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CLINICAL-LABORATORY PORTRAIT OF PATIENTS WITH CERVICAL CANCER WITH LATE RADIATION TOXICITY DUE TO RADIATION TREATMENT

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Ключевые слова: *рак шейки матки, лучевая терапия, поздние лучевые осложнения, лучевой цистит, лучевой ректит*

Abstract. Clinical-laboratory portrait of patients with cervical cancer with late radiation toxicity due to radiation treatment. Krasnoselskyi M.V., Hladkykh F.V., Kulinich H.V., Sevastianova V.S. *According to the National Cancer Registry of Ukraine, cervical cancer ranks second among cancer morbidity, in women of reproductive age and the first place (14.1% of all cases) in the mortality from malignant neoplasms in women aged 18-29, and in aggregate almost 1.7 thousand women die from this pathology in Ukraine annually. Radiation therapy plays a leading role in the treatment of this pathology. In turn, an increase in the survival rate after the course of combined treatment leads to an increase in the absolute number of patients with adverse effects of treatment, in particular, late radiation toxicity (LRT). A retrospective analysis of 254 case histories of patients with malignant cervical neoplasms (127 patients with late radiation toxicity and 127 patients without late radiation toxicity) was conducted. Depending on the nature of the genesis of the late radiation toxicity, it has been found that inflammatory changes occurr in 95.3% of patients (atrophic cystitis, radiation recticite, radial enterocolitis, radiation retropsychoiditis, etc.); in 32,3% – late radiation toxicity of fibrotic genesis (intrapulmonary radiation, ureter stenosis, fibrosis of the skin and subcutaneous tissue of the irradiation fields, etc.); in 25.2% – degenerative late radiation toxicity (radial ulcers, fistulas, etc.) and 30.7% – hematologic late radiation toxicity. The comparative analysis of clinical and laboratory parameters of patients before and after radiotherapy with regard to cervical cancer has shown that prognostic factors of late radiation toxicity such as increase in hematocrit and fibrinogen indices deserve attention. It has also been established that the presence of laboratory signs of a cytolytic syndrome (increased levels of aspartate aminotransferase, urea and total protein) in patients with cervical cancer prior to radiation therapy can be a prerequisite for the formation of late radiation toxicity. In addition, it has been shown that the presence of concomitant aggravating diseases of the endocrine system, blood system, musculoskeletal system, nervous system and digestive system is statistically significantly ($p<0,05$) increases the risk of LRT in patients with cervical cancer by 20,2; 7.0; 2.3; 1.8 and 1.6 times respectively.*

Реферат. Клинико-лабораторный портрет больных раком шейки матки с поздними радиационными осложнениями лучевого лечения. Красносельский Н.В., Гладких Ф.В., Кулинич Г.В., Севастьянова В.С. *По данным Национального канцер-реестра Украины, рак шейки матки занимает второе место среди онкологических заболеваний женщин репродуктивного возраста и первое место (14,1% всех случаев) в структуре смертности от злокачественных новообразований женщин в возрасте 18-29 лет, а совокупно от указанной патологии в Украине ежегодно умирает почти 1,7 тыс. женщин. Ведущую роль среди методов лечения данной патологии играет лучевая терапия. В свою очередь, увеличение срока выживаемости после проведенного курса комбинированного лечения вызывает рост абсолютного числа больных с неблагоприятными последствиями лечения, в частности поздними лучевыми осложнениями (далее – ПЛО). Проведен ретроспективный анализ 254 историй болезней пациенток со злокачественными новообразованиями шейки матки (127 пациенток с ПЛО и 127 пациенток без ППУ). В зависимости от характера генеза ПЛО установлено, что у 95,3% пациенток имели место воспалительные изменения (атрофический лучевой цистит, лучевой ректит, лучевой энтероколит, лучевой ретросигмоидит и др.), в 32,3% – ПЛО фибротического генеза (внутритазовый лучевой фиброз, стеноз мочеточников, фиброз кожи и подкожной клетчатки полей облучения и др.), в 25,2% – дегенеративные ПЛО (лучевые язвы, свищи и др.) и в 30,7% – гематологические ПЛО. Проведенный сравнительный анализ клинико-лабораторных показателей пациенток до и после лучевого лечения по поводу РШМ показал, что в качестве прогностических факторов развития ПЛО заслуживают внимания повышение показателей гематокрита и фибриногена. Также установлено, что наличие лабораторных признаков цитолитического синдрома (повышение уровня АсАТ, мочевины и общего белка) у пациентов, больных РШМ, перед проведением ПТ может быть предпосылкой формирования ПЛО. Кроме того, показано, шо наличие сопутствующих отягчающих заболеваний эндокринной системы, системы крови, костно-мышечной системы, нервной системы и органов пищеварения статистически достоверно ($p<0,05$) повышает риск возникновения ПЛО у больных РШМ, в 20,2; 7,0; 2,3; 1,8 и 1,6 раза соответственно.*

An increase in the incidence of malignancies, which in recent decades has reached 340 cases per 100,000 population with an increase in individual nosological forms from 2.0% to 30.0% necessitates the search for new and improvement of existing approaches to the treatment of cancer patients. Radiation therapy (RT) plays a leading role among the treatment regimens for the specified pathology. Effective RT involves the use of sufficiently high doses of radiation, it is just the reason for the success of combination therapy, including the increase in the contingent of patients with a survival rate of five years or more. In turn, the increase in survival after the course of combination therapy leads to an increase in the absolute number of patients with adverse effects of therapy, in particular late radiation complications.

The reproductive health status of the female population is a determining criterion for the health of the nation. Considering that in Ukraine oncological pathology ranks second in the structure of causes of death and fifth in the structure of morbidity, improvement in diagnostic and therapeutic approaches in patients with neoplasms is of relevance [1, 14]. According to the National Cancer Registry of Ukraine (NCRU), cervical cancer (CC) ranks second among oncology patients of reproductive age and first (14.1% of all cases) in malignant neoplasms mortality rate of women aged 18-29, and conjointly almost 1.7 thousand women die of mentioned pathology in Ukraine annually [3, 8].

