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# REMOTE RESULTS OF TREATMENT OF PATIENTS WITH CERVICAL AND OVARIAN CANCER ON THE BACKGROUND OF IMMUNOTHERAPY

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**Summary**

The aim of the investigation was to study the remote results of treatment of accompanying immunopharmacotherapy in patients with cervical cancer and ovarian cancer. Studies have concluded that the greatest effectiveness in reducing the side effects of chemotherapy in the complex treatment of patients with cervical cancer and ovarian cancer stage II-III, as well as in improving the subjective condition of patients and their quality of life, provides immunotherapy plan, which includes intermittent plasmapheresis followed by extracorporeal immunopharmacotherapy (EIPHT), which reduces the main clinical manifestations of chemotherapy, improve the indicators of the subjective condition of patients and their quality of life. The use of EIFT methods in the treatment of oncogynecological diseases can improve the five-year overall and one-time survival of patients with cervical cancer and ovarian cancer. Developed technique has great potential in cancer practice due to the possibility of eliminating the effects of cancer intoxication, as well as increased own system of antitumor protection of the body, which positively affects the outcome of the disease, as well as improves the quality and life expectancy of the patient.

**Key words:** ovarian cancer, cervical cancer, immunotherapy, extracorporeal immunopharmacotherapy, plasmapheresis, polychemotherapy, remote results of treatment.

Cervical cancer (CC) is one of the most common oncological diseases of the reproductive system in women and accounts for about 12-20% of malignant neoplasms of female genital organs [1,2]. Currently, cervical cancer ranks second place in the world in terms of incidence among all malignant tumors of the female reproductive system, and second in the structure of mortality from cancer of women under the age of 45, second only to breast cancer. In the structure of oncogynecologic diseases CC ranked 3rd in the overall oncological morbidity structure with a frequency of 4.7 cases per 100,000 population in 2015 in Uzbekistan [3,7].

Ovarian cancer (OC) continues to be the fourth leading cause of cancer death among women and continues to be the most fatal of gynecological tumors. The recurrence rate of patients with OC is approximately 75%, which is equivalent to approximately 2500 patients per year. In this group of patients with relapses, many patients have a life expectancy of 2 to 3 years, therefore, OC can be classified as a "chronic disease" [6,8].

It is known, that in CC and OC the 5-year survival rate is 30% excluding stage disease. Such treatment disappointing results due to the fact that 75% of patients with cervical cancer and ovarian cancer enter to the oncological establishment on III-IV stage of the process [10,12]. As the research data show, the survival of patients with CC and OC is determined not only by the stage of the disease and the chosen method of treatment. At present, it is known that the development of the oncological process is accompanied by violations of the state of adaptive (specific) immunity, which deepen in the conditions of extensive surgical interventions. It is established that immune dysfunctions make a significant contribution to the pathogenesis of generalized inflammation in the oncological process, and are not only a sign of its development, but largely ensure its occurrence and subsequent progress [3,4]. Proceeding from this, it is obvious that immunotherapy methods are needed for this category of patients that can effectively correct developing immune dysfunctions. Now it is proved that the most rational means of immunocorrection is the usage of immunotropic drugs. The versatility of the biological activity of these drugs makes it possible to rely on their correction not only to correct the manifestations of immune deficiency, but also to optimize the functioning of the entire immune system and its adequate interaction with other body systems [1,2]. Thus, according to modern literature, the most promising area of immunotherapy is extracorporeal

immunopharmacotherapy. This method has a number of advantages [3]: extracorporeal use of drugs allows them to be used in concentrations much lower than therapeutic ones; in vitro-induced cells act strictly purposefully and ensure the delivery of mediators to physiologically-targeted acceptor cells. Based on this, we developed and introduced into clinical practice a method of extracorporeal immunopharmacotherapy with a thymic drug.

**The aim of this study** was to study the remote results of treatment of accompanying immunopharmacotherapy in patients with cervical cancer and ovarian cancer.

