin-stimulated orange cells have active mitochondria: acridine orange, a 40-fold increase.

HCT assessment of peripheral blood neutrophils' metabolic activity showed that the number of totally

stained granulocytes of restored HCT in healthy people always exceeded 60% (Fig. 8).

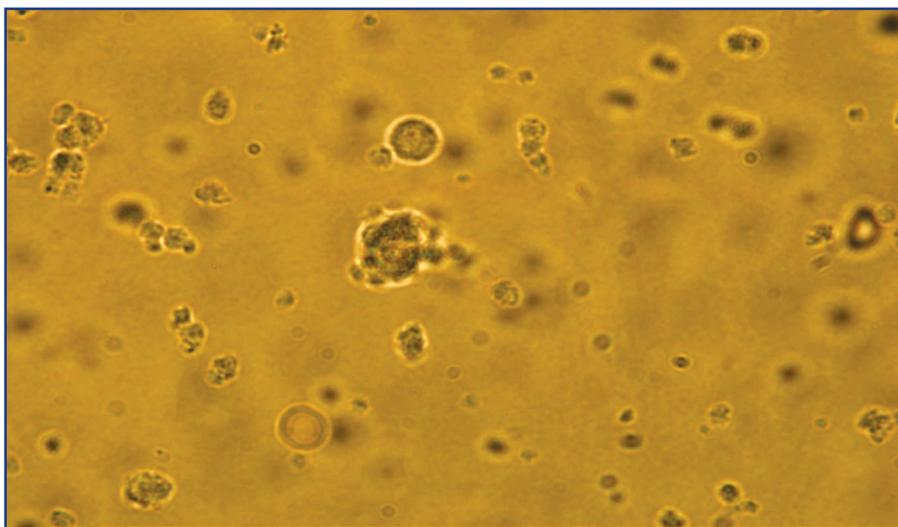


Figure 8 – The number of totally stained granulocytes recovered exceeds 60%: nitro blue tetrazolium, Patient G., 33 years old, a 40-fold increase

However, in immunosuppressive states, as well as during chemo- or radiation therapy, the content of lysosomes in granulocytes decreased sharply (Fig. 9).

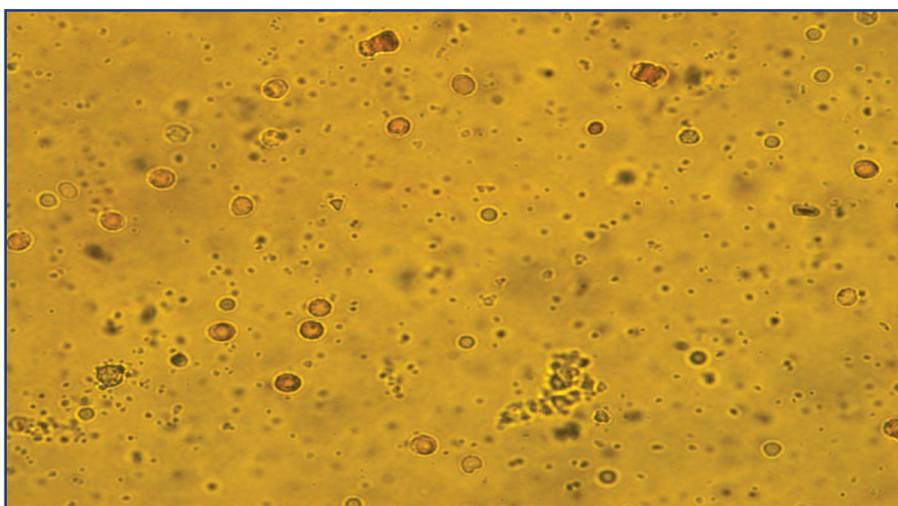


Figure 9 – Control: reduction in the number of lysosomes: nitro blue tetrazolium, a 40-fold increase

After obtaining the results, we conducted a series of laboratory studies in the experimental group where the subjects received Adenorelin 6 mg for 10 days, and in the control (placebo) group where the subjects did not receive Adenorelin. We conducted a quantitative and functional analysis of blood cells before the test and 10 days after.

#### Discussion.

In the experimental group 1, the number of cells with active mitochondria was 10-15% higher, and the number of non-viable ICC was 30-35% lower than in Group 2. The content of active mitochondria and lysosomes also increased pro-rata.

The laboratory analysis of Adenorelin efficacy has shown the high protective and preventive potential of Adenorelin to increase ICC survival under the adverse effects of chemotherapy and radiation therapy. Namely, we registered an increase by nearly 35% of the content of viable ICC with a high energy potential (increase in the number of mitochondria) and high protective potential (increase in the number of lysosomes inside the cell). This allows both quantitative and qualitative functional tests to define ICC phagocytic activity in order to predict possible infectious and oncological complications.

The laboratory results show the possibility of using functional tests to predict complications in the form of immunosuppression against the background of the planned chemotherapy.

#### Conclusions.

1. The use of the "Oncotest" software at the level of examination rooms and the district doctors significantly increases early detection of visually accessible tumors by more than 2.3 times ( $p < 0.001$ ).

