AZERBAIJAN REPUBLIC

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ABSTRACT

of the dissertation for the degree of Doctor of Science

ENHANCEMENT OF THE EFFECTIVENESS OF RADIATION THERAPY FOR PATIENTS WITH CERVICAL CANCER USING PERSONALIZED POLYRADIOSENSITIZATION AND INTERSTITIAL ADAPTIVE BRACHYTHERAPY CONSIDERING THE MAIN PROGNOSTIC INDICATORS

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GENERAL DESCRIPTION OF THE WORK

Relevance of the topic. Cervical cancer (CC) is one of the most widespread cancer diseases among women worldwide. According to GLOBOCAN 2018, 570,000 new cases of the disease and 311,000 deaths from cervical cancer were registered in the world, and 1,474,000 patients with cervical cancer were recorded[1]. In most cases (74%), cervical cancer occurs in developing countries, where it accounts for 15% of all cancers in women and is the second most common cause of cancer death, while in developed countries it accounts for 4.4% of new cases[2].

The intensive incidence rate among women of childbearing age for 2018 was 13.1 per 100,000 female population worldwide, being in fourth place after breast cancer, colorectal cancer and lung cancer[3]. In the structure of oncological diseases in the Azerbaijan Republic, cervical cancer among women takes fourth place after breast cancer, colorectal cancer and gastric cancer (extensive indicators are 34%, 7.6%, 7.4%, and 6.8%, respectively). The intensive incidence rate among women of childbearing age in Azerbaijan for 2018 amounted to 6.5 per 100,000 female population, being in third place after breast and stomach cancer, which amounted to 32.7 and 7.3 per 100,000. In 2018– In the current year, 397 women were diagnosed with cervical cancer in our country and 272 died during the same year[4].

Although there is an effective screening program to detect the early stages of the disease, in most cases cervical cancer is diagnosed in a prognostically unfavorable - late, locally advanced stage, so in 35–46% of patients the disease is diagnosed in stage III – IV. In Azerbaijan Republic in 2017, among the newly diagnosed cervical

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[1] International Agency for Research on Cancer, Global Cancer Observatory. GLOBOCAN 2018, http://gco.iarc.fr.

[2]Uşaqlıq boynu və cismi xərçəngi. Dərs vəsaiti / C.Ə.Əliyev [və b.] – Bakı: Təbib, – 2016. – 54 s.

[3]Siegel, R., Miller, K., Jemal, A. Cancer statistics // CA Cancer J Clin, – 2019, 69 (1), – p. 7-34.

[4]Исаев, И.Г. Первый опыт применения двухфракционной адаптивной внутриполостной/внутритканевой брахитерапии в лечении рака шейки матки / И.Г.Исаев, К.С.Акперов, Э.Г.Гулиев [и др.] // Казанский медицинский журнал, – 2018, 99 (2), – с. 336-341.

cancer patients, after examination, 74% of the disease revealed stage IIB - III stage of disease[5].

One of the main causes of cervical cancer is human papillomavirus infection (HPV), which is responsible for more than 95% of cervical tumors[6]. From our point of view, great interest of the study is the significance of HPV infection in predicting the results of chemoradiotherapy of cervical cancer. There is still no data in the literature on the prognostic value of HPV infection and the choice of a particular treatment tactic (using targeted drugs, immunotherapy, cytostatics in conjunction with radiation therapy or standard polychemotherapy), depending on the absence, and if available - the types of HPV infection. Also, there is still no reliable information on the most widespread types of high-risk HPV among the female population in Azerbaijan, which could help determine which polyvalent vaccine is best used in our country.

Today, surgery, radiation therapy, chemotherapy, and their combinations are standardly used in the treatment of cervical cancer[7]. The choice of treatment tactics depends on many factors characterizing the disease: the stage of CC, the size and form of tumor growth, its histological type, the presence of metastases in regional lymph nodes, the risks of complications of surgery or radiation therapy, the general condition of the patient, comorbidities, preferences in choosing a treatment method for the patient herself, and others[8]. Due to the achievements of recent years, today radiation therapy is used in the tre-

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[5]Алиев, Д.А. Сочетанная лучевая терапия рака шейки матки с применением полирадиосенсибилизации цисплатином и гемцитабином – непосредственные результаты исследования национального центра онкологии Азербайджана / Д.А.Алиев, И.Г.Исаев, К.С.Акперов [и др.] // Казанский медицинский журнал, – 2017, 98 (6), – с. 884-889.

[6]Parmin, N. Human Papillomavirus E6 biosensing: Current progression on early detection strategies for cervical Cancer / N. Parmin, U. Hashim, S. Gopinath [et al.] // Int J Biol Macromol, – 2019, №126, – p. 877-890.

[7]Cibula, D. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer / D. Cibula, R. Pötter, F. Planchamp [et al.] // Radiother Oncol, – 2018, 127 (3), – p. 404-416.

[8]Marth, C. ESMO Guidelines Committee. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up / C.Marth, F.Landoni, S. Mahner [et al.] // Ann Oncol, – 2017, 28 (4), – p. 72-83.

atment of the vast majority of patients with cervical cancer as an independent method, and as the main component of combined treatment. In the early stages of cervical cancer (stage I – IIA), definitive radiotherapy can be used as one of the treatment options, and in locally advanced stages of the disease (stage II – IVA), combined radiation therapy is not only the main but more often and the only possible treatment method[9]. As a result, today radiation therapy is an integral part of a number of standard protocols and recommendations for the treatment of cervical cancer, one of which is the leadership of the US - National Comprehensive Cancer Network[10].

In recent years, due to the introduction of modern technologies, appropriate software, and new radiotherapy equipment into clinical use, significant results have been achieved in the direction of individualizing radiation therapy planning for cervical cancer patients[11]. All this was the basis for the development of such highly precise methods of external beam radiation therapy (EBRT) as intensity-modulated radiation therapy (IMRT), volumetric arc therapy (VMAT), stereotactic body radiation therapy (SBRT), stereotactic radiosurgery (SRS), Image-Guided radiation therapy (IGRT) et al. [12] The standard daily dosesare 1.8-2.0 Gy, 5 fractions per week to a maximum total doseof 45-50 Gyto pelvis[13]. In the presence of metastatic lymph nodes, there is a need for an escalation of the total dose up to 60 Gy to the involved nodes (boost). Boost can be performed both sequentially and integrated with EBRT to the whole pelvis. In

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[9]Aghili, M. Concurrent Chemo- Radiobrachytherapy with Cisplatin and Medium Dose Rate Intra- Cavitary Brachytherapy for Locally Advanced Uterine Cervical Cancer / M. Aghili, B. Andalib, Z. Karimi Moghaddam [et al.] // Asian Pac J Cancer Prev, – 2018, 19 (10), – p. 2745-50.

[10]National Comprehensive Cancer Network (NCCN) Guidelines / https://www.nccn.org/

[11] Wang, W. Image-guided, intensity-modulated radiation therapy in definitive radiotherapy for 1433 patients with cervical cancer / W.Wang, F.Zhang, K.Hu [et al.] // Gynecol Oncol, – 2018, 151 (3), – p. 444-448.

[12]Rigaud, B. CBCT-guided evolutive library for cervical adaptive IMRT / B.Rigaud, A.Simon, M.Gobeli [et al.] // Med Phys, – 2018, 45 (4), – p. 1379-1390.

[13]Gelover, E. Patient's specific integration of OAR doses (D2 cc) from EBRT and 3D image-guided brachytherapy for cervical cancer / E. Gelover, C. Katherine, C. Mart [et al.] // J Appl Clin Med Phys, – 2018, 19 (2), – p. 83-92.

recent years, in order to confine a higher dose of radiotherapy to targets and at the same time reduce the dose to organs at risk (small intestine, rectum, bladder, femoral heads, pelvic bones), the simultaneous integrated boost (SIB) method using volumetric Arc therapy (VMAT) on linear accelerators is used[14]. At the same time, the whole pelvis (primary tumor and lymph nodes) receive 25 fractions in a daily doses of 1.8 - 2 Gy, and metastatic lymph nodes - 2.2-2.3 Gy, which in total is 45-50 Gy and 60 Gy, respectively (the equivalent dose of the classic 2 Gy fractionation, EQD2, and the index $\alpha / \beta = 10$ Gy). However, the effectiveness and safety of chemoradiotherapy of cervical cancer using SIB by VMAT has not been sufficiently studied and is one of the objectives of our study[15].

In order to increase the effectiveness of radiation therapy, brachytherapy is used, which allows to deliver higher doses of ionizing radiation directly to the tumor, while minimizing the dose to surrounding healthy organs and tissues. The introduction of 3D imaging techniques such as CT and MRI into the clinic, the development of CT / MRI compatible applicators, as well as the corresponding computer programs - 3D planning systems, ensured the development of image guided adaptive brachytherapy -IGABT[16]. However, during planning brachytherapy based on CT or MRI imaging and using standard intra cavitary applicators, it becomes clear that in most cases it is impossible to cover fullythehigh-risk clinical target volume HRCTV, which includes a residual tumor, cervix, and affected areas, with the prescribed dose of ionizing radiation[17]. In order to increase the dose in the peripheral zones of HRCTV, applicators have been developed that allow

[14]Bacorro, W. Dose-volume effects in pathologic lymph nodes in locally advanced cervical cancer / W.Bacorro, I.Dumas, A.Escande [et al.] // Gynecol Oncol, – 2018, 148 (3), – p. 461-467.

[15] Dang, Y. Efficacy and Toxicity of IMRT-Based Simultaneous Integrated Boost for the Definitive Management of Positive Lymph Nodes in Patients with Cervical Cancer / Y.Dang, P.Li, J.Li [et al.] // J Cancer, – 2019, 10 (5), – p. 1103-1109.

[16]Wu, P. MRI-guided adaptive brachytherapy for locally advanced cervix cancer: Treatment outcomes from a single institution in Hong Kong / P.Wu, T.Wong, Y.Yip [et al.] // Brachytherapy, – 2019, 18 (2), – p. 171-179.

[17] Horne, Z. Single-Institution Experience in 3D MRI-Based Brachytherapy for Cervical Cancer for 239 Women: Can Dose Overcome Poor Response? / Z.Horne, P.Karukonda, R.Kalash [et al.] // Int J Radiat Oncol Biol Phys, – 2019, 104 (1), – p. 157-164.

the insertion of hollow needles into the parametria with the subsequent possibility of loading with a radioactive source[18].

