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ANALYSIS OF THE IMMEDIATE RESULTS OF THE MULTIMODAL METHOD OF BREAST CANCER THERAPY IN COMPARISON WITH THE RESULTS OF CONVENTIONAL THERAPY

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ABSTRACT

An analysis of the immediate results of the multimodal method of breast cancer therapy in comparison with the results of traditional therapy showed that at the initial stages of breast cancer (BC), the applied non-traditional therapy, accompanied by immunocorrective drug therapy with preliminary exposure to medium frequency radio waves (350 + 15 kHz) is observed lysis of the tumor formation, reduction of the volume of the tumor and affected regional lymph nodes, as well as immunological parameters and improvement of the quality of life of patients. So, in the group on the background of traditional therapy, partial lysis of the tumor was observed on the 21st day, and in the main study group with non-traditional therapy on the 7th day. Clinical efficacy was monitored using clinical, laboratory and instrumental research methods. According to the ECOG and Karnofsky scales, there is a significant improvement in the quality of life in the main group of patients. Therefore, the advantage of the multimodal method of therapy was the easy tolerability of treatment procedures, the mild post-drug course of antitumor therapy, the early restoration of functional abilities, and the reduction in the incidence of complications, which ultimately affected the improvement in the quality of life of patients.

Key words: breast cancer, accompanying immunocorrective therapy, medium and low frequency radio waves, cellular and humoral factors of immunity.

INTRODUCTION

Relevance of the topic. It is known that breast cancer (BC) is a heterogeneous disease, the pathogenesis of which is due to the complex interaction of genetic, hormonal, metabolic, exogenous and other factors, and is the most common malignant neoplasm among women in the world [1,10,18,24,25] .

Breast cancer is the most common cancer in women in over 150 countries and the leading cause of cancer death in 110 countries. Approximately one in twelfth women will develop breast cancer during their lifetime. In 2020, approximately 685,000 women died from this disease. Most breast cancer cases and deaths occur in low- and middle-income countries (LMICs) [11,16].

Improving outcomes and survival is possible with a combination of early detection and subsequent effective treatment using existing methods - surgery, radiation therapy and drug treatment. In order to increase and enhance the effectiveness of treatment, there are different approaches and techniques. At stages I-III, the treatment of this disease requires an integrated approach that combines local (surgical and / or radiation) and systemic drug treatment [12,13,17,19,23].

With regard to immunotherapy, it is one of the most promising and rapidly developing areas in the treatment of cancer. However, it is constrained by a number of factors that do not allow this method to be completely successful. First, the tumor successfully masks or eliminates antigens that might be recognized by the immune system. Secondly, the tumor not only masks itself, but also actively affects the immune system, enhancing the tolerogenic and suppressive properties of its cells, reprogramming the functions of tumor-associated macrophages and suppressing cell killing reactions. Thirdly, the tumor behaves like a parasitic, alien organism, using all the mechanisms of Darwinian evolution. That is, it actively changes and adapts to adverse conditions arising from chemotherapy, radiotherapy or other methods of exposure. The most important issue is to increase the effectiveness of the methods and approaches used in treatment of breast cancer [14,17,20,22]. In this regard, recently in oncology and immunology, more and more attention is paid to areas that are focused on the need to mobilize the body's natural defense mechanisms against a tumor, i.e., antitumor immunity [2,5,6,9,20]. Thus, studies of the influence of electromagnetic fields on living organisms have been conducted for more than a decade. It is known that electromagnetic fields are an ecologically significant factor of the external environment, since all living organisms on the planet are under the influence of the natural geomagnetic field and man-made fields [8,9,12,13,19]. This information served as an impetus for the development of magnetotherapy, especially in oncology. Various authors provide data on the benefits of magnetic therapy in the rehabilitation treatment of cancer patients, which is expressed in the normalization of blood counts, the elimination of postoperative complications, the acceleration of reparative processes, and the removal of severe pain. Thus, the widespread use of electromagnetic fields, especially in oncology, contributes to the accumulation of information about the mechanisms of action of this physical factor on the course of the oncological

process. Actively studied are the mechanisms of antitumor immunity under the influence of electromagnetic fields, both at the cellular and molecular levels [20,21].