Therapeutic decision for CC is determined by a number of factors: the stage of the disease, the extent of spreading of tumor process, the depth of invasion into the underlying tissue, the morphological variant of the tumor, age and somatic state of the patient. Modern standards of treatment of CC patients are surgical (cone-shaped excision of the cervix, extirpation of the uterus, radical hysterectomy according to Wertheim, multiorgan surgery in the volume of anterior, posterior or total exenteration of the pelvis, etc.), radiation (distant RT, intracavitary RT, interstitial RT, etc.) and chemotherapy (platinum derivatives, 5-fluorouracil, bleomycin, cyclophosphane, etc.) [5, 11].

In radiotherapy, a combination of remote and intracavitary conformal RT became widespread, with the possibility of forming a field adapted to the shape and localization of the required irradiation zone. According to the literature [2, 7], intracavitary RT is usually performed by a single dose cell (SDC) of 10 Gy 1 time a week, 4-5 fractions or 7 Gy 1-2 times a week, 6-7 fractions each. Remote RT is performed by SDC of 3 Gy, 7-10 fractions for 2-3 weeks or SDC of 5 Gy 2 times a week, 8-10 fractions, etc., which provide the lowest percentage of radiation complications. The specified fractionation provides the achievement of total dose cell (TDC) in

the area of primary tumor in the paracervical triangle (point A) 70-75 Gy and in lateral portions of the parametrium and parauterine lymph nodes (point B according to the Manchester system) – 40-55 Gy [7].

In turn, the widespread use of RT in CC treatment along with improving the effectiveness of treatment inevitably leads to an increase in the likelihood of early and/or late radiation-induced complications (LRC) which poses the challenge of a detailed study of this problem.

Late radiation complications are pathological changes of organs and tissues that occur under the influence of ionizing radiation and present not earlier than 3 months after treatment, they are irreversible, require special treatment, and usually turn a chronic course [7, 9]. The incidence of LRC is 5-10%, but some authors point to a frequency of 40-50%, which is due to the lack of unified criteria for the evaluation of RT complications [6, 9, 12].

It should be noted that according to the NCRU, 22.0% of patients diagnosed with CC did not undergo treatment. The data of Pariy V.D. et al. (2019) direct attention that the average cost of treatment for one case of CC in terms of direct costs is 110 thousand UAH [8]. The above data point to the urgency of optimizing specialized treatment for CC patients, including minimizing of LRC incidence aimed at improving the quality of life and maintaining fertile function of reproductive age women after completing radical treatment.

The aim of the work is to conduct a comparative analysis of clinical and laboratory findings of patients with late radiation-induced complications and without the ones after radiation CC treatment.

MATERIALS AND METHODS OF RESEARCH

In order to study the peculiarities and differences of LRC development, there was made a retrospective analysis of 254 case histories (CH) of patients with malignant neoplasms of the cervix, who were hospitalized to the State Institution "Grigoriev Institute for medical Radiology NAMS of Ukraine" for the period from 1994 to 2018 with therapeutic modality including RT. Two groups of patients were formed: the main (127 people) – patients with LRC and the control (127 people) – patients without LRC. Patients were selected according to inclusion and exclusion criteria. The enrollment of patients in the control group was carried out in an equivalent number to the main group patients.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki for Biomedical Research "Ethic Principles for Medical Research with Human Involvement as a Research Object" (2008), the Council of Europe Convention on Human Rights and Biomedicine (2007), the Committee's recommendations on Bioethics at the Presidium of the National Academy of Medical Sciences of Ukraine (2002) and was approved by the Committee on Bioethics and Deontology of the State Institution «IMR named after S.P. Hryhoriev National Academy of Medical Sciences of Ukraine "(Minutes No. 1 of January 22, 2019).

For the purpose of a complex analysis of clinical and instrumental data of CH, a standardized digital information base was created. Statistical processing of the results was performed using the spreadsheet application «Microsoft Office Excel 2003; 2013 "(Microsoft Corporation, USA). The nature of the distribution of values in each sample group was assessed using the W- criterion of Shapiro-Wilk test. The homogeneity of variances was determined by Levene's test. To assess the significance of the differences found, the statistical parameters were analyzed using the Student's parametric t-test in cases of normal distribution, non-parametric rank U - Mann-Whitney criterion - in its absence, Fisher angular transformation in recording results in the alternative form. Quantitative assessment of the risk factors for the LRC development was performed with the calculation of values of the relative risk (risk ratio) and odds ratio (odds ratio). The differences were considered statistically significant at $p<0.05$. The numerical data in the case of a normal distribution of values are given as "M±m" (M±SE), where M is the arithmetic mean, m (SE) is the standard error of the arithmetic mean or M (95% CI: 5% – 95%) , where 95% CI: – 95% Confidence Interval (CI). In the case of an abnormal distribution of the values obtained, the data are presented as Me [LQ; UQ], where Me is the median, [LQ; UQ] is the upper limit of the lower quartile (LQ) and the lower limit of the upper (third) quartile (UQ) [10, 15].

RESULTS AND DISCUSSION

The average age of CC patients with LRC in the time following was 58 [52; 64] years (Fig. 1) and corresponds to the age structure of morbidity for the specified pathology [3].

Analysis of the distribution of patients by stages of the malignant process showed (Table 1) that in the vast majority ($p<0.01$) of patients in the main group stage II was diagnosed (53.5%). In the control group, in 46.9% of patients stage I and II was diagnosed and in 36.2% – stage III.