Over the past decade, a variety of methods have been actively developed to study the molecular genetic parameters of the tumor and the results of these studies have substantiated the introduction into clinical practice of radiation treatment of malignant tumors with the goal of radiosensitization with both cytotoxic (gemcitabine, paclitaxel, vinorelbine, etc.) and targeted drugs (cetuximab, sorafenib, erlotinib, lapatinib, etc.). It was found that the effectiveness of these drugs is largely determined by the molecular genetic structure of the cancer cell. It has been proven that the epidermal growth factor gene EGFR, along with KRAS, PIK3CA, RRM1, and other genes, provides signaling from receptors from the cell surface to the nucleus, stimulating the growth, repair, and reproduction of tumor cells[19]. Several studies have been conducted to determine the role of EGFR-KRAS-PIK3CA-RRM1 signaling systems in carcinogenesis of cervical cancer, of which two, conducted in 2014 and 2017, deserve special attention. So, Fukazawa E. et al. after investigation of EGFR, ErbB-2, and COX-2 genes'expression, concluded that the degree of expression of EGFR and COX-2 genes significantly increases with the progression of the process from cervical intraepithelial neoplasia of the first degree to invasive cervical cancer. In a study by Li Q. et al. with cervicitis and cervical cancer, EGFR expression was detected in 10 % and 79,2% of patients with cervicitis and cervical cancer, respectively. Amplification of EGFR was observed in 20.5% and 4.4% with cervical cancer and the inflammatory process[20]. As you

[18] Pötter, R. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies / R. Pötter, K. Tanderup, C. Kirisits [et al.] // Clin Transl Radiat Oncol, – 2018, 11 (9), – p. 48-60.

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know, one of the main mechanisms of action of ionizing radiation and antitumor drugs is damage to the DNA of cells. However, both for reduction and for the synthesis of new DNA, components are required - deoxyribonucleotides, which are formed from the corresponding ribonucleotides upon exposure to the ribonucleotide reductase (RR) enzyme. The molecule of this enzyme consists of two domains - large, catalytic (RRM1) and small, regulatory (RRM2 or RRM2B). Such an important role of RR in DNA synthesis makes it an attractive target for radiosensitization of tumors[21]. Currently, the clinic widely uses a cytotoxic drug that blocks RR - gemcitabine. The radiosensitizing effect of gemcitabine has been shown in several studies. So, Roy et al. adding to the standard chemoradiotherapy of 50 cervical cancer patients weekly infusions of gemcitabine at a dose of 125 mg / m^2 achieved a significant increase in two-year disease-free survival by 10%, and overall survival by 15%, however, a significant increase in early toxicity of treatment was noted[22].

In the literature, data concerning the specific features of the molecular genetic parameters of cervical cancer and the use of radiosensitizing agents depending on these parameters arelimited, studies have been performed in a small number of patients, and it is not possible to use that method based on these data. There is also no reliable information about the prognostic value of the degree of expression and mutations of certain genes, and the choice of appropriate treatment tactics, depending on this.

All above mentioned confirms the topicality of the problem and being a new direction in clinical oncology coming to the basis for the implementation of this study. It should be noted that this work was carried out in conjunction with the study of “The role of molecular genetic biomarkers in the individualized treatment of cancer patients”, carried out at the National Center of Oncology which

[21]Sagawa, M. Ribonucleotide Reductase Catalytic Subunit M1 (RRM1) as a Novel Therapeutic Target in Multiple Myeloma / M. Sagawa, H. Ohguchi, T. Harada [et al.] // Clin Cancer Res, – 2017, 23 (17), – p. 5225-37.

[22]Chen, Y. RRM1 expression and the clinicopathological characteristics of patients with non-small cell lung cancer treated with gemcitabine / Y. Chen, Y. Huang, D. Chen, [et al.] // Onco Targets Ther, – 2018, №11, – p. 5579-89.

wascoordinated by the Fund of Science Development at the President of the Azerbaijan Republic.

The aim of the study - improve the results of concurrent chemoradiotherapy of cervical cancer patients.

Research Objectives:

1.To study the features of the molecular genetic parameters of a tumor in cervical cancer in Azerbaijan and their influence on the results of treatment.

2.To study the role of human papillomavirus infection in cervical cancer in Azerbaijan and its effect on treatment outcomes.

3.To study the effectiveness and safety of combined intracavitary/interstitial brachytherapy in the treatment of locally advanced cervical cancer.

4**.** To study the comparative effectiveness of various schemes of combining radiation therapy with antitumor drugs (polyradiosensitization) in cervical cancer patients.

5.To study the influence of the main prognostic indicators on the results of the treatment of cervical cancer patients.

6.To study the reactions and complications of the combined treatment of cervical cancer patients and to develop methods for the prevention and treatment of these complications.

7.Investigate the quality of life of cervical cancer patients before, during and at various times after treatment.

Methods.

Results of the examination and treatment of 468 patients with IIA - IVA stage cervical cancer who were treated at the National Center of Oncology of the Ministry of Health of Azerbaijan Republic from 2013 to 2018 were analyzed.All patients included in the study were examined according to the standards for cervical cancer: anthropometry was performed, body surface area was calculated; after a clinical examination, the patients underwent a comprehensive laboratory and instrumental examination, which included the study of peripheral blood parameters (general and biochemical analyzes), chest x-ray, rectovaginal and bimanual vaginal examination, colposcopy with biopsy, morphological examination of biopsy samples, pelvic and abdominal ultrasound, MRI / CT scan of the pelvis and

paraaortic lymph nodes.Depending on the treatment tactics, patients were divided into two groups: group 1 (experimental) - patients received combined radiation therapy, consisting of radical radiation therapy and intracavitary/interstitial brachytherapy, in combination with antitumor drugs gemcitabine and cisplatin; group 2 (control) - patients received standard treatment: combined radiation therapy, consisting of radical radiation therapy and intracavitary brachytherapy, in combination with the antitumor drug cisplatin.

The main provisions to be defended.

1.The results of radiation therapy for patients with cervical cancer largely depended on the use of polyradiosensitization and combined intracavitary/interstitial brachytherapy, the presence of PIK3CA mutations and did not depend on HPV infection.

2.The developed technique of concurrent CRT for patients with cervical cancer using radical radiation therapy (volumetric arc therapy (VMAT) and combined intracavitary/interstitial brachytherapy with a high dose rate) and polyradiosensitization with cisplatin and gemcitabine increases the frequency of complete tumor responses, relapse-free and overall survival.

3.The use of combined radiation therapy in combination with polyradiosensitization statistically significant increases the frequency and severity of acute hematological reactions. Conducting symptomatic therapy allow to stop these reactions and complete the planned course of treatment.

Scientific novelty.

For the first time in Azerbaijan, molecular genetic changes were analyzed in cervical cancer. The effectiveness of chemoradiotherapy in combination with various antitumor drugs has been investigated. The effectiveness of radiotherapy was also studied depending on the stage of the disease, the spread of the process, and other clinical and biological data (histology, age, comorbidities, human papillomavirus infection etc.). Moreover, we analyzed the frequency and grade of early radiation toxicities and complications, as well as the toxicity of concurrent chemotherapy and the quality of life of patients according to the EORTC QLQ-C30 criteria (European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire).

Practical significance.

An analysis of molecular genetic changes in cervical cancer in the future will provide to identify groups of patients who could get more benefit from the combined use of certain anticancer drugs.

A comparative study of the results of concurrent chemoradiotherapy in patients with cervical cancer with the use of various radiosensitizers and intracavitary/interstitial brachytherapy made it possible to introduce the most effective and individualized method of radiation therapy into clinical practice.Studies on the effectiveness of various methods of chemoradiotherapy have made it possible to reasonably state targeted treatment regimens for cervical cancer depending on the stage of the disease, the results of pathological and molecular genetic analysis, radiosensitivity of the tumor, and the general condition of patients.

Putting the results of this study into practice will contribute the selection of the optimal method of chemoradiotherapy for cervical cancer patients, which, along with the expected high rates of relapse-free and overall survival, will reduce the number of tactical and clinical mistakes, and ultimately should lead to better results.

Approbation of the dissertation.

The dissertation materials were presented and discussed at the scientific conference "Evidence-based radiation therapy for common types of cancer" - ESTRO, National Center of Oncology of the Ministry of Health of Azerbaijan Republic (Baku, May 2010); VI Congress of Oncologists and Radiologists of the SSSR countries (Dushanbe, 2010); 29th Conference of the European Society of Oncology and Radiotherapy (ESTRO-29, Barcelona, September 2010); American Brachytherapy Society Annual Conference (ABS 2010, Atlanta, April 2010); materials of the completed dissertation were presented and discussed at a joint conference of the departments of radiation therapy, chemotherapy, gynecological oncology, oncohematology of the National Center of Oncology of the Ministry of Health of Azerbaijan Republic (Baku, March 2011); at a meeting of a scientific seminar on approbation of dissertations at the Dissertation Council of the National Center of Oncology of the Ministry of Health of Azerbaijan Republic (Baku, May 2011).

Results of the dissertation are reported and and discussed at the interdepartmental meeting of National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan (February 27, 2020, protocol N1), BED 1.02 Scientific seminar of the Dissertation Council of the Ministry of Health of the Republic of Azerbaijan (June 17, 2021, protocol N1).

The main theoretical and practical provisions of the dissertation are reflected in 54 published scientific papers. Scientific works on the subject have been published both in Azerbaijan (13 articles, 6 theses, 1 textbook, 1 methodical recommendation) and in foreign journals (8 articles, 25 theses).

Applying the results to practice.

The results of the present work are presented in the practical work of the National Center of Oncology (NCO) of the Ministry of Health of the Republic of Azerbaijan. It will be used in the educational process and lectures of the oncology department of the Azerbaijan State Institute of Improvement of Doctors named after Aliyev.

The implementation into practice of the results of this study contributed to the choice of the optimal method of chemoradiation therapy for patients with cervical cancer, which, along with the expected high rates of relapse-free and overall survival, made it possible to reduce the number of tactical and clinical errors, and, as a result, to achieve better results.

The dissertation was performed at the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan.

The structure and volume of the dissertation.

The dissertation materials are presented on 298 pages (499.664 signs) of a computer text and include an introduction (23.340 signs), a literature review (48.868 signs), three chapters of our own research (210.510 signs), conclusions (124.692signs), results (5020 signs), practical recommendations (1006 signs) and a list of references (81803 signs), including 360references. The work is illustrated by 53 tables and 84 figures**.**

MATERIAL AND METHODS OF THE RESEARCH

The basis for the implementation of this study was the results of the examination and treatment of 468 patients with cervical cancer IIA - IVA stage who were treated at the National Center of Oncology of the Ministry of Health of Azerbaijan Republic from 2013 to 2018.