It was previously known that magnetic fields increase blood circulation in tissues and stimulate the body's metabolism. Also, it has been proven that low and medium frequency electromagnetic waves inhibit the growth of malignant tumors, thereby stopping the neoangiogenesis necessary for tumor growth. Magnetic therapy induces weak electrical currents in tissues, which increases the surface potential of cells, which leads to increased blood circulation, oxygenation, nutrient supply and better removal of metabolic waste from the body. Also, magnetic fields have been used as natural pain relievers, promoting recovery and healing, reducing swelling, stiffness and acidity of wounds.

Aim of the study. To conduct a comparative analysis of the immediate results of the multimodal method of breast cancer therapy in comparison with the results of traditional therapy.

Material and methods of research. In this work, a number of combinations of some known therapeutic methods and an algorithm for their application are used. When carrying out complex treatment of breast cancer, a differentiated and selective combination was used. The treatment fits well into the system of traditional therapy and allows you to gradually influence the processes of tumor elimination. The therapies used are described below:

1. The course of therapy, which begins with non-specific physical correction of the immune system. As a device for non-specific immunocorrection, the "TOR" technology (technology of operative rehabilitation) was used with a non-localized point of influence using a copper coil on the patient's body, which affects the immune system with an alternating magnetic field in the medium frequency range of 350 + 15 kHz, at a wavelength of 909-857 meters and with an impact energy of 20V [4,9,10,14]. So, in the course of preliminary experiments, it was found that when exposed to a given alternating magnetic field, the number of T-lymphocytes and CD16 NK cells significantly increases. At the same time, the patient is taking an oral immunomodulatory drug "RCV" (Uzbekistan). It has been shown that this drug activates the cytotoxic functions of macrophages (i.e., it is likely that reprogramming from M2 to M1), intensively enhances the synthesis of interferons and increases the number of active CD4+ and CD8+ subpopulations of T-lymphocytes. According to the indications of the immunogram and the data of biochemical blood tests, additional immunotropic drugs, macro- and microelements, as well as vitamins and other drugs can be prescribed.

2. After such a preparatory course, antitumor treatment begins within 2-3 weeks. Low-dose chemotherapy or radiotherapy can be carried out for quite a long time (1-2 months) and even more. The main thing is to periodically carry out clinical and laboratory monitoring of the patient's condition, preventing deterioration of his condition. At the same time, one should not strive at all costs to destroy the entire tumor at once. The main thing here is not to suppress immune responses. The processes of tumor lysis, in conditions of full-fledged work of the immune system, will continue even after the end of the course of chemotherapy. Lysis can be carried out by activated cells of innate (M1 and NK cells) and acquired (CD8+ - T - cytotoxic lymphocytes) immunity. Even if small doses of chemotherapy no longer kill cancer cells, they can significantly change their metabolism. This already leads to a decrease in the immunosuppressiveness of tumor cells, a slowdown in their growth and, often, simply to aging. Moreover, low doses of cytostatics can very actively suppress angiogenesis in the tumor by blocking vascular endothelial growth factors (VEGF). All this further inhibits tumor growth.

3. Before the end of the course of chemotherapy (7-10 days in advance), the patient begins to take drugs that suppress the explosive growth of tumor cells. The group of such drugs may include Ablast (Uzbekistan), Celecoxib, Aspirin, Metformin, selenium preparations and others. This stage lasts for 15-25 days.

4. During the next, recovery stage (1-2 months), the patient takes adaptogens (Ginseng, Eleutherococcus, vitamin C and D3 and other drugs) and continues the course of therapy with TOR according to a certain scheme. At this time, the effectiveness of the completed course is determined. With incomplete destruction of the tumor, after the recovery period, the above course, taking into account the necessary adjustments, especially in chemotherapy agents, can be repeated. It should be noted that the goal of this optimized approach is at least partial regression of the tumor mass and the absence of its further growth.