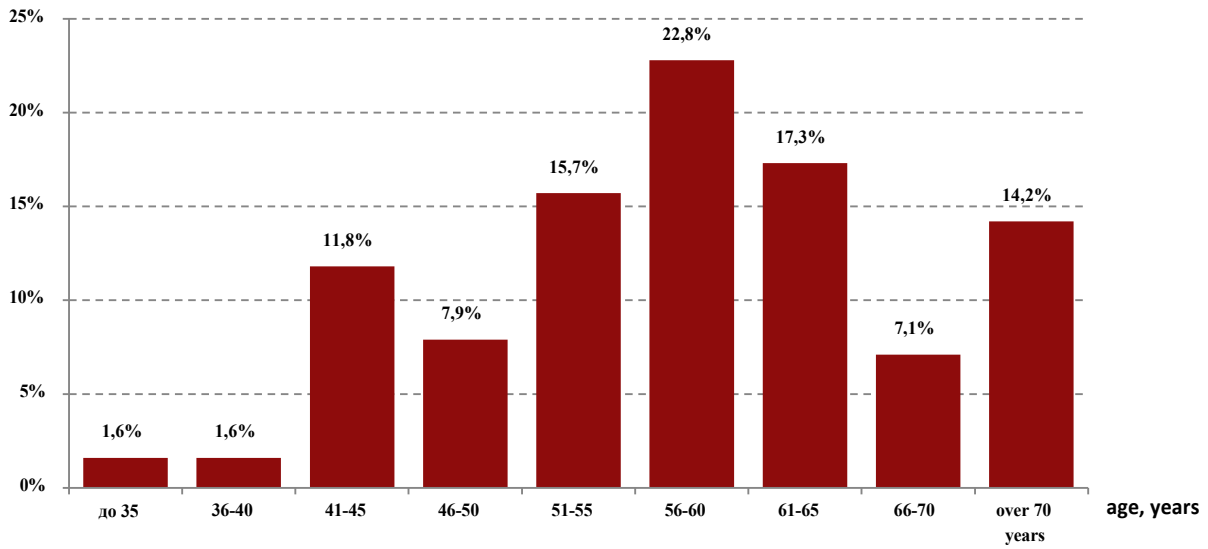

Fig. 1. Age-related distribution of CC patients with late radiation-induced complications, n=127

Histologically, patients of both groups had ($p<0.05$) squamous non-keratinizing cell carcinoma. The specified morphological structure of the neoplasm of the cervix was established in 67.8% of patients in the main and 49.6% of patients in the control group (Fig. 2).

Early radiation complications in anamnesis were detected in 79 patients (62.2±0.44%) of the main group and 80 patients (64.0%) of the control group, which indicates absence of correlation between the development of early and late RT complications in CC.

We found that LRC after radiotherapy for CC in the vast majority of patients (65.0%) was diagnosed within the first two years (3-24 months) after RT (Fig. 3).

Table 1

Distribution of CC patients by stages of the process according to FIGO-TNM[1] classification, n=254

Stage of the process	Main group (LRC patients, n=127), abs. (%)	Control group (patients without LRC, n=127), abs. (%)	Level of statistical probability[2]
Stage I (T_1 N_0 M_0)	23 (18.2%)	30 (23.6%)	p>0.05
Stage II (T_2 N_0 M_0)	68 (53.5%)	46 (22.8%)	p<0.01
Stage III (T_3 N_{0-1} M_0)	34 (26.8%)	44 (36.2%)	p>0.05
Stage VI (T_4 N_{0-1} M_{0-1})	2 (1.6%)	7 (5.5%)	p≤0.05

Notes: [1] – TNM International Classification of Malignancies, 7th Edition, 2009, together with the FIGO International Gynecological Obstetrics Classification, 2009 revision, [2] – Fisher's exact angular transformation criterion.

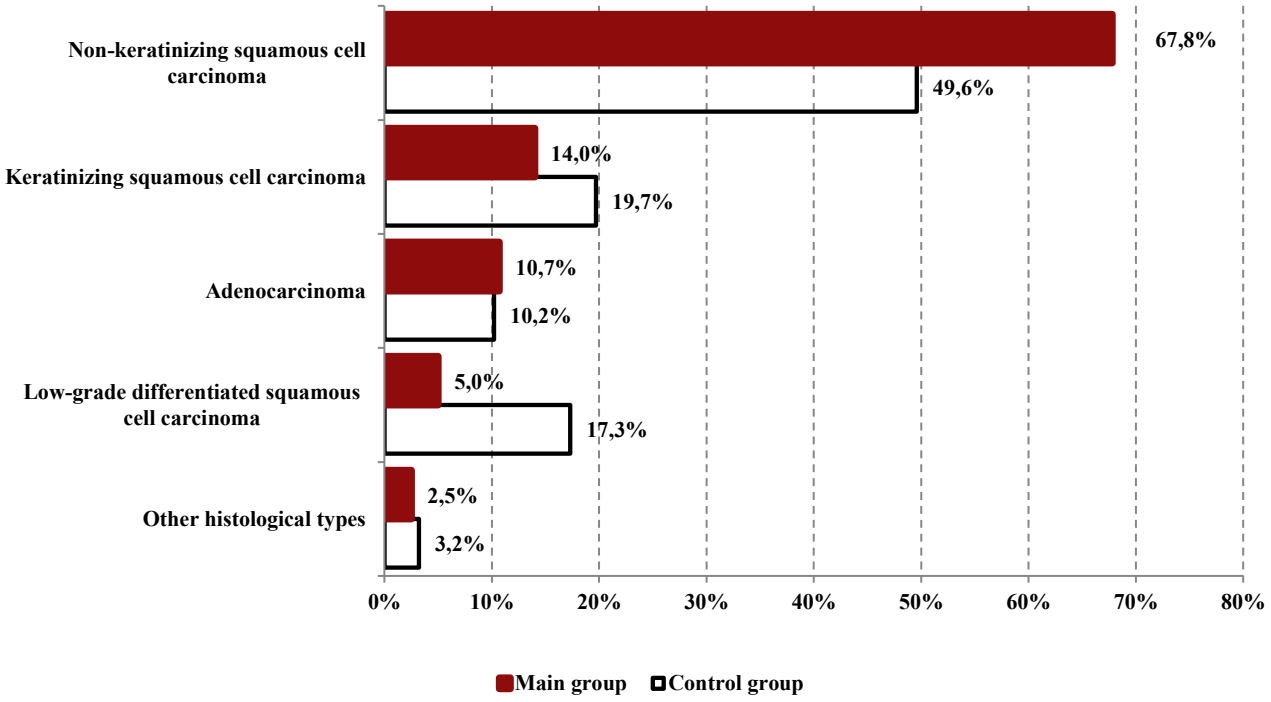

Fig. 2. Distribution of CC patients by histological type of neoplasm of the cervix, n=254

Depending on the nature of genesis of late RC, it was found that 121 individuals (95.3%) had inflammatory LRC (atrophic radial cystitis, radial rectitis, radial enterocolitis, radial retrosigioiditis, etc.); in 41 persons (32.3%) – LRC of fibrotic genesis (intrapelvic radiation fibrosis, ureteral stenosis, skin fibrosis and subcutaneous tissue of irradiation fields, etc.); in 32 individuals (25.2%) – degenerative LRC (radiation ulcers, fistulas, etc.) and in 39 ones (30.7%) – hematologic LRC.