The average age of the patients was 52.4 years (31 - 78). Most patients (54.1%) were between 40 and 60 years old. All patients included in the study were examined according to the standards for cervical cancer: anthropometry was performed, body surface area was calculated; after a clinical examination, the patients underwent a comprehensive laboratory and instrumental examination, which included the study of peripheral blood parameters (general and biochemical analyzes), chest x-ray, rectovaginal and bimanual vaginal examination, colposcopy with biopsy, morphological examination of biopsy samples, pelvic and abdominal ultrasound, MRI / CT scan of the pelvis and paraaortic lymph nodes.

The clinical study included patients with the following criteria: age 18 years and older, morphologically verified diagnosis of cervical cancer, stage IIA – IVA cervical cancer, general condition according to the WHO / ECOG scale: 0–2, according to the Karnowski scale ≥ 50, satisfactory peripheral blood parameters: hemoglobin $\geq$ 100 g / l (with or without blood transfusion), white blood cells $\geq 4 \times$ 109 / l, neutrophils $\geq 1.5 \times 109$ / l, platelets $\geq 130 \times 109$ / l, creatinine ≤ 120 mmol / l. The study protocol did not include patients: with a history of any type of malignant process, with the exception of the underlying disease (cervical cancer), who had previously received specific antitumor treatment, had distant metastases, pregnant women, breast-feeding, and severe comorbid diseases.

The general condition of patients on the WHO / ECOG scale was 0 points in 249 (53.2%), 1 - in 147 (31.4%), 2 - in 72 (15.4%) patients. Most patients (77.8%) at the time of treatment had cervical cancer IIB and IIIB stages. A morphological study revealed 428 (91.5%) cases of squamous cell carcinoma, 23 (4.9%) cases of adenocarcinomas, and 17 (3.6%) cases of anaplastic cancer. As can be seen from the figures, squamous cell carcinoma of varying degrees of

differentiation predominated in the analyzed material.

Depending on the treatment tactics, patients were divided into two groups:

-Group 1 (experimental) - patients received combined radiation therapy, consisting of radical radiation therapy and intracavitary/interstitial brachytherapy, in combination with antitumor drugs gemcitabine and cisplatin

-Group 2 (control) - patients received standard treatment: combined radiation therapy, consisting of radical radiation therapy and intracavitary brachytherapy, in combination with the antitumor drug cisplatin.

The distribution of patients in groups I and II was carried out by the method of fixed block randomization.

Group I included 236 patients whose average age was 51.8 years (from 31 to 71 years). As a result of the examination of cervical cancer, stage IIA was determined in 29 (12.3%) cases, IIB - in 103 (43.6%), IIIA - 9 (3.8%), IIIB - 88 (37.3%), IVA - in 7 (3%) cases, respectively. A histological examination revealed squamous cell carcinoma in 217 (92%), adenocarcinoma in 9 (3.8%) and undifferentiated cancer in 10 (4.2%) patients. Tumor size <5 cm was established in 98 (41.5%), and ≥ 5 cm in 138 (58.5%) cases. Metastases of regional lymph nodes were determined in 42 (17.8%) patients. The distribution of patients in general condition before treatment in this group was: 0 points - 131 (55.5%), 1 point - 62 (26.3%), 2 points - 43 (18.2%) people, respectively.

Group II included 232 patients whose average age was 54.3 years (from 35 to 69 years). As a result of the examination of cervical cancer, stage IIA was determined in 42 (18.1%) cases, IIB - 91 (39.2%), IIIA - 12 (5.2%), IIIB - 82 (35.1%) and IVA - in 5 (2.2%) cases, respectively. A histological examination revealed squamous cell carcinoma in 211 (90.9%), adenocarcinoma in 14 (6%) and undifferentiated cancer in 7 (3.1%) patients. Tumor size <5 cm was established in 107 (46.1%), and ≥ 5 cm in 125 (53.9%) cases. Metastases of regional lymph nodes were determined in 56 (24.1%) patients. The distribution of patients according to the general condition before the start of treatment in this group was: 0 points -

118 (50.9%), 1 point - 85 (36.6%), 2 points - 29 (12.5%) people, respectively.

Mostly exophytic growth of tumor was observed in 22.4%, endophytic in 31%, mixed exo-endophytic in 46.6% of cases.

The EBRT regimens were the same in both groups. Planning of EBRT was carried out using computer tomography (CT) simulation. A dose per fraction on PTV was 1.8–2.0 Gy, once a day, 5 times a week, with total doses of 45–50 Gy. Dose calculation was performed using the ECLIPSE planning system. In the case of metastases of the regional lymph nodes, we assigned simultaneously integrated boost (SIB) 2.3 Gy per fraction to the metastatic lymph nodes with a total dose of 57.5 Gy, which corresponds to 60 Gy by isoeffect. This method allowed to reduce the treatment time by an average of 10 days (in the case of a sequential boost of 1.8 - 2.0 Gy to 14 - 16 Gy).

Patients in the control group received intravenous infusions of cisplatin in a standard dose of 40 mg / m2 (maximum 70 mg) once a week, 5 weeks (5 infusions in total). In order to reduce the nephrotoxicity of the drug, hyperhydration (1.5 liters iv) was performed. Patients of the experimental group underwent concurent chemotherapy, but in this group we used the method of polyradiosensitization by introducing two cytostatic drugs - cisplatin and gemcitabine. Identically to the control group, cisplatin was administered in a standard dose of 40 mg / m2 (maximum 70 mg) once a week, 5 weeks (5 infusions in total). Additionally, to increase the radiosensitivity of the tumor, patients in this group also received weekly gemcitabine infusions. Gemcitabine was administered intravenously, drip, simultaneously with cisplatin at a dose of 75 mg / m2 once a week, 5 weeks (5 infusions in total).

All patients at the 5th week of treatment underwent a second pelvic MRI examination to determine the residual tumor and the borders of the high risk volume (HRCTV, high risk clinical target volume), which includes a residual tumor, cervix, and affected areas of the parametrium in order to prepare for brachytherapy (adaptive brachytherapy). For brachytherapy, a 24-channel afterloading system machine with a high-dose rate 192Ir radiation source was used, dose per fraction was 7 Gy, twice a week, only 4 fractions with total dose

of 28 Gy. The procedure for introducing intracavitary ring applicators of the ring / tandem type together with the parametric needles was performed under general intravenous and / or spinal anesthesia. Using transrectal ultrasound control, the intrauterine part of the applicator (metrostat, tandem) was inserted into the uterus. After visualization (ultrasound confirmation), the vaginal part of the applicator (colpostat, ring) was installed and fixed in the correct position of the metrostat. For interstitial brachytherapy (the first group), a special colpostat was used with channels along the periphery through which interstitial needles were subsequently drawn. The dose was assigned to the volume of HRCTV, which was contoured on a series of MRI (in T2 mode) images with an applicator and needles in place. Brachytherapy planning was done using the Brachyvision 3D planning system.

The total dose of brachytherapy was 28 Gy (4x7 Gy), and the total dose of EBRT was 45 Gy, but taking into account the radiobiological aspects, the total equivalent dose fractionation (EQD2) for the tumor (α / β 10) and late-reacting tissues (α / β 3) was 83,9Gy and 99.2 Gy, respectively.

To determine the PIK3CA gene mutations, the method of parallel sequencing of single-stranded sets of fragmented DNA of analyzed tissue samples was used. The studies were carried out in the molecular genetics laboratory of the National Center of Oncology using equipment (sequencer) with high throughput produced by Thermo Fisher Scientific.

To assess the therapeutic efficacy and side effects of the treatment, we used the following criteria: immediate treatment results, survival rates (relapse-free and overall survival), quality of life, toxic effects of treatment, results of molecular genetic analyses.

Immediate treatment results were evaluated according to the RECIST criteria. To evaluate the reactions and complications of treatment, we used the RTOG / EORTC classification "Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) and the US National Cancer Institute (Common Terminology Criteria for Adverse Events v3 .0- CTCAE V3.0). The quality of life (QOL) of

patients was studied using a questionnaire approved by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - EORTC QLQ-C30.

In the statistical processing of data, we adhered to general recommendations for medical research by determining the arithmetic mean (M), standard deviation (SD), the error of the mean (m), median (Me), 95% confidence interval, for qualitative data - frequency (%) and standard error. Differences were considered statistically significant at $p < 0.05$ (95% significance level) and $p < 0.01$ (99% significance level). The student's test was used with adjusted for Bonferroni. Survival analysis was performed according to the Kaplan – Meyer method. Statistical processing of the obtained data was carried out using Microsoft Excel and SPSS 15.0 in the Windows 10 operating system.

RESULTS AND DISCUSSION

Immediate results of the treatment of cervical cancer patients.

466 patients out of 468 successfully completed the planned course of combined radiation therapy and fully received the prescribed doses of both EBRT and brachytherapy.

In the first group, 88 (37.4%) patients out of 236 who subjected to chemoradiotherapy with polyradiosensitization received all 5 infusions of gemcitabine; due to the development of thrombocytopenia, neutropenia, anemia, grade III and IV diarrhea, renal failure and other acute complications 92 (38.9%) patients received 4 infusions, 32 patients (13.6%) were limited to only three gemcitabine infusions, 24 (10.1%) - with only two gemcitabine infusions. The median number of gemcitabine infusions was - 4 (from 2 to 5). In the same group, 140 (59.2%) patients out of 236 treated by chemoradiotherapy with polyradiosensitization received all 5 infusions of cisplatin, 64 (27.2%) patients received 4 infusions of cisplatin; 29 patients (12.3%) were limited to three cisplatin infusions; and only 3 (1.3%) patients received two infusions of cisplatin. The median of the number of cisplatin infusions in the first group was 5 (from 2 to 5).

In the second group, 149 (64.2%) of the 232 patients treated by ChemoRT with cisplatin alone received all 5 cisplatin infusions, 62 (26.7%) patients received 4 cisplatin infusions; 15 patients (6.5%) were limited to three infusions of cisplatin; and only 4 (1.7%) patients received two infusions of cisplatin; two patients (0.9%) underwent 6 cisplatin infusions due to the extension of treatment time regarding the holiday weekend in the clinic. The median of the number of cisplatin infusions in the first group was - 5 (ranging from 2 to 6). While comparing the number of courses of competitive chemotherapy, despite the expected higher toxicity of polyradiosensitization, we did not reveal a statistically significant difference between the groups.

Table 1 shows a comparative analysis of the frequency and degree of tumor response in groups. As can be seen from the table in group I (ChemoRT with polyradiosensitization), complete tumor response was observed in 226 (96%) cases, partial response in 9 (3.6%), and the progression of the process was only in 1 (0.4%) case. The stabilization of the process in this group was not observed. In group II (ChemoRT in the classical mode), complete tumor response tumors were noted in 201 (86.6%) cases, partial response in 23 (9.9%), stabilization of the process in 7 (3%) cases, and progression of the process only in 1 (0.5%) case.