An analysis was made of the immediate results of treatment of 120 patients with breast cancer in the initial stages who were treated in the branches of the **RSRPMCOaR** of the Ministry of Health of the Republic of Uzbekistan in the period from 2018 to 2022. Patients were divided into two groups: the control group (64 patients) who received traditional therapy and the main group (56 patients) who received traditional therapy with modulated accompanying immunocorrective drug therapy with preliminary exposure to medium frequency radio waves (350+15 kHz).

The age of the studied women ranged from 31 to 73 years: 30-40 years-16 (13.5%); 41-50 years old - 32 (27.2%), 51-60 years old - 41 (34.7%), 61-70 years old -25 (21.2%), 71 and older - 4 (3.4%) . 83 (70.3%) patients were young and of working age.

The histological picture is presented: infiltrative form - 59 (50%) patients, invasive - 33 (28%), ductal - 18 (15.3%), adenocarcinoma - 7 (5.9%) and Paget's cancer 1 (0.8%). Depending on the molecular genetic features of breast cancer, Luminal subtype A occurred in 8 (6.9%) patients, Luminal subtype B in 20 (16.5%), HER2-positive subtype in 33 (28%) and "Triple negative" subtype in 27 (23%) and 30 patients (25.6%), molecular genetic testing was not performed.

For the diagnosis of breast cancer, a complex of laboratory and instrumental studies was used. General clinical blood tests, detailed immunograms were performed in almost all patients at admission and during treatment according to the standard method. Studies were carried out: biochemical parameters of blood, coagulograms, blood electrolytes. To assess the functional state of the liver, pancreas, kidneys, patients underwent biochemical studies and paid attention to the levels of bilirubin, total protein, sugar, transaminase, amylase, etc. diagnostics, monitoring, control of treatment effectiveness). MSCT, chest MRI and mammogram data were taken into account in preoperative preparation. With pathological changes, corrective therapy was carried out, the effectiveness of which was evaluated by repeating the study.

Non-invasive intervention in patients with breast cancer was performed in different combinations. Table 1 shows combinations of the optimized approach.

Table 1.

Distribution of patients depending on the stage of the tumor and types of treatment

Stages of breast cancer	**Types of treatment for the main group**					**TOTAL**	Traditional Therapy (control group)						**Total**
	EMRWT+CT	**CT+ EMRWT**	**CT+ Surgery + EMRWT**	**CT + CPI + EMRWT**	**CT + CPI**		**NPCT+PP Lymphdis+ APCT+R-T**	**NPCT +RME according Modden + APCT + R-T**	**NPCT + palliative mastectomy + APCT +*BPhT***	**NPCT + Right mastectomy + APCT+R-T**	**Sectoral resection + PCT + R-T**	**PPCT+ hygienic amputation +Б *BPhT***	
T1N0M0	1	1	1	1	2	6	3	5	-	-	2	-	10
T2N0M0	1	-	1	2	1	5	2	3		2	3		10
T2N1MO	6	11	2	5	3	27	4	16	-	2	9	-	31
T3N2MO	-	5	2	2	-	9	-	7	1	-	-	-	8
T4N2M1	-	1	5	1	-	7	-	-	2	-	-	3	5
Total	8	18	11	11	6	**54**	9	31	3	4	14	3	**64**
%	**14,8 %**	**33,3 %**	**20,4 %**	**20,4%**	**11,1 %**	**100 %**	**14 %**	**48%**	**4,8%**	**6,4 %**	**21,9 %**	**4,8 %**	**100%**

In most cases, EMRWT (electromagnetic radio wave therapy) was performed with a frequency of 350 kHz in 20 patients, as well as 345 kHz in 18 patients and 330 kHz in 10 patients.

An important task was to ensure the comparability of the main and control groups, without which it is impossible to objectively compare the immediate results of treatment. Comparability was achieved by individual selection of patients in the control group according to the parameters of individual patients of the main group. In this case, only age, stage of the process, a combination of drug therapy and an assessment of the quality of life according to the international scale ECOG and Karnovsky were taken into account.