2. The use of the "Oncotest" software does not improve the efficiency of early detection in the case of internally localized tumors (cancer of the esophagus, stomach, lung, etc.) due to the low availability of additional examinations for that group of patients, especially in rural areas.

3. The use of sodium nucleonate – Adenorelin spray for medical rehabilitation in the first line of chemotherapy for breast cancer according to the AC scheme has significantly reduced the number of hematological complications in the form of leukopenia from 39.02% to 14.7% vs. the placebo group ( $p < 0.001$ ).

4. According to echocardiograms, the use of Adenorelin reduces the number of cardiological complications of anthracyclines in the first line of chemotherapy for breast cancer according to the AC scheme from 25.1 % to 6.0% ( $p < 0.001$ ).

5. The administration of IGS4000 drug, 10 capsules a day, for medical rehabilitation in the first line of chemotherapy for breast cancer according to AC scheme, has allowed completing the entire course of chemotherapy and to reduce the number of hematological complications in the form of leukopenia from 39.02% to 30.4% vs. the placebo group ( $p > 0.05$ ).

6. The use of Adenorelin for medical rehabilitation after radiation therapy allows reducing the period of recovery and relief of radiation reactions by almost 2.5 times – from 7.4 days to 3.3 days ( $p < 0.001$ ).

7. The laboratory analysis of Adenorelin efficacy has shown its high protective and preventive potential in increasing the survival of ICC exposed to chemo- and radiation therapy

effects, namely, the increase by nearly 35% of the content of viable ICC with high energy potential (increase in the number of mitochondria), high protective potential (increase in the number of lysosomes inside the cell).

8. More comprehensive implementation of medical rehabilitation in the pilot regions (Burlinsky District of West Kazakhstan Region; Central district hospital in Shetpe, Mangystau Region; the town of Rudny, Kostanay Region) has reduced the one-year mortality by more than 11.8% without significant expenses, especially in remote rural areas, proving it as an essential reserve for reducing mortality from malignant neoplasms.

The scientific work was funded by a grant from the Kazakh Institute of Oncology and Radiology for 2017. The results of the study were reported at the International Conference with the participation of representatives of Russia, Japan, South Korea and Kazakhstan on October 4, 2019, in Almaty which hosted an Expert International Council with examination of patients who have given informed consent to participate in the project, as well as at the VIII Congress of Oncologists and Radiologists of Kazakhstan held on October 17-18, 2019 in Nur-Sultan.

#### References:

1. Kaydarova D.R., Chingisova Z.H.K. et al. Pokazateli onkologicheskoy sluzhby Respubliki Kazakhstan. Statisticheskiye materialy (Indicators of the Oncological Service of the Republic of Kazakhstan. Statistical materials). – Almaty. – P. 95-162 [in Russian];
2. Abisatov Kh.A. Klinicheskaya Onkologiya (Clinical Oncology). – Almaty, 2007. – P. 3 [in Russian];
3. Kuznetsov V. P. Interferony v kaskade tsitokinov: istoricheskiy i sovremennyy aspekt (Interferons in the cascade of cytokines: historical and modern aspects) // Materials of the VIII International Congress on Immunorehabilitation. – France, Cannes, April 19-24, 2002 [in Russian];
4. Pfreundschuh M., Trumper M., Kloes M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL // Blood. – 2004. – Vol. 104(3). – P. 634;
5. Thatcher N, Girling DJ, Hopwood P, et al: Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: Results of a British Medical Research Council Multicenter Randomized Trial—Medical Research Council Lung Cancer Working Party // J Clin Oncol. – 2000. – Vol. 18. – P. 395-404;
6. Minanenko S.V. Primeneniye glikozilirovannogo granulotsitarnogo analogichnogo chelovecheskomu rekombinantnogo koloniyestimuliruyushchego faktora lenograstima (Granotsit) dlya profilaktiki infektsionnykh slozhnennykh khimioterapii (The use of glycosylated granulocyte recombinant colony-stimulating lenograstim factor (Granocyte) similar to human for the prevention of infectious complications of chemotherapy) // Materials of the V Congress of Immunologists and Allergists of the CIS Countries. – Russia, St. Petersburg, July 5-11, 2003 [in Russian];
7. Nurgaziyev K.SH., Shortanbayev A. A. , Rakisheva A.S. , Tumanova A.K., Baltabekov N.T. Novyye podkhody k immunoterapii s ispol'zovaniyem naderina pri sotsial'no znachimyykh zabolovaniyakh, vklyuchaya rak molochnoy zhelezy, tuberkulez, gepatit S (grant KazNMU na 2013 god) (New approaches to immunotherapy using naderin in socially significant diseases, including breast cancer, tuberculosis, hepatitis C (grant of KazNMU for 2013) // Onkologiya i Radiologiya Kazakhstana (Oncology and Radiology of Kazakhstan). – 2013. – № 4. – P. 19-21 [in Russian];
8. Baltabekov N.T. Problemy meditsinskoy reabilitatsii v onkologii (Problems of medical rehabilitation in oncology) // Onkologiya i Radiologiya Kazakhstana (Oncology and Radiology of Kazakhstan). – 2019. – № 4. – P. 19-21 [in Russian].