Table 1

Comparative assessment of the frequency and degree of tumor response depending on the treatment method

Group	Complete regression		Partial regression		Stabilisation		Progression		Total
	n	%	n	%	n	%	n	%	n (%)
I	226	96*	9	3,6*	0	0	1	0,4	236 (100%)
II	201	86,6*	23	9,9*	7	3	1	0,5	232 (100%)
Cəmi	427	91,2	32	6,8	7	1,5	2	0,5	468 (100%)

*the differences are statistically reliable ($p<0,05$)

During analyzing the objective effect of treatment (OE, the sum of complete and partial responee), the following was revealed: in the first group, the objective effect was obtained in 99.6% of cases, and in the standard ChemoRT group - in 96.5%; while in the group of polyradiosensitization a large proportion of complete response was noted. Thus, in comparison with group II in concurrentchemoradiotherapy group (group I) immediate results were statistically significantly better obtained**.**

Totally 428 patients received treatment with squamous cell cervical cancer. An objective effect was noted in 421 (98.3%) cases. 392 (91.6%) of these patients had complete response, and 29 (6.8%) had partial response. Stabilization of the process with this type of tumor was observed in 6 (1.4%) patients. Disease progression was observed only in one (0.2%) case. In the group of patients who received ChemoRT with polyradiosensitization (217 patients), OE was observed in 216 (99.4%) cases. Complete regression of the tumor was observed in 208 (95.8%) of these cases, partial regression - in 8 (3.6%). Stabilization of the disease was not observed in this subgroup of patients. Progression of the process during this treatment was noted only in one (0.6%) case.

Among patients with squamous cell cervical cancer who received standard ChemoRT (211 patients), an objective effect was observed in 205 (97.1%) cases. Complete response of tumors was observed in 184 (87.2%) of these cases, partial response - in 21 (9.9%). Stabilization of the process during this treatment was noted in 6 (2.9%) cases. Disease progression in this subgroup of patients was not observed.

The results demonstrate the high efficiency of ChemoRT with polyradiosensitization in locally advanced squamous cell cervical cancer, which is seen when comparing the frequency of complete tumor response in the first group with the standard ChemoRT group (group II).

In total, 23 patients with cervical adenocarcinoma received treatment. OE was noted in 21 (91.3%) cases. 18 (78.2%) of these patients had complete response, and a partial response was observed in 3 (13%) patients. Stabilization of the process with this type of tumor was observed in one (4.4%) patient. Disease progression was obser-

ved in 4 (4.4%) patients. As can be seen from the figures, the results of the treatment of patients with adenocarcinoma were significantly worse than in patients with squamous cell cervical cancer ($p = 0.041$). Moreover, the results of treatment of patients with cervical adenocarcinoma in the first group (although not reliably, possibly due to the small number of patients, $p = 0.184$) were better than in the standard ChemoRT group: for example, an objective response was achieved in the first and second groups in 100% and 85.7% of cases, respectively.

Thus, an analysis of the effectiveness of the studied and control treatment regimens for cervical cancer IIA - IVA stages depending on the histological type of the tumor revealed the advantage of combined ChemoRT with concurrent poly-chemotherapy over standard chemoradiotherapy. Moreover, with the squamous cell form of the disease, this advantage was statistically significant ($p <0.05$). Polyradiosensitization in cases of adenocarcinoma also led to an increase in the frequency of OE, however, the difference was not significant.

We also carried out a comparative analysis of the direct results of cervical cancer treatment depending on the form of tumor growth. So, out of 105 patients with exophytic tumors, 103 (98%) observed complete tumor response and 2 (2%) partial response. The stabilization and progression of the process were not observed in this subgroup of patients.

An analysis of the direct results, depending on the form of tumor growth, revealed that the number of complete responses is significantly higher with exophytic cervical cancer (98%) than with endophytic and mixed growth of cervical cancer (89.2%). However, among patients with endophytic and mixed forms of tumor growth in the group of radiosensitization (group I), complete response was noted much more often than in the standard ChemoRT group (group II). We also analyzed the results of treatment depending on the form of tumor growth and the method of chemoradiotherapy. So, there were no significant differences between the groups with exophytic tumors. However, among patients with endophytic and mixed forms of tumor growth, the immediate results of treatment in the first group (polyradiosensitization) were significantly (reliably) better than in the standard chemoradiotherapy group ($p = 0.013$).

Also was performed a comparative analysis of the results of treat-

ment depending on the size of the primary tumor. From the 205 patients with the initial tumor size <5 cm, 199 (97.1%) showed complete regression of the tumor, 5 (2.4%) showed partial regression, and only in one case did the process stabilize. There was no progression of the process in this subgroup of patients. The number of complete responses in the first group was greater than in the standard ChemoRT group, although the difference was not statistically significant.

From the 263 patients with an initial tumor size ≥ 5 cm, complete response was achieved in 228 (86.6%), partial response in 27 (10.3%), and in 6 (2.3%) stabilization of the process, and only in one - the progression of the process.

We also analyzed the results of treatment depending on the size of the tumor and the method of chemoradiotherapy. So, with a tumor size <5 cm, was not determined significant differences between the groups. However, with a tumor size ≥ 5 cm, the immediate treatment results in the first group (polyradiosensitization) were significantly (reliably) better than in the standard chemoradiotherapy group ($p = 0.013$).

Thus, as can be seen from the above data, chemoradiotherapy with polyradiosensitization compared with standard chemoradiotherapy improved the immediate results of treatment of patients with locally advanced cervical cancer ($p < 0.05$), which is especially noticeable with such unfavorable factors as adenocarcinoma, endophytic and mixed forms of tumor growth, primary tumor sizes ≥ 5 cm.

According to the results of molecular genetic analysis, totally of 205 (43.8%) out of the 468 patients included in the study revealed PIK3CA mutations. In the first group 109 (46.2%) patients, in the second group - 96 (41.4%) patients were with detectable PIK3CA mutations.

We also analyzed the immediate results of treatment depending on the status of the PIK3CA gene. For the convenience of comparison, we divided all patients into two groups: with and without identified PIK3CA mutations.

In the group of patients with detectable PIK3CA mutations 174 cases (84.8%) achieved complete tumor regression, 23 cases (11.2%) achieved partial regression, 6 cases (2, 9%) - stabilization of the process and 2 cases (1.1%) developed tumor progression. Among patients, without detectable PIK3CA mutations, 253 cases (96.2%) deve-

loped complete tumor regression, 9 cases (3.4%) observed partial regression, only one case (0.4%) - stabilization of the process. Tumor progression was not observed in this group of patients.

Statistical processing of the obtained data by non-parametric analysis of two independent samples (Mann-Whitney and Wilcoxon tests) revealed reliable differences with significantly better immediate treatment results in the group of patients without PIK3CA mutations ($p = 0.001$). So, among patients with PIK3CA mutations, complete tumor response was achieved in 174 cases (84.8%), while among patients without PIK3CA mutations, complete tumor response was achieved in 253 cases (96.2%), which was much more. Thus, in our study, the presence of PIK3CA mutations was an unfavorable factor that significantly worsened the results of chemoradiotherapy of locally advanced forms of cervical cancer.

We also analyzed the treatment results depending on the presence of PIK3CA mutations in cervical cancer and the method of chemoradiotherapy. So, among patients without detectable PIK3CA mutations, no significant differences between the groups were determined. The number of patients with complete tumor regression was 98.4% and 94.1% in the first and second groups, respectively.

However, during analyzing the results of treatment depending on the method of chemoradiotherapy was found that among patients with PIK3CA mutations, complete regression of the tumor was achieved in 92.6% and 76% of cases in the first and second groups, respectively. The immediate treatment results in the first group (polyradiosensitization) were significantly (reliably) better than in the standard chemoradiotherapy group ($p = 0.011$). Thus, in our study, the presence of PIK3CA mutations was an unfavorable factor that significantly worsened the results of chemoradiotherapy of locally advanced cervical cancer. However, as can be seen from the above data, chemoradiotherapy with polyradiosensitization compared with standard chemoradiotherapy increased the direct results of treatment of a prognostically unfavorable group of patients with locally advanced cervical cancer with PIK3CA gene mutations ($p <0.05$).

According to the results of biochemical analyses carried out by the above-mentioned methodology, a total of 294 (62.8%) samples from

468 included in the study revealed an HPV infection. HPV type 16 was determined in 237 (80.6%) cases and HPV of type 18 - in 57 cases (19.4%). At the same time, both types of viruses (16 and 18) were determined in 28 patients (9.5%) simultaneously. We also analyzed the immediate results of treatment, depending on the status of the HPV infection. For the convenience of comparison, we divided all patients into two groups: with and without detectable HPV infection.

In a group of patients with detected HPV infection, in 272 cases (92.5%) was achieved a complete regression of the tumor, in 18 cases (6.1%) - a partial regression, in 2 cases (2,9%) - stabilization of the process and in 2 cases (1.1%) - tumor progression developed. Among the patients without a detectable HPV infection, in 155 cases (89.5%) it was possible to achieve complete tumor regression, in 14 cases (8.1%) - partial regression, in 5 cases (2.4%)) - stabilization of the process. Tumor progression was not observed in this group of patients.

We also analyzed the treatment results depending on the presence of HPV infection in invasive cervical cancer and the method of chemoradiotherapy. Among the patients of the first group (polyradiosensitization) in whom HPV infection was not detected, in 86 cases (94.5%) it was possible to achieve complete tumor regression, in 5 cases (5.5%) - partial regression, stabilization of the process and tumor progression was not observed in this group of patients. Among patients of the second group (standard chemoradiotherapy) who did not have an HPV infection, in 69 cases (83.2%) they managed to achieve complete tumor regression, in 9 cases (10.7%) - partial regression, in 5 cases (6.1%) - stabilization of the process. Tumor progression was not observed in this group of patients.

Among patients with detected HPV infection in the first group (polyradiosensitization), complete regression of the tumor was achieved in 140 cases (96.6%), in 4 cases (2.8%) was achieved partial regression, and only in one case (0,6%), tumor progression was observed. The stabilization of the process in this group of patients was not observed. Among the patients of the second group (standard chemoradiotherapy) who were diagnosed with HPV infection, in 132 cases (88.6%) it was possible to achieve complete tumor regression, in 14 cases (9.4%) partial regression, in 2 in cases (1.3%) - stabilization of

the process and in one case (0.7%) tumor progression was observed.