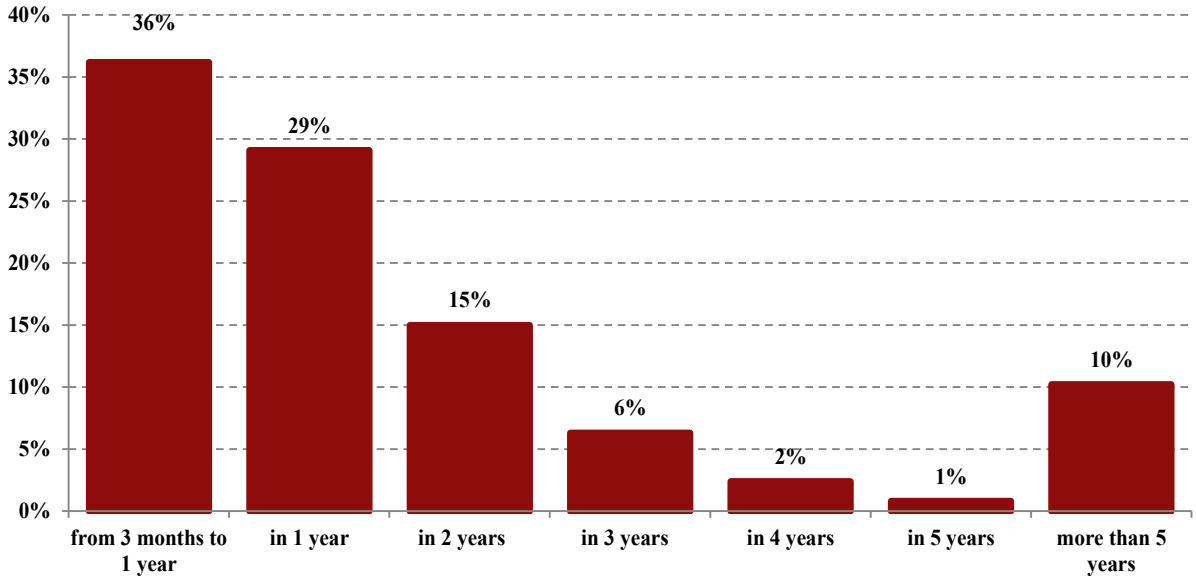

Fig. 3. Distribution of CC patients by the term of late radiation complications of radiation therapy, n=127

Mass-growth coefficients (BMI) of patients in the main and control groups had no significant differences, the vast majority of patients had normal body weight (52.0% and 44.0%, respectively). Overweight and obesity of I-III degrees were noted in 33.8% of patients with LRC and in 41.0% of patients without ones, which indicates the absence of probable prognostic significance of obesity as a factor in the development of LRC in CC patients (Fig. 4).

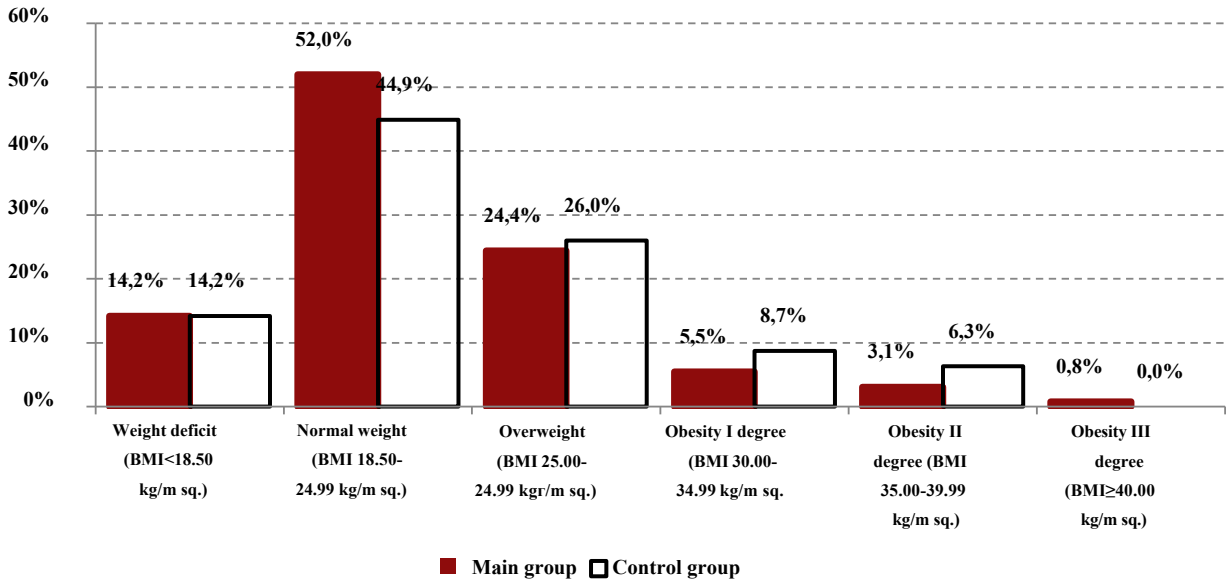

Fig. 4. Distribution of CC patients by mass-growth findings, n=254

Analyzing the distribution of patients according to the type of special treatment (Fig. 5), we found that LRC more often developed in CC patients who underwent chemotherapy as a part of complex treatment (31 individuals – 24.6%) or combination of DRT and ICRT with surgical intervention (14 people – 11.1%). This is consistent with the literature data that chemotherapy may be a risk factor for LRC in CC patients [4].