**Material and methods.** The study included 235 patients with cervical cancer $T_{2-3}N_{0-1}M_0$ stages (II-III clinical stages), as well as 198 patients with $T_{2-3}N_{0-1}M_0$ stage (II-III clinical stages) who underwent examination and treatment in oncogynecology and autohemotherapy departments of the Republican Cancer Research Center, Tashkent.

All patients with cervical cancer received complex treatment including a two-stage combined radiotherapy, including remote telegammatherapy (RT), split-off course at a 2 Gy fraction dose, to 50 Gy summary dose, 5 times a week, and intracavitary brachytherapy at a of fraction dose 5 Gy to summary dose 45-55 Gy, every other day. Systemic or intra-arterial polychemotherapy with a cisplatin regimen of 50 mg/m$^2$+5-fluorouracil 1000 mg/m$^2$ for 4 days for 4-6 courses was given once every 3 weeks. Radiation therapy and chemotherapy were performed in both adjuvant and neoadjuvant regimens. Surgical treatment was performed in the form of a radical operation. Chemotherapy was performed in both adjuvant and neoadjuvant regimens.

Extracorporeal immunopharmacotherapy was performed by exfusion of 500-1000 ml of autoblood in "Gemakon" or "Terumo" sterile containers and its centrifugation at 3000 rpm for 30 minutes. 50-80 ml of the supernatant of blood plasma, containing antibodies, circulating immune complexes, cytokines, products of cellular metabolism were removed. Then the obtained leukotrombomass and erythrocytic mass were incubated with thymalin in a total dose of 30 mg (for 3 procedures) at 37° C for 60-100 minutes, with the subsequent return of the conjugate to the circulatory system of patients. In total, patients received 2 sessions of extracorporeal therapy at the beginning of admission to hospital and before discharge from the hospital.

Depending on the type of extracorporeal therapy being performed, 4 groups of patients with cervical cancer and OC were isolated. The 1st group included patients of the control group i.e. those patients with cervical cancer and OC who did not receive immunotherapy. In 2$^{nd}$ (96 patients) cervical cancer and 84 patients with OC, immunotherapy in the form of subcutaneous injections of thymomimetics (thymalin, thymogen) in standard doses for 10-14 days was performed. The third group included 83 patients with cervical cancer and 78 patients with OC who underwent extracorporeal immunotherapy (EIPHT) and group 4 comprised 67 patients with CC and 73 patients with OC used EIPHT in combination with plasmapharesis. The overall cumulative five-year survival was assessed by Kaplan E.L. et Meier R. in patients with cervical cancer and ovarian cancer, depending on the different options of immunotherapy in complex treatment [11].

**Results and discussion.** Evaluation of the effect of extracorporeal immunopharmacotherapy on remote results of treatment was carried out by studying the indices of total and disease-free survival of patients with cervical cancer and OC. Figure 1 presents the result of a study of the total cumulative 5-year survival rate for CC, depending on the type of immunotherapy used. Figure 2 presents the results of studies of the total cumulative 5-year survival in patients with OC, depending on the type of immunotherapy used. The analysis showed that the overall 5-year survival rates of patients with oncogynecologic diseases after complex therapy in combination with immunotherapy allowed to reveal the lowest level of five-year survival in the 1$^{st}$ group of patients in the control group, where immunotherapy was not used and whose indices were very low. So, in Figure 1 it is shown that in the 2$^{nd}$ group of CC patients receiving thymomimetics, the total cumulative five-year survival was 57.3±6,2% (P=0.029); in the third group of patients with cervical cancer receiving EIPHT, this indicator was 69.3±6.2% (P=0.037); and the 4$^{th}$ group of patients with cervical cancer consisted of patients who received EIPHT with plasmaphoresis - 74.3±3.1% (P=0.041). This group of patients as a result of the treatment during chemotherapy and radiation therapy had the highest results of the total cumulative five-year survival.