The optimized course of the multimodal approach begins with a non-specific correction of the immune system: patients are exposed daily for 14-15 days during the daytime to an alternating magnetic field with radio waves 909-857 meters long with a medium frequency range of the electromagnetic spectrum of the hardware (TOR) technology of an external oscillatory circuit 350 + 15 kHz and a voltage of 12-16 V for 45-60 minutes with amplitude modulation for the 1st course of therapy [10-14 sessions], then the 2nd course of a similar effect is repeated [minimum 10 sessions] in the dynamics of treatment with a 10-15 day interval. At the same time, the radio waves of the medium frequency range generated by the generator of the original design are transmitted to the solenoid coil and, directly in contact with the human body, begin to act systematically. After such a preparatory course, a course aimed at the destruction of the tumor begins. Preference has been directed to low-dose chemotherapy which can be carried out for a sufficiently long time. Before the end of the course of chemotherapy (7-10 days) according to the standard scheme, the patient begins to take drugs that suppress the explosive growth of tumor cells. The group of such drugs may include Ablast, Celecoxib, Aspirin, Metformin, selenium preparations and others (total duration 15-25 days). During the next, recovery stage (1-2 months), patients take adaptogens (Ginseng, Eleutherococcus, vitamin C and D3, etc.) and continue the course of EMRVT according to a certain scheme.

For comparison, a group of control patients was selected, who, in the period from 2020 to 2022, underwent a traditional scheme according to international standards. Of these: NPCT + Radical Modden Mastectomy + APCT + Radiation therapy in 31 (48%), NPCT + Radical Resection with lymphdissixia + APCT + Radiation therapy in 9 patients (14%), Sectoral breast resection + PCT + Radiation therapy in 14 (21.9%), NPCT+palliative mastectomy+APCT+BPhT in 3 (4.8%) and PPCT+hygienic breast amputation+BPhT in 3 (4.8%).

It should be noted that the goal of this multimodal approach is at least partial regression (lysis) of the tumor mass and the absence of its further growth. One should not strive to quickly and by any means destroy the entire tumor to the last cell, as this can enhance the already pronounced effects of intoxication of the body and immunosuppression.

Immunological studies were carried out with the study of the main subpopulations of lymphocytes by flow cytometry using US monoclonal antibodies. Accordingly, CD4+ - T-helpers, CD8+ - T-cytotoxic lymphocytes, CD16+, CD56+ - natural killer cells, CD20+ - B-lymphocytes, CD38+ - precursors of T- and B-lymphocytes and CD95+ - lymphocytes with a receptor for physiological or pathological apoptosis were determined.

The results obtained and their discussion. Evaluation of the effectiveness of the proposed methodology of the multimodal approach was carried out depending on the time of onset of partial lysis, reduction in the volume of tumor formation and regional lymph nodes, changes in immunological parameters, and improvement in the quality of life of patients.

One of the evaluation criteria was the time of onset of tumor lysis. A statistically significant difference was shown during the proposed EMRWT and its combinations in comparison with the traditional one, in the control group, the onset of lysis was 21 days, in the main group - 7 days.

In visual diagnostics (ultrasound was preferred, except for MSCT and mammography), the size of the tumor and regional lymph nodes, regression of the perfocal inflammatory process, echocardiography of tumor lysis were determined. There was a difference in the onset time and a decrease in the volume of tumor formation, enlarged regional lymph nodes of the proposed multimodal approach compared to the traditional one ($p<0.05$): in the control group - 7 days, the main one - 21 days.