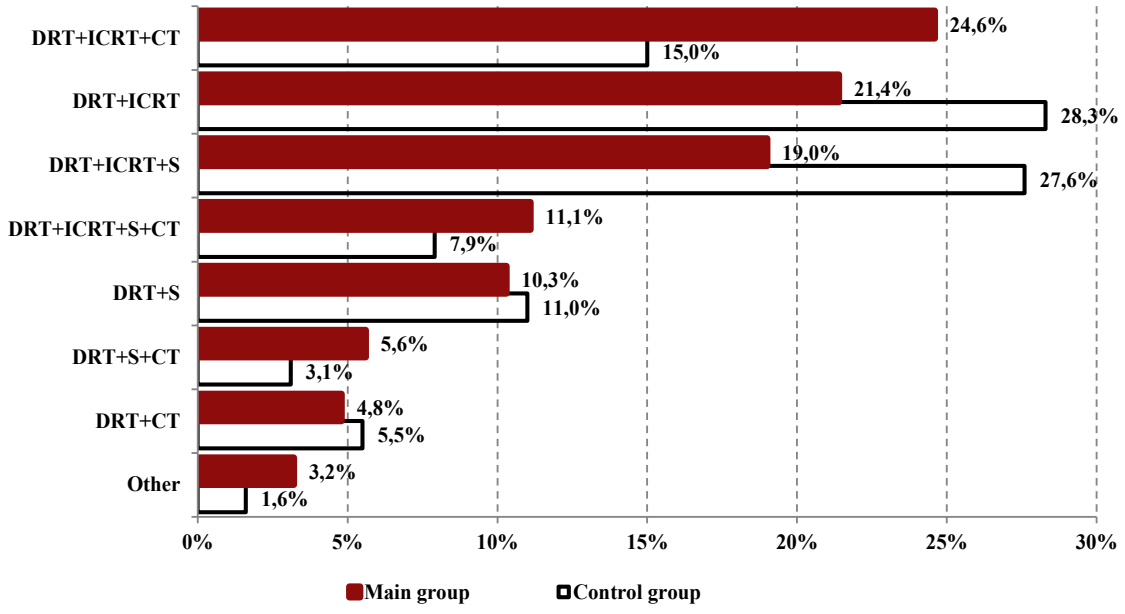

Fig. 5. Distribution of CC patients by the type of treatment, n = 254 (note: DRT – distant radiation therapy, ICRT - intracavitary radiation therapy, S - surgery, CT - chemotherapy)

Assessment of the distribution of patients according to the present concomitant pathology (Fig. 6) showed that LRC in CC is statistically significant ($p \leq 0.05$) more often formed on the background of diseases of the digestive system (78 people - 61.4%), with diseases of the nervous system (60 people – 47,2%), diseases of the musculoskeletal and connective tissue (39 people – 39,7%), diseases of the blood system (28 persons – 22,0%) and on the background of diseases of the endocrine system (20 persons – 15.7%). The revealed features correspond to the well-known statement that concomitant pathology is a risk factor for the development of LRC [4].

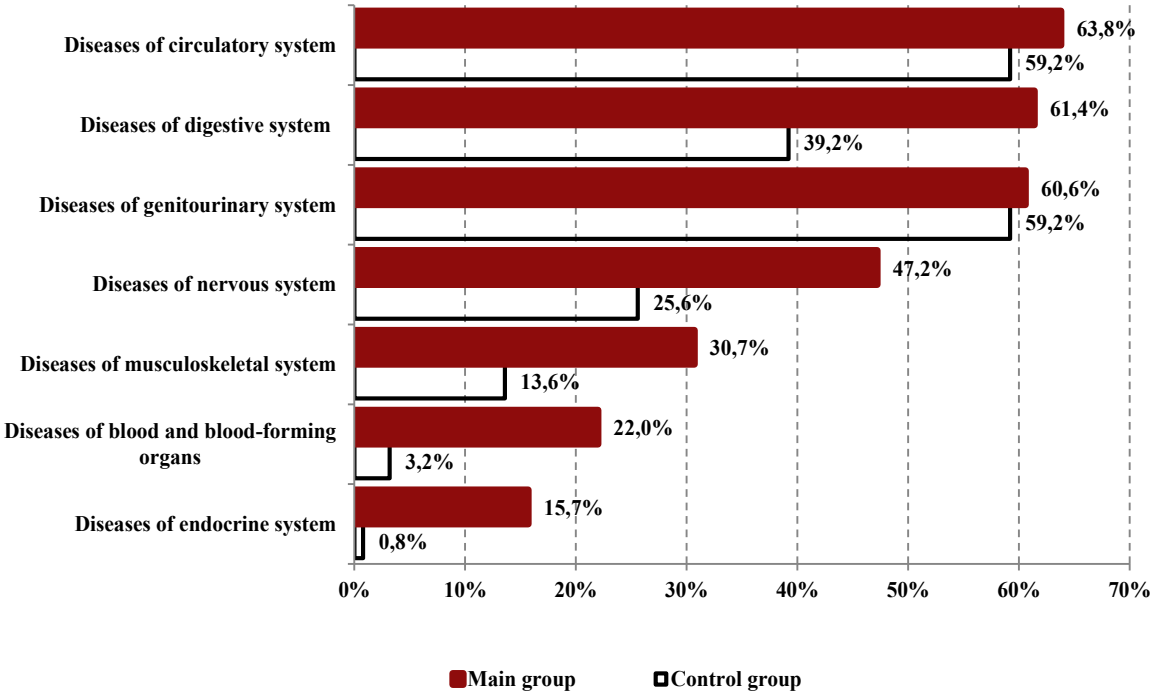

Fig. 6. Frequency of concomitant pathology in CC patients, n=254

Further analysis of LRC incidence on the background of concomitant pathology showed (Table 2) that the diseases of the endocrine system by 20.2 (95% CI: 2.8-148.0) times statistically significantly ($p<0.05$) increase the incidence rate of LRC and the chances of developing LRC are by 23.8 times higher than in CC patients without concomitant endocrine pathology. We also found that the chances of developing LRC on the background of diseases of the blood and blood-forming organs are higher by 8.7 (95% CI: 2.95-25.62) times ($p<0.05$), and on the background of diseases of musculoskeletal and connective tissue – by 2.9 (95% CI: 1.52-5.41) times ($p<0.05$), on the background of nervous system diseases – by 2.7 (95% CI: 1, 56-4.52) times ($p<0.05$). Other concomitant diseases increased the chances of RC development by not more than 2 times.

In addition, it was found that lesions with concomitant pathology of 4 or more systems were statistically more likely ($p<0.05$) to be present in patients in the main group (59 people – 45.7%) than in CC patients of control group (24 people – 18.9%).

Assessment of hematologic indices (Table 3) showed that the level of hematocrit ($p<0.01$) in patients with LRC (main group) before RT was statistically significantly lower by 7.0% ($p<0.01$) and leukocyte count was lower by19.1% relative to CC patients wihtout LRC and made up 4.7 [4.0; 6.3]$\times 10^9$/L. Intergroup differences of other hematologic indices before RT did not exceed 3.0% ($p>0.05$).