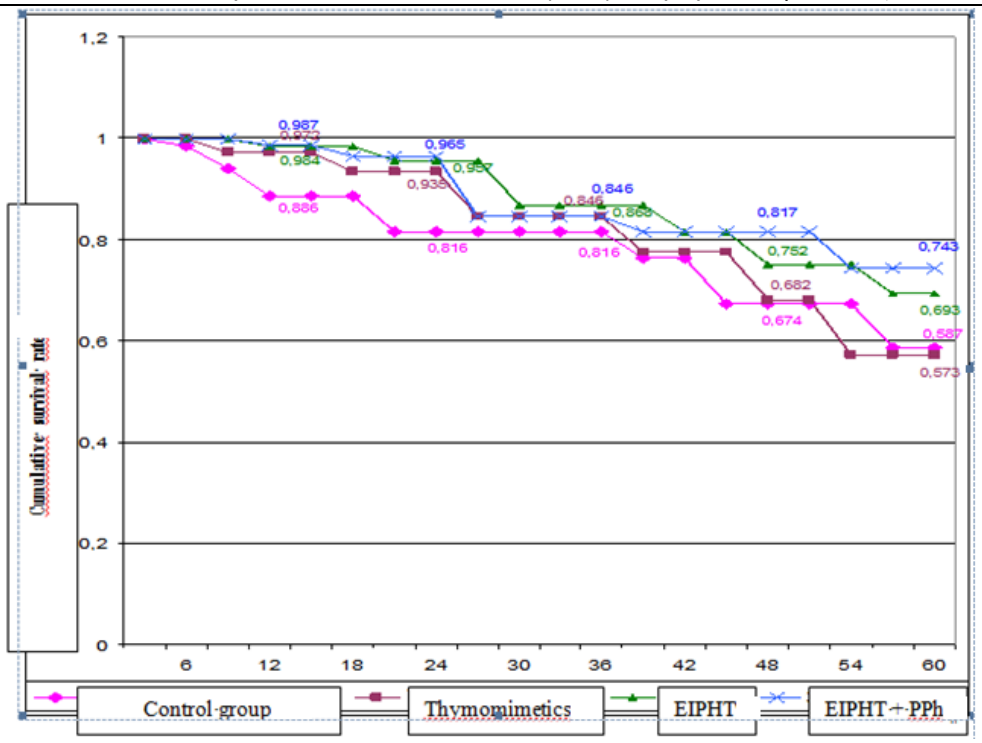


*Figure 1. Comparative evaluation of the total cumulative 5-year survival rate of patients with CC, depending on the type of immunotherapy in complex treatment by Kaplan E.L. et Meier P.*

Further, the analysis of the overall 5-year survival of patients with oncogynecologic diseases after complex therapy in combination with immunotherapy in the group of patients with ovarian cancer was carried out. The analysis also revealed that the lowest level of five-year survival in the 1st group of patients of the control group with no immunotherapy and whose indices turned out to be very low was 62.8±3,6%. Thus, in figure 2 it is shown that in the 2nd group of patients with OC who received thymomimetics, the total cumulative five-year survival was 63.7±4,1% (P=0.032); in the third group of patients with OC receiving EIPHT, this indicator was 81.4±5,1% (P=0.036); and the 4th group of patients with OC consisted of patients who received EIPHT with plasmaphoresis – 81,2±5,3% (P=0.043). The last group of patients as a result of the treatment during chemotherapy and radiation therapy had the highest values of the total cumulative five-year survival.

