

# Disorders of the cardiovascular system performance in the early post-castration period in patients with locally advanced cervical cancer and their correction with the low-dose xenon therapy

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## Aims

The aim hereof is to study the cardiovascular system disorders in the early post-castration period in patients with locally advanced cervical cancer and a possibility of correction of such disorders with the low-dose xenon therapy.

## Materials and methods

The study involved 28 female patients of reproductive age ( $49.8 \pm 0.5$  years) diagnosed with locally advanced cervical cancer. The main test group consisted of 16 patients, who received the xenon therapy in addition to the main treatment in the early post-castration period. The reference group included 12 female patients without xenon therapy. The cardiovascular system functional state was evaluated with cardiac analyzer Cardiocode at three stages: before surgical intervention, on postsurgery day 3 and upon the completion of the therapy.

## Results and conclusions

Early manifestations of the post-ovariectomy syndrome in the postsurgery period in female patients with locally advanced cervical cancer were accompanied by a disorder in the cardiovascular bio-adaptive and metabolic regulatory mechanisms of the uncompensated distress type, an excess of the phosphocreatine concentration and a decrease in the oxygen level in the myocardium. Upon the completion of the therapy in the reference group patients, changes in the coronary vessels hemodynamics, the dominance of the anaerobic energy

exchange in the myocardium, pronounced neurovegetative and psychoemotional disorders have been revealed. The use of the low-dose xenon therapy in the main test group patients has contributed to normalization of myocardial metabolism, recovery of the aerobic energy exchange, and neutralization of neurovegetative and psychoemotional manifestations of the post-ovariectomy syndrome. Thus, the diagnostics of cardiovascular disorders in the early postsurgery period as well as the correction of the disorders and abnormalities with the low-dose xenon therapy are of great importance in the prevention of cardiovascular diseases in oncogynecologic patients with the post-ovariectomy syndrome.

## Keywords

Locally advanced cervical cancer, Post-ovariectomy syndrome, Xenon therapy, Electrocardiogram, Myocardial metabolism, Baevsky adaptive tension index\*

## Imprint

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## Introduction

As evidenced by the annual world statistics data, cervical cancer (CC) is diagnosed in 529,400 patients [1], ranked the 7th among all malignant tumors and the 3rd among tumors in the cohort of female patients [2]. Treatment of patients with locally advanced CC is a complex, stage-by-stage process, including the surgical stage (an extended nerve-sparing extirpation of the uterus with appendages, the upper third of the vagina with pelvic lymphadenectomy) supported by chemoradiotherapy [3,4].

As a result of the surgical treatment, against the background of a sudden discontinuance of the ovarian functions, menopause with clinical manifestations of the post-castration syndrome [5,6], which are expressed by neurovegetative and psychoemotional disorders [7], develops already in the early postsurgery period. Against the background of the neurovegetative disorders, under a deficit of the ovarian hormones,

noted are disorders and abnormalities in the cardiovascular system performance [8], associated with the development of coronary oxidative stress [9], death of myocardial cells [10], disturbances of ion transport in cardiomyocytes [11,12] as well as of myocardial contractility functions [13].

As a rule, conventional hormonal methods are most often used for correction of the post-ovariectomy syndrome manifestations, but in fact, there is no unified standard plan or schedule to eliminate the symptoms of the induced menopause in oncogynecologic patients of reproductive age after their antitumor treatment [14]. Taking into account that minimally invasive methods of regenerative therapy are preferred for this category of patients, the use of the inert gas xenon, which produces not only analgesic, but also cardioprotective, immunomodulatory and hormonomodulating effects [15,16], is a promising way to solve the above formulated problems.

## Aim

The aim of this study is to identify disorders and abnormalities in the cardiovascular system functional state in the early postsurgery period in female patients after ovariectomy and assess the possibility of their correction with the use of the low dose xenon therapy.

## Materials and methods

Our study has covered 28 female patients of reproductive age ( $39.4 \pm 3.7$  years), diagnosed with locally advanced cervical cancer, who have completed their complex treatment in a hospital maintained by the Rostov Research Institute of Oncology, Ministry of Healthcare of the Russian Federation, in 2016-2017. The first stage of the treatment includes the nerve-sparing extirpation of the uterus with appendages and the upper third of the vagina with pelvic lymphadenectomy. According to the TNM classification, the degree of the tumor process spread has corresponded to pT1bN0M0 (n=12), pT2aN0M0 (n=16), and according to the histological analysis, it has been classified as squamous cell carcinoma cancer of different degrees of differentiation.

The main test group has included 16 patients, who have been treated with the use of xenon (XeMed® (medical xenon), RU No. LS-000121) in addition to the basic anticancer therapy. The xenon therapy sessions have been performed by an anesthesiologist employing therapeutic complex KTK-01. The xenon-ox-

xygen mixture is supplied to the face mask within a closed circuit (a gas container volume is 4 liters). During the session, a patient is in a state of superficial sleep, but she remains capable of maintaining the possibility of verbal contact. The session duration is 15-20 minutes, and after its completion, an additional oxygenation is provided. In order to reduce the risk of a negative response in case of an increased sensitivity to the therapy, the course of xenon therapy begins with a low dose of xenon in the xenon-oxygen mixture, up to 10-12%, followed by a 2-4% increase, reaching the recommended therapeutic dose of 20-22% by the fifth session. In the reference group of 12 patients no xenon therapy has been applied.