Against the background of RT, some indices had differently directed changes (Fig. 7), so the platelet count decreased by 3.2% ($p=0.3$) in patients with LRC, while in control patients a similar indicator statistically significantly ($p<0.01$) increased by 12.4%; hemoglobin level in patients of the main group decreased by 5.6% ($p<0.01$), while in patients of the control group it increased by 3.7% ($p=0.1$) compared to baseline ones and made up 121.1±1.65 (95% CI: 117.9-124.4) g/L.

Table 2

Relative risk and odds ratio of late radiation complications in cervical cancer patients against concomitant autology

Concomitant pathology	Relative risk, M±m (95% ДІ)	Odds ratio, M±m (95% ДІ)
Circulatory system diseases	**1.10±0.10 (0.90-1.33)**	**1.26±0.26 (0.76-2.09)**
Digestive system diseases	**1.59±0.13* (1.23-2.06)**	**2.53±0.26* (1.53-4.02)**
Genito-urinary system diseases	**1.04±0.10 (0.85-1.28)**	**1.10±0.26 (0.67-1.82)**
Nervous system diseases	**1.85±0.18* (1.32-2.67)**	**2.66±0.27* (1.56-4.52)**
Musculoskeletal system diseases	**2.29±0.26* (1.37-3.84)**	**2.87±0.32* (1.52-5.41)**
Blood, blood-forming system diseases	**7.00±0.52* (2.53-19.38)**	**8.70±0.55* (2.95-25.62)**
Endocrine system diseases	**20.16±1.02* (2.75-148.0)**	**23.75±1.03* (3.13-179.8)**

Note. * – statistical probability (p≤0.05) index.

Leukocyte count statistically significantly decreased in patients in both groups, but in patients with LRC it was more than three times less pronounced than in patients in the control group. Thus, in patients without LRC, the number of leukocytes decreased by 21.4% (p<0.001), while against the background of LRC development, this indicator decreased by only 6.4% (p<0.05) and amounted to 4.4 [3,7; 5.5]×10^9/L. A slight decrease in the number of leukocytes in patients with LRC is consistent with the fact that in 95.3% of patients late radiation complications were of inflammatory genesis.

Table 3

Dynamics of hematologic indices of women against radiation therapy of cervical cancer (M±m, 95% CI, Me [LQ; UQ], n=254)

Index, units of measurement	Main group (patients with LRC, n=127)		Control group (patients without LRC, n=127)	
	Before RT	After RT	Before RT.	After RT
Erythrocytes, × 10^{12} / l	**4,1 [3,6; 4,3]**	**4,0 [3,6; 4,5]**	**4,0 [3,5; 4,4]**	**3,8 [3,2; 3,3] ***
Hemoglobin, g / l	**118,4±1,68 (95% CI: 115,1-121,7)**	**111,8±1,73# (95% CI: 108,4-115,2)**	**117,0±1,77 (95% CI: 113,5-120,4)**	**121,1±1,65* (95% CI: 117,9-124,4)**
Color index	**0,89 [0,85; 0,94]**	**0,90 [0,87; 0,95]**	**0,90 [0,86; 0,93]**	**0,90 [0,87; 0,94]**
Average hemoglobin content in erythrocyte, pg	**29,7 [28,4; 31,3]**	**30,2 [29,1; 31,5]**	**30,0 [28,6; 31,3]**	**30,0 [28,7; 31,4]**
Average erythrocyte volume, fl	**90,9 [86,6; 95,1]**	**91,0 [88,1; 94,1]**	**90,0 [85,1; 93,7]**	**90,1 [85,0; 95,4]**
Platelets, × 10^9 / L	**220 [182; 267]**	**213 [181; 259]**	**225 [188; 270]**	**197 [177; 242] #**
Hematocrit,%	**36,9 [33,3; 38,6]**	**36,6 [33,6; 40,0]**	**34,3 [29,9; 37,9] ***	**33,4 [29,5; 36,1] ***
Leukocytes, × 10^9 / L	**4,7 [4,0; 6,3]**	**4,4 [3,6; 5,3] #**	**5,6 [4,4; 7,6] ***	**4,4 [3,7; 5,5] #**
Erythrocyte sedimentation rate, mm / h.	**12,0 [7,5; 22,0]**	**13,0 [8,0; 23,0]**	**12,0 [7,0; 22,0]**	**23,5 [12,0; 35,0] *#**

Notes: 1. * – p≤0.05 relative to the patients of the main group in the respective study periods, 2. # – p≤0.05 relative to indices of patients before RT.

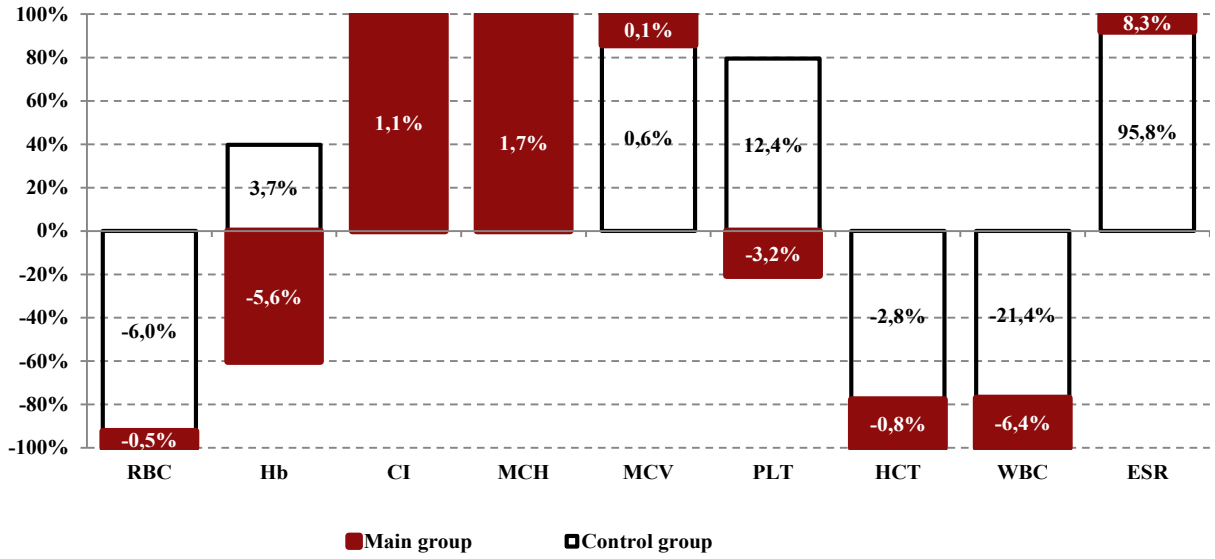

Fig. 7. Dynamics of hematologic indices of CC patients after radiotherapy, n=254 (note: RBC - erythrocytes, Hb - hemoglobin, CI - color index, MCH - mean corpuscular hemoglobin, MCV - mean erythrocyte volume, PLT - platelets, HCT - hematocrit, WBC - leukocytes)

Evaluation of the dynamics of erythrocyte sedimentation rate (ESR) showed increase of the mentioned index by 95.8% ($p<0.001$) in patients of the control group and by 11.5 times less increase (8.3%, $p=0.2$) in patients of the main group.