Statistical processing of the obtained data by non-parametric analysis of two independent samples (Mann-Whitney and Wilcoxon tests) did not reveal a significant difference in the direct results in the groups of patients depending on the presence of HPV infection ($p = 0.357$). Thus, in our study, the presence of HPV infection did not affect the results of chemoradiotherapy of locally common forms of cervical cancer.

To evaluate the effectiveness of combined intracavitary/interstitial, a comparative analysis of the results of the treatment of locally advanced cervical cancer using intracavitary and interstitial brachytherapy was performed. For brachytherapy was used a 24-channel afterloading system apparatus with a radiation source of 192Ir high dose rate, dose per fraction was 7 Gy, 2 times a week, only 4 fractions up to total dose - 28 Gy; the dose was assigned to the HRCTV volume, which was contoured on a series of MRI images with an applicator in place. In order to improve the visualizations both the tumor and the cervix and the applicators with or without needles, MRI scans were performed in the transversal plane perpendicular to the colpostat and the axis of the cervix (parallel to the plane of the annular part of the applicator) in T2 mode. The total doses of EBRT and brachytherapy were calculated using a linear-quadratic model taking into account α/β 10 Gy for the tumor and the early effects of radiation therapy, and α/β 3 Gy for late-reacting tissues.

In the intracavitary brachytherapy group, the average dose to HRCTV (D90 HRCTV - the average dose covering 90% of the high-risk volume) was 79.2 Gy (standard deviation of 12 Gy) when recalculated to classical fractionation of 2 Gy (EQD2). In the interstitial brachytherapy group, the average dose to HRCTV due to the use of interstitial needles was significantly higher and amounted to 88.7 Gy with a standard deviation of 8 Gy (EQD2; $p < 0.05$). During the application, 2 to 6 needles were injected into the parametrical tissue, most often 4.

Survival rates for cervical cancer patients after treatment.

The median follow-up was 29 months (3–73 months). The mean follow-up was 31.6 months (standard deviation 17.2). As a result of treatment, a complete remission of the disease was achieved in

only 427 (91.2%) patients. The relapse of the disease was recorded in 89 (20.8%) cases. Of these, locoregional relapse (LRR) was detected in 34 (38.2%) cases, distant metastases (DM) - in 55 (61.8%), combined relapses with both locoregional relapse and distant metastases at the same time - in 9 (10.1%) -, in 46 cases (51.7%) only distant metastases were observed. The most frequent localizations of metastases were paraaortic lymph nodes (11 cases; 20%), bones (16 cases; 29.1%), lungs (9 cases; 16.4%), mediastinal lymph nodes (5 cases; 9.1%) , supraclavicular lymph nodes (8 cases; 14.5%), multiple (6 cases; 10.9%).

Among patients of the first group (CRT with polyradiosensitization and interstitial HDRBt brachytherapy), complete response was observed in 226 cases (96%). In 37 (16.4%) of these patients, was established a relapse of the disease. In 12 (32.4%) cases, there were locoregional relapses in the pelvis, in 25 (67.6%) cases - distant metastases, and in 3 (8.1%) cases - combined relapses.

In the second group (classical CRT), a complete response was observed in 201 cases (86.6%). In 52 (25.9%) of these patients, was established a relapse. In 22 (42.3%) cases, there were locoregional relapses in the pelvis, in 30 (57.7%) cases - distant metastases, and in 6 (11.5%) cases - combined relapses.

As can be seen from the above data, the recurrence rate was significantly higher in the second group (standard chemoradiotherapy) compared with the experimental group: 52 (25.9%) and 37 (16.4%) cases, respectively ($p \leq 0.005$).

The obtained figures revealed a significant decrease in the likelihood of locoregional relapse in the first group compared with the second: 32.4% (12 patients) and 42.3% (22 patients), respectively. This fact was probably due to the interstitial component of brachytherapy, which allowed a significant increase in the dose of ionizing radiation in the area of the primary tumor, the use of a simultaneous integrated boost during EBRT for metastatic regional lymph nodes, as well as an additional increase in the sensitivity of the tumor to radiation therapy using polyradiosensitization.

Loco-regional disease free survival (LCDFS) by years after treatment for all patients with complete response was: by the end of the

first year - 88%, two-year LCDFS - 82%, three-year DFS - 77%, 5-year-old LCDFS - 74%. When analyzing the loco-regional disease-free survival depending on the treatment method, the following were revealed: annual, two-, three- and five-year LCDFS survival rates were respectively, in the first group - 95.2%, 87.4%, 83.2% and 80.7%, in the second group - 90.5%, 78.8%, 72.1% and 67.2%, respectively (Fig. 1).

Thus, a comparative analysis of indicators of loco-regional disease-free survival showed that the effectiveness of treatment of patients with locally advanced cervical cancer IIA - IVA stages increase with the simultaneous use of cisplatin and gemcitabine as a radiomodifying agent and interstitial brachytherapy compared to standard chemoradiotherapy ($p = 0.029$) . It should also be noted that distant metastasis and local relapses were more common in the standard chemoradiotherapy group than in the polyradiosensitization group.

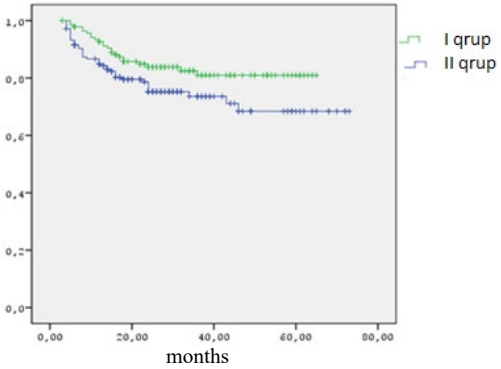

Fig. 1. Loco-regional disease-free survival of patients with locally advanced cervical cancer, depending on the treatment method.

The analysis of loco-regional disease-free survival depending on the presence of metastases in regional lymph nodes revealed the following: annual, two-, three- and five-years LCDFS survival rates were 93.8%, 88.4%, 86.6% and 83.1% in the absence of metastases in regional lymph nodes , and 87.2%, 78.7%, 72.1% and 68.4% in the presence of metastases in the regional lymph nodes. Thus, the

presence of metastatic regional lymph nodes was an unfavorable factor that significantly worsened the treatment results. However, with a more detailed study of relapse-free survival among patients with metastases in regional lymph nodes, we found that the treatment results were significantly better in the group of radiosensitization than in the standard chemoradiotherapy group (see Fig. 2).

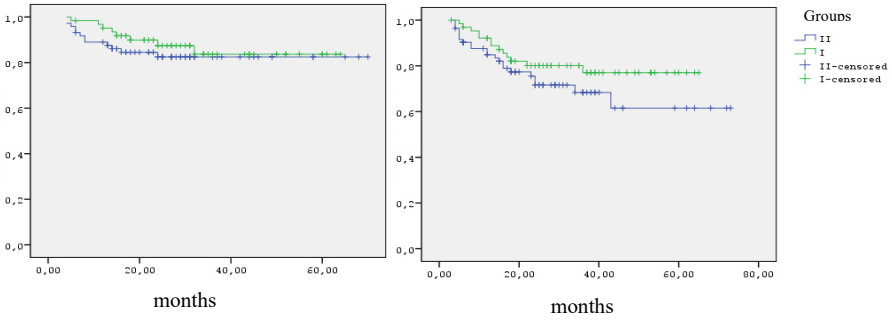

Fig. 2. Loco-regional disease-free survival of patients with locally advanced cervical cancer in the absence of (A) and presence of (B) metastases in regional lymph nodes, depending on the treatment method.

Overall survival (OS) for all 468 patients included in the study by the end of the first year was 92%, two-year OS - 82%, three-year OS - 75%, 5-year OS - 66%. When analyzing the overall survival depending on the treatment method, the following was revealed: annual, two, three, and five-year OS, in the first group - 96.7%, 89.4%, 87.2%, and 76.1%, in the second group - 91.5%, 79.9%, 70.3%, and 62.4% respectively (see Fig. 3).

So, a comparative analysis of overall survival data showed that the effectiveness of the treatment of patients with locally advanced cervical cancer IIA - IVA stages increase with the simultaneous use of cisplatin and gemcitabine as a radiomodifying agent and interstitial brachytherapy compared to standard chemoradiotherapy ($p < 0.05$).

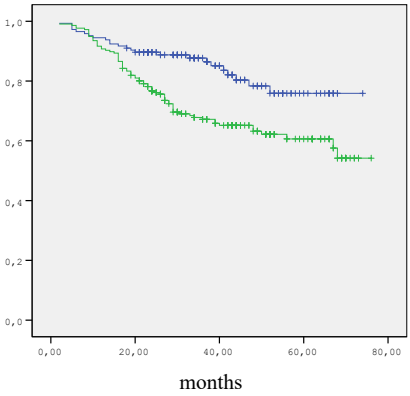

Fig. 3.Overall survival of patients depending on the method of treatment.

In a comparative analysis of overall survival depending on the treatment method, we analyzed and compared the performance of patients with IIB and IIIB stages of cervical cancer due to the fact that in the majority of patients (78%), cervical cancer was diagnosed in these stages. The analysis of overall survival depending on the stage of the disease revealed the following: annual, two-, three- and five-year OS survival rates were 95.1%, 90.7%, 84.1% and 78.4% for stage IIB cervical cancer and 92.3%, 81.2%, 76.3% and 64.5% for stage IIIB cervical cancer, respectively. According to the obtained OS results, survival was significantly better in stage IIB cervical cancer than in stage IIIB ($p < 0.05$) (see Fig. 4).

We also conducted a comparative analysis of overall survival rates depending on the status of human papillomavirus (HPV 16 and 18). The analysis of overall survival, depending on the presence of HPV 16/18 infection, revealed the following: annual, two-, three-, and five-year survival rates were 91.7%, 81.9%, 79.6%, and 71.4% in the absence of HPV 16/18 infection and 91.6%, 80.6%, 73.7% and 64.1% in the presence of HPV 16/18 infection. As can be seen from the above data, there was no statistically significant difference between the curves ($p = 0.494$). So, our results did not reveal a significant difference in the overall survival rates depending on the presence of HPV 16/18 infection in locally advanced cervical cancer (see Fig. 5).

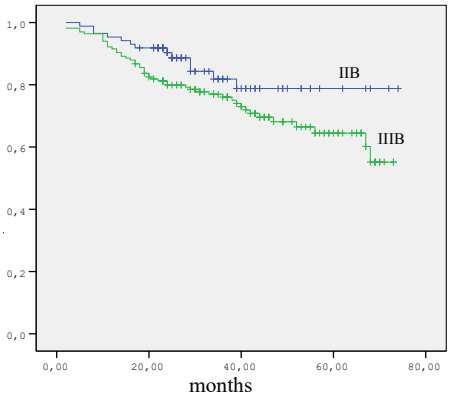

Fig. 4.Overall survival of patients depending on the stage of cervical cancer.