It is known that the leading role in the antitumor defense of the body is given to the cellular link of immunity, where T-lymphocytes play a key role. Thus, the expression of T-cell markers of lymphocytes was determined by the relative number of CD3+T-lymphocytes, CD4+T-helpers/inducers and CD8+ T-cytotoxic lymphocytes, as well as by the value of the CD4+/CD8+ ratio (immunoregulatory index - IRI). When analyzing the T-cell link of immunity, including the characteristics of subpopulations of CD4+T-helpers and CD8+T-lymphocytes, suppression of the subpopulation of CD4+T-helpers relative to the control group was revealed in patients. Thus, the relative and absolute content of CD4+T-helpers in patients was significantly lower compared to the data of the control group ($p<0.001$). The relative number of CD4+T-helpers in patients before treatment was

suppressed by 1.4 times compared to the value of the control group. Moreover, the absolute number of CD4+T-helpers in oncology is suppressed by 2.7 times compared with the data of the control group. Obviously, the deficiency of the T-lymphocyte population in cancer patients is due to the predominant suppression of the number of CD4+T-helpers/inducers, which are a necessary link in the formation of killer cells that directly eliminate tumor cells. A study of the content of T-cytotoxic lymphocytes in patients showed that there was a significant increase in the relative number of CD8 + T-lymphocytes compared with the data of the control group ($p<0.05$). Thus, the relative number of CD8+T-lymphocytes was increased by 1.54 times against the value of the control group. The CD4+/CD8+ ratio (IRI) was significantly suppressed in comparison with the value of the control group by 1.8 times ($p<0.05$). The range of individual IRI values in patients ranged from 0.4 to 1.14, but in most patients IRI was below 1.0. Obviously, the decrease in IRI was observed due to the suppression of the relative number of CD4+T-lymphocytes and the increase in the relative content of CD8+T-lymphocytes. Consequently, T-cell immunodeficiency was identified in cancer patients, which was associated with an imbalance in the main immunoregulatory subpopulations of T-lymphocytes (CD4+T-helper/inducers and CD8+T-cytotoxic lymphocytes). Expression of CD20+ on B-lymphocytes was significantly increased in the group of patients compared with the data of the control group. Thus, the relative number of CD20+B-lymphocytes in the group of patients increased by 1.2 times relative to the control ($p<0.05$). The absolute number of B-lymphocytes was suppressed in comparison with the value of the control group. Of the natural protection factors, we have studied the expression of CD16+ and CD56+ on NKC. It is known that NK are the main cellular effectors of the immunobiological surveillance system. It is known that CD16+ is a type 3 membrane low-affinity IgG receptor. The CD56+ NKC marker appears on lymphocytes at the earliest stage of their development. So, it is determined on pre-NKC, when the cell does not yet have the ability to lyse. The analysis of the data obtained showed that in the group of patients a significant increase in the number of CD16+NKC and CD56+NKC by 1.3 and 1.5 times, respectively, was revealed, which had a significant difference from the data of the control group ($p<0.05$). It is possible that an increase in CD16+NKC and CD56+NKC indicates a significant increase in immature forms of NKC, which is often observed in malignant processes [5,8,18,22]. Of the markers of lymphocyte activation, we studied the expression of CD95+ and CD38+ on lymphocytes. Expression of CD95+ on activated lymphocytes in patients with oncology was significantly suppressed compared to the value of the control group ($p<0.05$). The expression of CD38+ activation markers on lymphocytes was characterized by a