From the data of biochemical studies we found (Table 4) that in patients of the main group before the RT, there were higher rates of total protein by 4.5% ($p<0.01$) and aspartate aminotransferase (AsAT) – by 17.1% ($p<0.01$) relative to patients without LRC in similar terms of the study, indicating the presence of cytolytic syndrome even before the onset of radiotherapy and may be a prognostic factor for LRC development.

In addition, patients with LRC before RT had lower levels of urea by 11.1% ($p<0.05$) and creatinine by 8.1% ($p=0.09$) relative to patients without late complications of RT.

Table 4

Dynamics of biochemical parameters of blood in women against radiation therapy of cervical cancer (M±m, 95% CI, Me [LQ; UQ], n=254)

Parameter, unit of measurement	Main group (patients with LRC, n=127)		Control group (patients without LRC, n=127)	
	Before RT	After RT	Before RT	After RT
Total protein, g / l	72.8±0.74 (95% CI: 71.4-74.3)	71.3±0.54 (95% CI: 70.2-72.3)	69.6±0.66* (95% CI: 68.3-70.9)	68.3±0.67* (95% CI: 67.0-69.6)
Urea, mmol / l	4.5 [3.9; 5.6]	5.5 [4.5; 6.3] #	5.0 [4.1; 6.2] *	4.6 [3.7; 5.9] *
Creatinine, μmol / L	73.1 [69.5; 83.5]	76.7 [71.0; 90.0]	79.0 [70.0; 90.0]	77.0 [67.3; 87.0]
Bilirubin, μmol / l	14.1 [11.5; 17.2]	14.2 [11.2; 17.2]	14.2 [11.2; 16.5]	12.9 [10.2; 16.2] *#
Glucose, μmol / l	5.6 [5.1; 6.1]	5.5 [5.0; 6.0]	5.6 [4.9; 6.0]	5.6 [5.1; 6.1]
Alanine aminotransferase, μmol / h × l	17.7 [12.8; 25.4]	18.0 [12.9; 26.7]	17.7 [12.3; 23.4]	17.3 [12.8; 23.9]
Aspartate aminotransferase, μmol / year × l	20.0 [16.0; 25.2]	20.7 [16.7; 26.3]	18.0 [14.2; 21.5] *	17.2 [14.9; 24.8] *

Notes: 1. * – p≤0.05 relative to the patients of the main group in the respective study periods, 2. # – p≤0.05 relative to indices of patients before RT.

Assessment of changes in biochemical parameters in the dynamics against the background of RT (Fig. 8) showed that in patients of the main group against the background of RT, urea level increased by 21.1% (p<0.001) and amounted to 5.5 [4.5; 6.3] mmol/l, while in patients without LRC, the level of urea after RT decreased by 8.0% (p=0.07). Except for indicated changes in patients with LRC there was noted increased creatinine level by 4.9% (p=0.07), alanine aminotransferase (ALT) – by 3.5% (p=0.2), and virtually unchanged bilirubin (+0.7%) compared to its statistically significant (p=0.02) decrease by 9.2% relative to baseline values before RT in control patients.

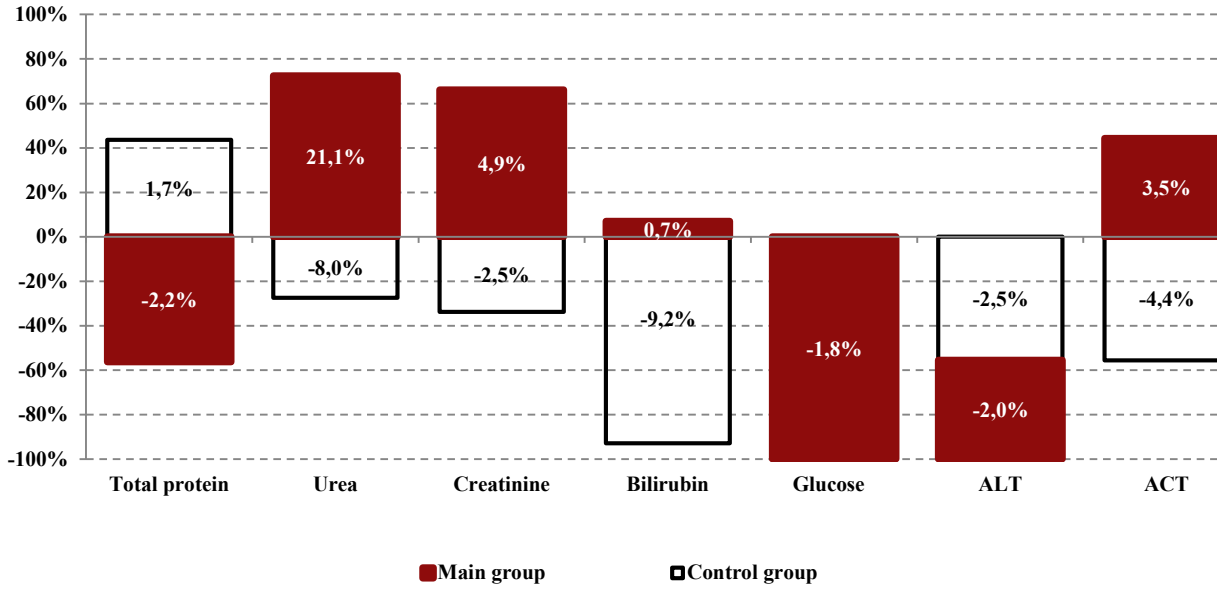

Fig. 8. Dynamics of biochemical parameters in cervical cancer patients after radiotherapy, n=254

Describing the parameters of the blood coagulation system (Table 5), it should be noted that in patients of the main group before RT there was noted higher (p = 0.4) clot time by 10.8%, which was 8.3, [6.2; 9.8] minutes respectively, relative to the index of patients without LRC (7.4 [6.3; 10.0] min.), lower fibrinogen level (3.3 [2.6; 4.6] g/l (p=0.08) by 6.1%. Intergroup differences of other indicators did not exceed 3.0%.