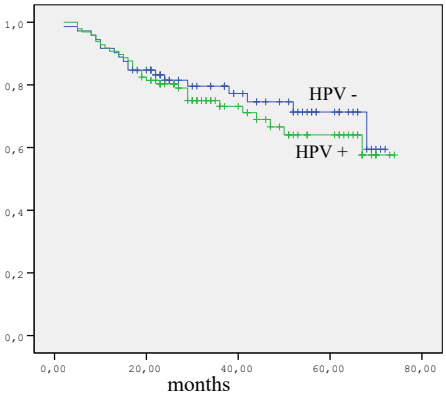

Fig. 5. The overall survival of patients with locally advanced cervical cancer depending on the human papillomavirus (HPV 16/18) infection.

The analysis of overall survival depending on the presence of mutations in the PIK3CA gene revealed the following: annual, two-, three-, and five-year survival rates were 92.5%, 81.2%, 75.2%, and 70.1% in the absence of mutations in the PIK3CA gene and 91.3%, 82.4%, 76.5% and 63.7% in the presence of mutations in the PIK3-CA gene. Although overall survival rates were lower among patients with mutations in the PIK3CA gene, there was no statistically signifi-

cant difference between the curves (p> 0.05). Thus, our results did not reveal a significant difference in the overall survival indices depending on the presence of mutations in the PIK3CA gene in locally advanced cervical cancer (see Fig. 6).

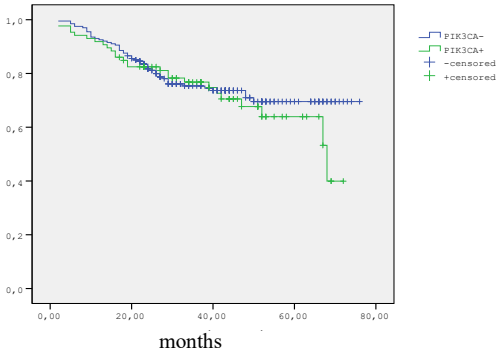

Fig. 6. The overall survival of patients with locally advanced cervical cancer depending on the presence of mutations in the PIK3CA gene.

Reactions and complications of radiation therapy of patients with cervical cancer.

One of the most common early reactions was hematologic toxicity, which was caused using concurrent chemotherapy in both groups of patients. In order to evaluate hematological toxicity, we performed a comparative analysis of the content of hemoglobin, leukocytes, neutrophils and platelets in the peripheral blood before, during, and immediately after treatment (the lowest values were recorded).Acute hematologic toxicity was determined according to RTOG criteria. The average concentration of hemoglobin at the time of admission to the hospital was 116.5 g/l in group I (SD - 17.2), in group II - 121.8 g/l (SD - 19.3). The average of the minimum values were: in group I - 88.4 g/l (SD - 11.7), in group II - 94.3 g/l (SD - 13.1). In 278 (59.4%) patients, anemia of different degree was observed. Moreover, 140 (29.9%) patients developed grade I anemia, 111 (23.7%) grade II, 26 (5.6%) grade III anemia, and only in one case (0.2%) - IV degree according to RTOG Acute Toxicity Criteria. Anemia developed not only due to chemotherapy but also as a result of prolon-

ged and/or heavy bleeding from the genital tract.In all cases, grade III–IV anemia was eliminated by blood transfusion and did not cause treatment interruption.In group I, 155 (65.7%) patients had anemia of varying degrees.Grade I, II, III, and IV anemia occurred in 89 (37.7%), 49 (20.8%), 16 (6.8%), and 1 (0.4%) cases, respectively. In group II, anemia of varying degrees was observed in 123 (53%) patients. Grade I, II, and III anemia was observed in 51 (22%), 62 (26.7%), and 10 (4.3%) cases, respectively. When comparing the incidence and severity of anemia depending on the treatment method, it was revealed that anemia of degree I was significantly (values close to reliable, $p = 0.0521$) more often found in group I (polychemioradio-sensitization) than in the standard chemoradiotherapy group - 89 (37.7%) and 51 (22%) cases in groups I and II, respectively. However, there was no significant difference in the frequency of development of anemia degrees II and III between the groups - 65 (27.6%) and 72 (31%) cases in groups I and II, respectively ($p = 0.426$). And- in the II group, there were no cases of anemia of the IV degree. Thus, between the groups, there were no significant differences in the criterion of the occurrence of anemia of the II-IV degrees.

The average number of neutrophils in the peripheral blood among all patients before treatment was $6.07x10^9/l$ (standard deviation - $2.73x10^9/l$). The number of neutrophils varied from $1.89x10^9/l$ to $12.47x10^9/l$ (range - $10.58x10^9/l$). In patients of the first group, the average number of neutrophils before treatment was $5.58x10^9/l$ (standard deviation was $2.11\ x10^9/l$). The number of neutrophils varied from $1.89x10^9/l$ to $12.47x10^9/l$ (range - $10.58x10^9/l$). In patients of the second group, the average number of neutrophils before treatment was $6.01\ x10^9/l$ (standard deviation - $2.85 \cdot x10^9/l$). The number of neutrophils varied from $3.74\ x10^9/l$ to $11.32\ x10^9/l$ (range - $7.58\ x10^9/l$).There was no significant difference between the groups by the number of neutrophils in the peripheral blood before treatment ($p = 0.636$). The relatively high neutrophil counts associated with leukocytosis before treatment can be explained by the inflammatory reaction associated with the development of a secondary infectious process in the vagina as a result of copious discharge from the tumor.

As a result of treatment, among all patients, grade 0 neutrope-

nia was observed in 272 (58.1%) patients, grade I in 105 (22.4%) patients, grade II in 57 (12.3%) patients, grade III in 28 (5.9%) patients and grade IV - in 6 (1.3%) cases out of 468 patients. The average from the minimum number of neutrophils during treatment among all patients was 2.54 $x10^9$/l (standard deviation was 1.71 $x10^9$/l). The number of neutrophils varied from 0.01 $x10^9$/l to 5.67 $x10^9$/l (range - 5.66 $x10^9$/l).

In group I, neutropenia of 0, I, II, III and IV degrees was found in 125 (52.9%), 63 (26.8%), 27 (11.4%), 17 (7.2%) and 4 (1.7%) cases, respectively. In this group, in 125 (52.9%) patients, the number of neutrophils did not fall below normal values. The average from the minimum number of neutrophils during treatment among patients of the first group was 2.35 $x10^9$/l (standard deviation was 2.13 $x10^9$/l). The number of neutrophils varied from 0.01 $x10^9$/l to 5.67 $x10^9$/l (range - 5.66 $x10^9$/l).

In group II, neutropenia of 0, I, II, III and IV degrees was observed in 147 (63.3%), 42 (18.2%), 30 (12.9%), 11 (4.7%) and 2 (0.9%) cases, respectively. In this group, in 147 (63.3%) patients, the number of neutrophils did not fall below normal values. The average from the minimum number of neutrophils during treatment among patients of the second group was 2.73 $x10^9$/l (standard deviation was 1.88 $x10^9$/l). The number of neutrophils varied from 0.01 $x10^9$/l to 5.69 $x10^9$/l (range - 5.68 $x10^9$/l). When comparing the incidence and severity of neutropenia depending on the treatment method, it was revealed that grade I neutropenia was significantly more common in group I (polychemoradiosensitization) than in the standard chemoradiotherapy group - 63 (26.8%) and 42 (18.2 %) cases in groups I and II, respectively (the difference is significant, $p = 0.0433$) (see tab. 4.4). However, no significant difference was observed between the groups of grade II-IV neutropenia between the groups - 48 (20.3%) and 43 (18.5%) cases in groups I and II, respectively ($p = 0.437$). Thus, between the groups, there were no significant (reliable) differences according to the criterion of the occurrence of neutropenia II-IV degree.

In group I, thrombocytopenia of 0, I, II, III and IV degrees was found in 125 (52.9%), 63 (26.8%), 27 (11.4%), 17 (7.2%) and 4

(1.7%) cases, respectively. In this group, the platelet count did not fall below normal values in 125 (52.9%) patients. The average from the minimum platelet count during treatment among patients of the first group was 116.4 $x10^9$/l (standard deviation - 29.7 $x10^9$/l). The platelet count ranged from 12 $x10^9$/l to 183 $x10^9$/l (range - 171 · 109 / L). In group II, thrombocytopenia of 0, I and II degree was observed in 185 (79.7%), 37 (15.9%), 10 (4.4%) cases, respectively. A decrease in platelet level III and IV degree was not observed. In this group, the platelet count did not fall below normal values in 185 (79.7%) patients. The average of the minimum platelet count during treatment among patients of the second group was 131.6 $x10^9$/l (standard deviation - 41.2 $x10^9$/l). The platelet count ranged from 61 $x10^9$/l to 210$x10^9$/l. According to the results obtained hematological toxicity in the form of neutropenia and thrombocytopenia was more pronounced in the first group of patients (who received infusions of cisplatin and gemcitabine). Moreover, only acute neutropenia and thrombocytopenia of the first degree were significantly more likely to occur in the first group ($p < 0.05$). However, there were no significant differences in hematological toxicity of the II - IV degrees between the two groups.

In the first group of patients, acute gastrointestinal toxicity in the form of vomiting of varying degrees was observed in 201 cases (85.2%). Moreover, vomiting of I, II, III, and IV degrees was observed in 112 (47.6%), 75 (31.8%), 11 (4.6%) and 3 (1.2%) cases, respectively (see tab. 4.7). There were no vomiting in 35 (14.8%) patients. In the second group of patients, acute gastrointestinal toxicity in the form of vomiting of varying degrees was observed in 99 cases (42.7%). Moreover, vomiting of I, II and III degrees was observed in 59 (25.4%), 38 (16.4%) and 2 (0.9%) cases, respectively. There were no vomiting in 133 (57.3%) patients. When comparing the incidence and degree of vomiting depending on the treatment method, it was revealed that vomiting of 0 - I degree was significantly more common in group II (standard chemoradiotherapy) than in group I (polychemioradiosensitization) - 147 (52.4%) and 192 (82.7%) cases in groups I and II, respectively (the difference is significant, $p = 0.016$). However, cases of development of vomiting of II - III degree

were more common in group I (polychemioradiosensitization) than in group II (standard chemoradiotherapy) - 86 (35.4%) and 40 (17.3%) cases in groups I and II, respectively (the difference is significant, p = 0.008). Thus, vomiting of the II – III degree was significantly more common in group I (polychemioradiosensitization) than in group II (standard chemoradiotherapy). Moreover, in only 3 cases, vomiting of the fourth degree developed among the patients of the first group, which is only one case caused a forced interruption in treatment for 3 days.