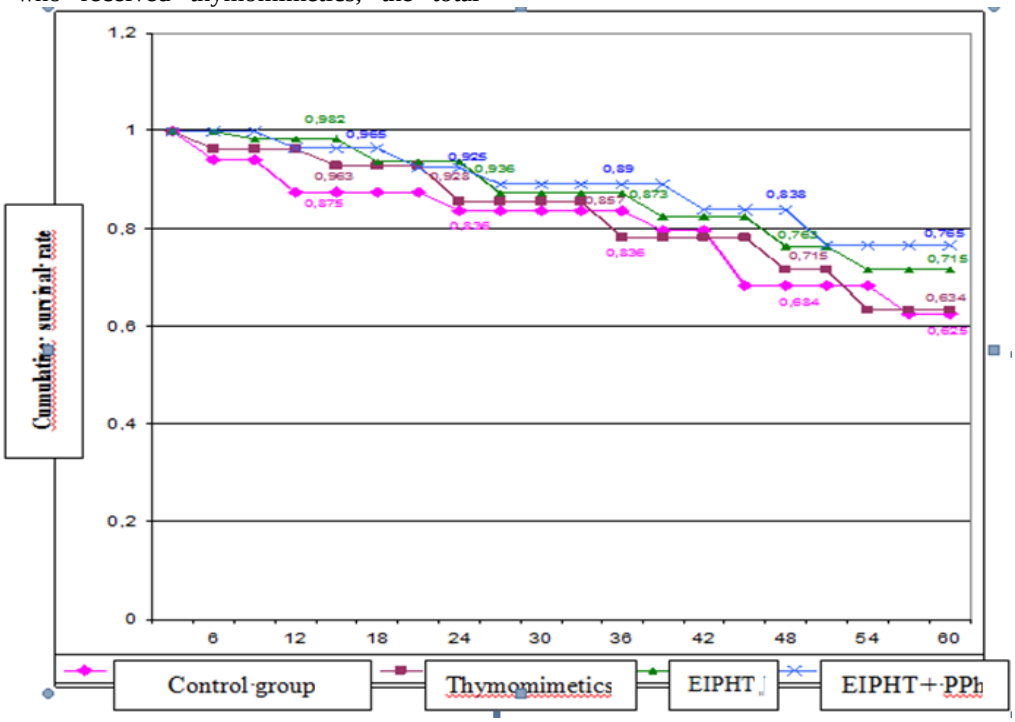


*Figure 2. Comparative evaluation of total cumulative 5-year survival rate of patients with OC depending on the type of immunotherapy in complex treatment by Kaplan E.L. et Meier P.*

Therefore, it is evident that the scheme of immunotherapy including intermittent plasmapheresis with subsequent EIFT, the use of which in complex therapy of oncogynecologic diseases, has made it possible to increase the parameters of five-year general and disease-free survival of patients is the most effective in the complex treatment of patients with cervical cancer and stage II-III.

It should be noted that the EIPHT technique developed and proposed by us has great prospects in oncological practice in connection with the ability to remove the consequences of cancer and chemoradiation intoxication, as well as activate its own system of antitumor protection of the organism [4,7]. This has a positive effect on the outcome of the disease and leads to an increase in the quality and life expectancy of the patient. It is known that multi-course polychemotherapy often leads to suppression of the immune system, including by increasing lymphocyte death, thereby aggravating the course of the disease and forming a deep immunodeficiency [1,2,5]. In addition, based on the results of numerous studies, it has been established that a defect in the functional activity of T-lymphocytes is diagnosed already in the early stages of cancer. Therefore, it seems appropriate to include in the course of treatment immunotherapy, which affects the immune system, as an accompaniment therapy. In turn, thymomimetics, which accompany various approaches to immunotherapy, have a stimulating effect on the state of functional activity of T lymphocytes. It is believed that the effects of immunotherapy are the stimulation and proliferation of T-lymphocytes, natural killers and lymphokine-activated killers [10]. Inclusion of these drugs in the traditional treatment regimen allows not only activation of the immune system, but also improvement of the antitumor response due to direct antiproliferative action on tumor cells due to inhibition of the expression of oncogenes, an increase in the expression of tumor cell membrane antigens and hormone receptors [8,11].

**Conclusion**

Thus, the conducted studies led to the conclusion that the greatest effectiveness in reducing side effects of chemotherapy in the complex treatment of patients with CC and stage II-III stage II, as well as in improving the subjective state of patients and their quality of life, has an immunotherapy scheme that includes intermittent plasmapheresis with subsequent EIPHT, which reduces the main clinical manifestations of toxicity of chemotherapy, improves the indicators of the subjective state of patients and the quality of their life. In addition, the use of EIPHT methods in the complex therapy of oncogynecologic diseases makes it possible to increase the parameters of the five-year total and disease-free survival of patients with cervical cancer and ovarian cancer. EIPHT technique developed by us has great prospects in oncological practice in connection with the possibility to remove the consequences of cancer and chemoradiation intoxication, and also to activate our own system of antitumor protection of the organism, which positively affects the outcome of the disease and leads to an increase in quality and the life expectancy of the patient.

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