significant increase against the control group. Consequently, the cellular immune response in cancer was characterized by some features: pronounced T - cellular immunodeficiency, which manifested itself as a deficiency of CD4 + T-helpers / inducers against the background of an increase in the number of CD8 + T-lymphocytes. However, despite the increased number of CD8+T-cytotoxic lymphocytes, there was a suppression of their absolute values, the main biological purpose of which is the sanitation of the body from foreign agents and the destruction of tumor cells. Perhaps the decrease in the absolute number of T-cytotoxic lymphocytes indicated an inferiority of the immune response. As a result of the imbalance of T-lymphocyte subpopulations, a significant decrease in the immunoregulatory index was noted, which is an indicator of the inadequacy of the immune response. In addition, an imbalance in the cellular link caused pronounced changes in humoral protective factors. The study of the functional activity of B-lymphocytes revealed the presence of a certain imbalance in the production of immunoglobulins. Natural protective factors were characterized by an increased activity of CD16+ and CD56+ expression on NKC. Markers of lymphocyte activation were characterized by an increase in CD38+ expression and suppression of CD95+ expression on lymphocytes. Therefore, we can conclude that the state of the immune system in oncology is characterized by an imbalance in the main subpopulations (CD4+ and CD8+) and activation of the humoral immunity. There is an increase in the ratio of helper/suppressor subpopulations of T-lymphocytes in favor of T-helpers/inducers, which affects the increase in the immunoregulatory index (IRI) and the increase in CD16+ killer cells, which is a positive criterion for assessing immunological, therapeutic and clinical improvement. Moreover, at the molecular level, exposure to an electromagnetic field alters the production of major cytokines, interleukins, and chemokines by cells of the immune system, thereby exerting anti-inflammatory activity, which has been demonstrated according to our materials, by suppressing the secretion of pro-inflammatory cytokines such as IL-6, IL-8, TNF. -α and increased production of anti-inflammatory cytokines such as IL-4 and IL-10. Since inflammation is closely related to the oncological process and probably increases the risk of oncological progression due to chronic subclinical inflammation, exposure to electromagnetic waves may be a potential method of cancer treatment due to the possibility of producing cytokines with a pronounced anti-inflammatory potential. Our results are of great clinical and immunological interest, requiring a more detailed analysis of the mechanisms of formation of the antitumor immune response. We know that, according to preclinical studies, it was concluded that the therapeutic apparatus "TOR" has an immunomodulatory effect, while stimulating the body's adaptive reactions.

The results of preclinical testing of this equipment showed that under the influence of such waves, a decrease in tumors in laboratory animals was observed. Consequently, the effect of magnetic fields on blood and bone marrow cells did not adversely affect their immunological and growth characteristics. On the contrary, the phagocytic activity of leukocytes increased, and a positive trend in the content of T-lymphocytes was observed. In this regard, data on an increase in the phagocytic activity of peripheral blood leukocytes of cancer patients are interesting. Such an effect has a pronounced anti-stress, self-organizing systemic effect inherent in non-specific reactions of the anti-stress type, and is accompanied by an increase in non-specific antitumor resistance, intensification of metabolic processes in blood neutrophils, due to which phagocytosis is activated. Thus, during treatment with the TOR device and complex therapy in combination with the appointment of an immunocorrective drug, activation of antitumor resistance and modulation of T-cell immunity with stimulation of T-cytotoxic lymphocytes, an increase in the ratio of helper/suppressor subpopulations of T-lymphocytes in favor of T-helpers are observed. / inducers, which affects the increase in IRI and the increase in CD16 + killer cells, as well as a decrease in the content of immunoglobulin A and circulating immune complexes of various sizes, suppression of the secretion of pro-inflammatory cytokines - IL-6, IL-8, TNF-α and increased production of anti-inflammatory cytokines - IL- 4 and IL-10, and intensification of metabolic processes in blood neutrophils due to which phagocytosis is activated.

Evaluation of the effectiveness of therapy in the main group showed that 79% had a complete effect, 16%, and 8% had an objective improvement in their condition. No tumor progression was observed in any of the cases. In the control group of 64 patients, 44 (68.8%) had a complete effect, 14 (21.8%) had a partial effect, and 6 (9.4%) had progression of the tumor process ($p<0.05$).

Thus, to activate antitumor immunity, both physical and drug agents can be used, which enhance the cytotoxic reactions of the cellular immune response. Immunity correction prior to oncolytic therapy makes it possible to effectively carry out measures for the destruction of tumor tissue. Degraded tumor antigens can already be perceived by the immune system and an immune response can be developed against them. At the same time, the tumor becomes more “recognizable” for the immune system. It is very important that under conditions of immunosuppressive effects of chemotherapy or radiotherapy, the functional activity of the immune system remains within the physiological norm. Due to this, the previous immunocorrection reduces the toxic effects of oncolytic therapy. The most important point of the proposed method is the prevention of "explosive"

recurrent tumor growth, which, as a rule, follows oncolytic therapy in case of survival of cancer stem cells. Despite the large number of existing studies, there is no unambiguous information about the mechanisms of the antitumor effect of EMF, questions about the mechanisms of physiological and analgesic effects remain unclear or controversial, and this determines the prospects for their further study.

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