In the first group of patients, acute gastrointestinal toxicity in the form of diarrhea of varying degrees was observed in 131 cases (55.5%). Moreover, diarrhea of I, II, III, and IV degrees was observed in 81 (34.3%), 38 (16.1%), 9 (3.8%) and 3 (1.3%)) cases respectively (see tab. 4.9). There was no diarrhea In 105 (44.5%) patients.

In the second group of patients, acute gastrointestinal toxicity in the form of diarrhea of varying degrees was observed in 119 cases (51.3%). Moreover, diarrhea of I, II, III, and IV degrees was observed in 91 (39.2%), 21 (9.1%), 5 (2.2%) and 2 (0, 9%) cases, respectively (see tab. 4.9). There was no diarrhea in 113 (48.7%) patients.

When comparing the incidence and degree of diarrhea depending on the treatment method, it was found that 0 - I degree diarrhea was much more common in group II (standard chemoradiotherapy) than in group I (polychemioradiosensitization) - 186 (78.8%) and 204 (87.9%) cases in groups I and II, respectively (the difference is significant, p = 0.035). However, cases of development of diarrhea of the II – IV degree were more common in group I (polychemioradiosensitization) than in group II (standard chemoradiotherapy) —50 (21.2%) and 28 (12.2%) cases in groups I and II, respectively (the difference is significant, p = 0.016). Thus, II – IV degree diarrhea was much more common in group I (polychemioradiosensitization) than in group II (standard chemoradiotherapy). Moreover, in only 3 cases among the patients of the first group developed grade IV diarrhea, which in two cases caused a forced interruption in treatment for 2 and 5 days (see tab. 2).

Table 2

The frequency and degree of diarrhea depending on the method of treatment

Group	Acute toxicity degree					Total
	0	I	II	III	IV	
I	105 (44,5%)	81 (34,3%)	38 (16,1%)	9 (3,8%)	3 (1,3%)	236 (100%)
II	113 (48,7%)	91 (39,2%)	21 (9,1%)	5 (2,2%)	2 (0,9%)	232 (100%)
Total	218 (46,6%)	172 (36,8%)	59 (12,5%)	14 (3%)	5 (1,1%)	468 (100%)

As a result, a comparative analysis of acute radiation reactions reliably revealed more toxic reactions of the hematopoietic system (acute hematological toxicity such as neutropenia and thrombocytopenia) and to the gastrointestinal tract (nausea/vomiting and diarrhea) in the polychemioradiosensitization group. Moreover, the phenomena of local radiation reactions practically did not differ between groups. However, in the vast majority of cases, these reactions quickly stopped, and only in rare cases led to interruptions in treatment.

Late radiation complications of the rectum, with the nearly same time of occurrence in both groups and averaged (median) for all patients 13 months. A total of 427 patients who achieved complete tumor response were included in the analysis of late rectitis. We examined syndromes such as bleeding, fistula, proctitis, and stenosis of the rectum. Some symptoms of late complications of the rectum were noted in 108 patients (25.3%). The most common complications of the above were proctitis and bleeding.

In total, 66 patients (15.5%) had proctitis of varying degrees. At the same time, proctitis of the I, II and III degrees was observed in 53 (12.4%), 11 (2.6%), and 2 (0.5%) cases, respectively. Late proctitis was not observed in 361 (84.5%) patients. Proctitis IV degree was not observed. In the first group, a total of 31 patients (13.7%) had proctitis of varying degrees. Moreover, proctitis of I, II, and III degrees was observed in 25 (11.1%), 5 (2.2%), and 1 (0.4%) cases, respecti-

vely. Late proctitis was not observed in 195 patients (86.3%). In the second group, only 35 patients (17.4%) had proctitis of varying degrees. Moreover, proctitis of I, II, and III degrees was observed in 28 (13.9%), 6 (2.9%), and 1 (0.6%) cases, respectively. Late proctitis was not observed in 166 patients (82.6%). When comparing the incidence and degrees of proctitis depending on the method of treatment, it was revealed that proctitis of I - III degrees was more common in group II (standard chemoradiotherapy) than in group I (polychemioradiosensitization) - in 31 (13.7%) and 35 (17.4%) cases in groups I and II, respectively (the difference is not significant, $p = 0.358$). Thus, between the groups, there were no significant (reliable) differences according to the criterion of late proctitis.

In the first group, only 24 patients (10.6%) had rectal bleeding of varying degrees. At the same time, bleeding of I, II and III degrees was observed in 14 (6.2%), 9 (4%), and 1 (0.4%) cases, respectively. Late bleeding was not observed in 202 (86.3%) patients. Grade IV bleeding was not observed. In this group, in 18 (8%) patients, both proctitis and rectal bleeding were observed simultaneously. In the second group, only 28 patients (13.8%) had rectal bleeding of varying degrees. Moreover, bleeding of I, II and III degrees was observed in 19 (9.6%), 7 (3.6%), and 2 (0.6%) cases, respectively. Late bleeding was not observed in 173 patients (86.2%). Grade IV bleeding was not observed.In this group, in 14 (7%) patients, both proctitis and rectal bleeding were observed simultaneously. When comparing the frequency of occurrence and degrees of rectal bleeding, depending on the treatment method, it was found that I-III degree bleeding was more common in group II (standard chemoradiotherapy) than in group I (polychemioradiosensitization) - in 24 (10,6%) cases and in 35 (17.4%) cases in groups I and II, respectively (the difference was close to significant, $p = 0.076$). Rectal bleeding IV degree was not recorded in both groups. Thus, between the groups,there were no significant (reliable) differences according to the criterion of the occurrence of late postradiation bleeding from the rectum.

We also analyzed the frequency and degree of late radiation complications of the rectum, depending on the time elapsed since the end of treatment. Radiation reactions began to be recorded from the

12th month and reached a maximum until the 36th month. The greatest rise was observed during the period from the 12th to the 26th months (see Fig. 7). When analyzing the frequency of occurrence, severity, and time of occurrence of more pronounced (II – V degrees) late radiation complications from the rectum depending on the treatment method, we also did not reveal a statistically significant difference between the groups ($p > 0.05$) (see fig. 7).

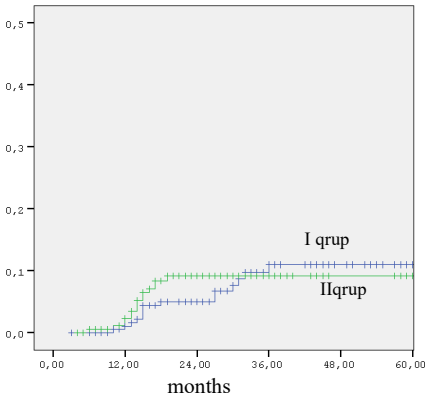

Fig. 7.The likelihood of late rectal toxicity of all degrees, depending on the method of treatment.

Late radiation complications of the bladder, with the nearly same time of occurrence in both groups and averaged (median) for all patients 14 months. We examined syndromes such as cystitis, incontinence, and stenosis. Those or other phenomena of late complications from the bladder were noted by 101 patients (23.7%). The most common complications of the above were cystitis and urinary incontinence. A total of 69 patients (16.2%) had cystitis of varying degrees. Moreover, cystitis of the I, II and III degrees was observed in 31 (7.3%), 35 (8.2%), and 3 (0.7%) cases, respectively. Symptoms of late cystitis were not observed in 358 patients (83.8%). Cystitis IV degree was not observed (see tab. 3). In the first group, only 34 patients (15%) had some degree of post-radiation cystitis. At the same time, cystitis of I, II and III degrees was observed in 14 (6.2%), 19 (8.4%), and 1 (0.4%) cases, respectively. Late cystitis was not obser-

ved in 192 (85%) patients. In the second group, only 35 patients (17.8%) had post-radiation cystitis of varying degrees. At the same time, cystitis of I, II and III degrees were observed in 17 (8.6%), 16 (7.9%) and 2 (1.1%) cases, respectively. Symptoms of late cystitis were not observed in 166 patients (82.4%). Cystitis IV degree was not observed (see tab. 3).

Table 3

The frequency and severity of late radiation cystitis, depending on the method of treatment

Group	Acute toxicity degree					Total
	0	I	II	III	IV	
I	192 (85%)	14 (6,2%)	19 (8,4%)	1 (0,4%)	0	226 (100%)
II	166 (82,4%)	17 (8,6%)	16 (7,9%)	2 (1,1%)	0	201 (100%)
Total	358 (83,8%)	31 (7,3 %)	35 (8,2 %)	3 (0,7 %)	0	427 (100%)

When comparing the incidence and severity of late radiation cystitis depending on the treatment method, it was revealed that cystitis of the I-III degree with the same frequency was found both in group I (polychemioradiosensitization) and in group II (standard chemoradiotherapy) - in 34 (15%) and in 35 (17.8%) cases in groups I and II, respectively (the difference is not significant, $p = 0.68$). Cystitis IV degree was recorded in both groups. Thus, between the groups, there were no significant (reliable) differences according to the criterion of the occurrence of late radiation cystitis.

A total of 41 patients (9.6%) had incontinence of varying degrees. Moreover, incontinence of I and II degree was observed in 26 (6.1%) and 15 (3.5%) cases, respectively. The symptoms of post-radiation urinary incontinence were not observed in 386 patients (90.4%). Grade III and IV incontinence was not observed. In the first group, a total of 22 patients (9.7%) had some degree of post-radiation urinary incontinence. At the same time, incontinence of I and II and degrees was observed in 15 (6.6%) and 7 (3.1%) cases, respectively.

Urinary incontinence was not observed in 204 (90.3%) patients. Grade III, IV incontinence was not observed. In the second group, only 19 patients (9.5%) had some degree of post-radiation urinary incontinence. Moreover, incontinence of I and II and the degree was observed in 11 (5.5%) and 8 (3.1%) cases, respectively. Urinary incontinence was not observed in 182 patients (90.5%). Grade III, IV incontinence was not observed. When comparing the incidence and severity of post-radiation urinary incontinence depending on the method of treatment, it was found that incontinence of I - II degree with the same frequency was found both in group I (polychemioradiosensitization) and in group II (standard chemoradiotherapy) - in 22 (9.7%) and 19 (9.5%) cases in groups I and II, respectively (the difference is not significant, p = 0.38). Thus, between the groups there were no significant (reliable) differences according to the criterion of the occurrence of post-radiation urinary incontinence.

We also analyzed the frequency and degree of late radiation complications of the bladder, depending on the time elapsed since the end of treatment. Radiation reactions began to be recorded from the 12th month and reached a maximum until the 36th month. The greatest rise was observed in the period from the 12th to the 26th months (see Fig. 8).