Table 5

Dynamics of parameters of blood coagulation in women against radiation therapy of cervical cancer (M±m, 95% CI, Me [LQ; UQ], n=254)

Parameter, unit of measurement	Main group (patients with LRC, n = 127)		Control group (patients without LRC, n = 127)	
	Before RT	After RT.	Before RT	After RT
Prothrombin time	16.0 [14.0; 17.0]	15.0 [14.0; 16.0]	16.0 [14.3; 17.8]	16.6 [15.0; 17.0] *
Prothrombin index, r.u..	94.1 [88.9; 100.0]	93.7 [93.1; 100.0]	95.0 [88.9; 100.0]	93.1 [86.7; 100.0] #
Activated partial (partial) thromboplastin time	36.7 [32.8; 40.0]	33.0 [28.0; 37.0] #	35.0 [31.1; 40.0]	34.0 [30.0; 39.0]
Clot time, min	8.3 [6.2; 9.8]	7.4 [6.2; 9.4]	7.4 [6.3; 10.0]	8.2 [5.4; 10.3]
International normalized ratio, r. u.	1.1 [1.0; 1.1]	1.1 [1.0; 1.1]	1.1 [1.0; 1.2]	1.1 [1.0; 1.2] *#
Fibrigogen, g/l	3.3 [2.6; 4.6]	3.4 [2.7; 4.2]	3.1 [2.4; 3.6]	4.1 [3.0; 5.2] *#
Soluble fibrin-monomer complexes, mg / dl	3.5 [3.5; 3.5]	3.5 [3.5; 3.5]	3.5 [3.5; 3.5]	4.5 [3.5; 3.5] *#

Notes: * – p≤0.05 relative to patients in the main group at appropriate study time, 2. # – p≤0.05 relative to parameters of patients before RT.

The analysis of changes in blood clotting system against RT in dynamics showed (Fig. 9) statistically significant (p=0.008) decrease in activated partial (partial) thromboplastin time (APTT) by 10.0% in patients with LRC while in patients in the control group this indicator decreased only by 2.9% (p=0.2).

Insignificant changes in the level of fibrinogen (+3.5%, p=0.05) and the concentration of soluble fibrin-monomer complexes in the patients of the main group, attract attention, while in patients of the control group, these indicators statistically significant (p<0.01) increased by 32.5% and 27.1% respectively.

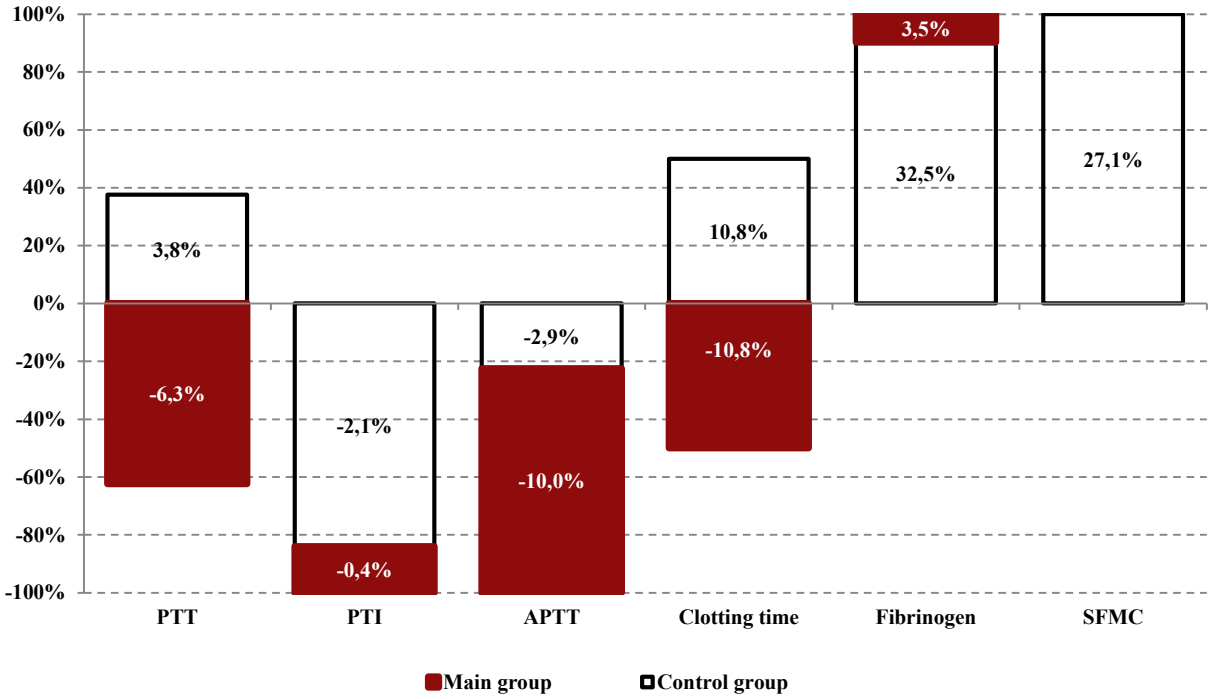

Fig. 9. Dynamics of blood coagulation in patients with cervical cancer after radiation therapy, n=254

CONCLUSIONS

1. The study has shown that such clinical laboratory parameters as increase in hematocrit and fibrinogen values before radiotherapy are worth considering as prognostic factors in cervical cancer patients.
2. The presence of laboratory signs of cytolytic syndrome (increased levels of aspartate aminotransferase, urea and total protein) in cervical cancer patients before radiotherapy is a prerequisite for development of late radiation complications.
3. The presence of concomitant aggravating diseases of the endocrine system, blood system, musculoskeletal system, nervous system and digestive system statistically significantly (p<0,05) increases the risk of late radiation complications in cervical cancer patients by 20, 2; 7.0; 2.3; 1.8 and 1.6 times, respectively.

Conflict of interests. The authors declare no conflict of interest.

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