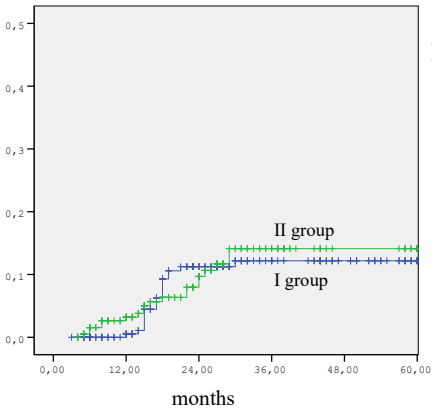

Fig. 8. The likelihood of late bladder toxicity of all degrees depending on the method of treatment

When analyzing the frequency of occurrence, degree and time of occurrence of more pronounced (II – V degrees) late radiation complications of the bladder depending on the treatment method, we also did not reveal a statistically significant difference between the groups ($p > 0.05$) (see fig. 8).

Quality of life of patients with cervical cancer. To study the quality of life of patients, we used a questionnaire approved by the European Organization for Research and Treatment of Cancer - EORTC QLQ-C30, (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire).This questionnaire was filled in by all patients before treatment, during treatment (on the 4th week), and those who were in complete remission at various times after completion of the therapy before the onset of relapse (control points - after 3 months, 6 months, 1, 2 and 3 years). Their general condition was evaluated based on the sum of the points scored (from 0 to 100), and the effect of the treatment on the level of quality of life was subsequently determined by the difference in points.

In order to study the QOL of patients, we compared the indicators of physical (PF2), emotional (EF) and social functioning (SF) before, during and at various times after treatment. It should be noted that the initial quality of life indicators in the compared groups was determined by the prevalence of the process, the form of tumor growth, and there were no significant differences in the status of the general condition, symptomatic and functional scales, which gives grounds to consider the groups to be comparable. We have tracked the values of the above-mentioned indicators at each control point, depending on the method of treatment. Starting from the 2nd control point (3 months after treatment), we examined only 427 patients with complete tumor regression.

All patients showed a deterioration in physical functioning at the second control point compared to baseline. In both groups, a significant PF2 worsening was associated with the toxicity of competitive CLT ($p> 0.05$).Starting from the 3rd control point (3 months after the end of treatment) was recorded almost complete restoration of the physical condition to normal values which significantly exceeded the initial figures. However, at the 5th and 6th control points (1 and 2 ye-

ars after the end of treatment), a decrease in PF2 values was again observed, associated with late complications of radiation therapy. Thus, when analyzing the physical condition of patients with cervical cancer, depending on the treatment method, a more significant worsening and the slow recovery of this indicator were revealed in connection with the treatment in group I compared with group II.

In a comparative analysis of EF, as well as in the case of PF2, a significant worsening was observed in connection with the treatment (2nd control point). However, unlike PF2, the severity of depression was almost the same in both groups, and to restore the emotional status to significantly higher values compared to the initial ones, the patients took longer (2-3 years).

One of the main indicators in assessing QOL of oncological patients is also social functioning. In both groups, a marked SF deterioration was initially observed, which is explained by acute (early) toxicity of chemoradiotherapy. However, after resolving acute radiation reactions, SF indices are equalized at the 3rd and 4th control points. At the 5th point (2 years after treatment), a slight deterioration in SF is again noted, almost the same in both groups, which we associate with the development of late radiation complications.

Thus, a comparative analysis of QOL of patients with cervical cancer according to various criteria shows that in patients with complete remission there is a significant improvement in QOL indicators. However, during treatment, there is a significant deterioration in QOL associated with acute toxicity of chemoradiotherapy with further, rather quick recovery to values much higher than the initial ones.

As a result of this study, we came to the conclusion that, according to the data obtained (tumor response, overall and relapse-free survival), competitive CRT using polyradiosensitization and combined intracavitary and interstitial brachytherapy provides higher treatment efficiency for patients with locally advanced cervical cancer compared to standard CRT. At the same time, the study of radiation reactions and complications revealed a more pronounced early (hematological and gastrointestinal) toxicity of CRT with polyradiosensitization, although late toxicity was almost the same in both groups. All the above confirms the great efficacy of CRT using polyradiosen-

sitization and combined intracavitary and interstitial brachytherapy both in terms of curing patients and in terms of quality of life and social rehabilitation of cervical cancer patients. Thus, CRT using polyradiosensitization and combined intracavitary and interstitial brachytherapy is an effective and fairly safe method of treating locally advanced cervical cancer with acceptable toxicity and can be performed in routine clinical practice.

CONCLUSIONS

1. A new multimodal method has been developed and clinically tested for the treatment of patients with locally advanced cervical cancer of stage IIA - IVA, including the simultaneous use of combined radical radiation therapy (volumetric arc therapy (VMAT) and combined intracavitary/interstitial brachytherapy with a high dose rate) and polyradiosensitization of cisplatin and gemcitabine [14, 19, 22].
2. In patients with locally advanced cervical cancer, concurrent chemoradiotherapy using polyradiosensitization and combined intracavitary/interstitial brachytherapy compared to standard chemoradiotherapy significantly improves the immediate results of treatment (complete tumor response was observed in 96% and 86.6% of cases in groups I and II, respectively), relapse-free survival of patients (five-year relapse-free survival was 80.7%, and 67.2% in groups I and II, respectively); overall survival of patients (five-year overall survival was 76.1%, and 62.4% in groups I and II, respectively) [22, 48, 51]..
3. The use of combined intracavitary and interstitial brachytherapy in chemoradiotherapy of locally advanced cervical cancer makes it possible to significantly increase the dose of ionizing radiation to the target volume (HRCTV) at the same doses to healthy organs and tissues at risk (the average dose in HRCTV was 88.7 Gy and 79.2 Gy in groups I and II, respectively). Combined intracavitary/interstitial brachytherapy is a fairly safe and effective treatment for locally advanced cervical cancer and can be performed in routine clinical practice [21, 26, 35].

4. A comparative analysis of acute radiation reactions reliably revealed more pronounced toxicity from the hematopoietic system (acute hematological toxicity such as neutropenia and thrombocytopenia) and the gastrointestinal tract (nausea/vomiting and diarrhea) in the group of chemoradiosensitization. However, in the vast majority of cases, these reactions quickly stopped, and only in rare cases led to interruptions in treatment. The timing of the occurrence of late radiation complications in both groups did not differ much (they began to register from the 12th month and reached a maximum until the 36th month). Analysis of late radiation injuries did not reveal any significant differences between the standard chemoradiotherapy and polyradiosensitization groups using combined intracavitary / interstitial brachytherapy [24, 36, 49, 52].
5. Analysis of the quality of life (QOL) of patients with cervical cancer according to various criteria shows that patients with complete remission have a significant improvement in QOL compared to baseline. However, during treatment, there is a significant deterioration in QOL associated with acute toxicity of chemoradiotherapy with further, rather quick recovery to values much higher than the initial ones [23, 27, 39, 52].
6. According to the results of molecular genetic analysis, PIK3CA mutations were detected in 43.8% of cervical cancer patients. The presence of PIK3CA mutations was an unfavorable factor that significantly worsened the immediate results of chemoradiotherapy of locally advanced cervical cancer (among patients with PIK3CA mutations, complete tumor response was achieved in 84.8% of cases, while among patients without PIK3CA mutations complete tumor responses were achieved in 96.2% of cases). Our study did not reveal a significant difference in survival rates depending on the presence of mutations in the PIK3CA gene in locally advanced cervical cancer. The presence of PIK3CA mutations in a large number of cervical cancer patients in Azerbaijan could potentially designate PIK3CA as an aim for targeted therapy (or targeted radiosensitization) in the future [21].
7. HPV infection was detected in 62.8% of patients with locally advanced cervical cancer in Azerbaijan. 80.6% of these cases deter-

mined HPV type 16, and in 19.4% - HPV type 18. Moreover, in 9.5% of patients, both types of the virus (16 and 18) were determined simultaneously. Our study did not reveal a significant difference in the immediate results of treatment or in the survival rates of patients depending on the presence of HPV infection. Thus, in our study, the presence of HPV infection did not affect the results of chemoradiotherapy of locally advanced cervical

8. Chemotherapy with locally advanced cervical cancer, including combination of radiation therapy (volumetric arc therapy (VMAT) and combined intracavitary/interstitial brachytherapy with a high dose rate) and radiosensitization with cisplatin and gemcitabine, is an effective and fairly safe method of treating locally advanced cervical cancer and can be used in routine clinical practice [13, 23, 24, 51, 52, 54].

PRACTICAL RECOMMENDATIONS

1. Patients with cervical cancer stages IIA - IVA are recommended to carry out with combined radiotherapy, consisting of external beam radiation therapy with dose per fraction 1.8-2.0 Gy to a total dose of 45-50 Gy and combined intracavitary/interstitial brachytherapy with a high dose rate with dose per fraction - 7.0 Gy and totally - 28 Gy.
2. Competitive chemotherapy is recommended according to the following scheme: cisplatin at a dose of 40 mg / m2 iv and gemcitabine 75 mg / m2 iv starting from the first day of radiation therapy, once a week during EBRT.
3. Prescribed EBRT doses to metastatic regional lymph nodes are 2.2-2.3 Gy per fraction by the method of simultaneous integrated boost (SIB).
4. Prevention of local and general side effects and complications is recommended from the first days of treatment: blood transfusion, infusion therapy, uroseptics, local repair stimulants, diet.
5. Temporary deterioration in the quality of life of patients during treatment should not be considered as a basis for the interruption of radiation therapy.

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Abbreviation list

BED – biological effective dose
CIN – cervical intraepithelial neoplasiya
CTV – clinical target volume
DFS – disease free survival
EBRT – external beam radiotherapy
DVH – dose-volume histogram
EGF – epidermal growth factor
EQD2 – equivalent dose
GTV – gross tumor volume
HDR – high dose rate
HDRBt – high dose rate brachytherapy
QL – quality of life
HPV – human papillomavirus
PR – partial regression
HRCTV – high risk clinical target volume
IGABT – image guided brachytherapy
IMRT – intensity modulated radiotherapy
CT – computed tomography
LCDFS – loco-regional disease free survival
LDR – low dose rate
LDRBt – low dose rate brachytherapy
LRR – locoregional relaps
MDR – medium dose rate
MRI – magnetic resonance imaging
OE – objectiv effect
OS – overall survival
PET – positron emission tomography
PP – progression of the process
PTV – planned treatment volume
SD – standard deviation
VMAT – volyumetric arc-therapy
CT – computed tomography

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