To diagnose the post-ovariectomy syndrome, the modified menopausal Kupperman-Uvarova index has been used.

An ECG has been recorded with cardiometric device Cardiocode at three stages: before surgery, on postsurgery day 3 and upon completion of the therapy (on the day of discharge from the hospital). A single-lead ECG and a Rheogram of each patient have been produced synchronously for 30 seconds in the lying position and 30 seconds in the sitting position. The ECG and Rheogram electrodes are placed in accordance with the recommended procedure [17].

The durations of the cardiac cycle phases and the respective parameters of hemodynamics, namely stroke volume (SV, ml), minute volume (MV, l/ml), volumes of blood entering the ventricle during the early diastole (PV1, ml) and the atrial systole (PV2, ml), blood volumes ejected by the ventricle during rapid ejection phase (PV3, ml) and slow ejection phase (PV4, ml) have been calculated noninvasively using the hemodynamics equation by G. Poyedintsev - O. Voronova [8] supported by the Cardiocode software [17].

The stability of the regulatory system state has been determined on the basis of the Baevsky TI values: the TI values ranged from 100 to 500 arbitrary units have been considered as the norm, the values exceeding 500 have been classified as overtension, and those under 100 have been considered as a weak state of the regulatory systems [17].

The cardiac metabolic processes have been assessed by parameters of the oxygen, lactate and phosphocreatine concentrations, computed by the S.A. Dushanin method, aided by the Cardiocode software. As to the aerobic process, the parameter values varying in the ranges 0.7 ... 0.85, 0.6 ... 0.65, 0.5 ... 0.55 have

been considered as the norm; the normal values for the anaerobic-glycolytic process have been assumed to be 3.0 ... 7.0, and the normal levels for the anaerobic-allocation process have been taken to be 2.0 ... 4.0, respectively [17].

The statistics data have been analyzed with the Statistica 10.0 software (StatSoft, USA). The comparison of the cardiovascular activity parameters at different stages of the studies has been carried out using the Student's criterion. Taking into account the Bonferroni correction, the values  $p < 0.013$  have been considered to be significantly reliable.

The experimental study has been completed in accordance with the ethical principles for medical research involving human subjects (Declaration of Helsinki, Finland, 1964).

## Results

Our assessment of the performance of the cardiovascular system before the surgical treatment has shown no significant disorders in hemodynamic functions, and the relevant parameters have been found to be within the age-related norm (see Table 1 herein). However, it has been noted that all patients have demonstrated the state of compensated distress, under the conditions of which the mean TI value has reached  $402 \pm 12.6$  arbitrary units. At the same time, the calculated metabolic values have indicated that there has been a significant accumulation of lactate in the myocardium up to 21.27 arbitrary units, under a normal oxygen concentration of 0.52 arbitrary units and the phosphocreatine level of 3.76 arbitrary units. (see Figure 1 herein).

An analysis of the neurovegetative and psychoemotional status in patients of both groups on postsurgery day 3 has shown that 85% of the patients have had a clear tendency to increasing the degree of the major

manifestations of the postovariectomy syndrome and that in 15% only the tendency has been reported to be weak. The most frequently recorded neurovegetative disorders are the following: increased arterial blood pressure (67%), headaches and sweating (66%), dizziness (68%) and elevated excitability (75%). There mentioned should be also complaints about frequent changes in mood (85%), memory loss and irritability (68%) and anxiety (87%).

On postsurgery day 3, in the reference group patients and in the main test group patients, despite the absence of significant changes in the hemodynamic parameters, TI has increased by 1.3 times and reached  $530 \pm 21.3$  arbitrary units, that indicates an aggravation of the uncompensated distress. At the same time, the oxygen concentration in the myocardium has decreased to the lower limit of the norm (0.49 arbitrary units), the elevated lactate level has decreased by 2 times reaching 10.8 arbitrary units ( $p < 0.01$ ), but even these lactate values have exceeded the norm. Despite the fact that the level of phosphocreatine has increased to 5.03 arbitrary units ( $p < 0.01$ ), the change in the metabolism parameters bears witness to an imbalance in the processes of the energy metabolism with the dominance of the anaerobic respiration (see Figure 1 herein).

In the patients of the main test group, upon completion of the xenon therapy, no disorders in the hemodynamic parameters have been found (see Table 1 herein). The calculated cardiometric parameters have demonstrated that there is a unidirectional tendency to normalization of the bioadaptive and metabolic processes in the myocardium. Despite the fact that the TI value of  $666.7 \pm 24.7$  arbitrary units has indicated a retardation of the transition of the uncompensated distress into a compensated form thereof, the change in the metabolic processes has been clearly revealed.

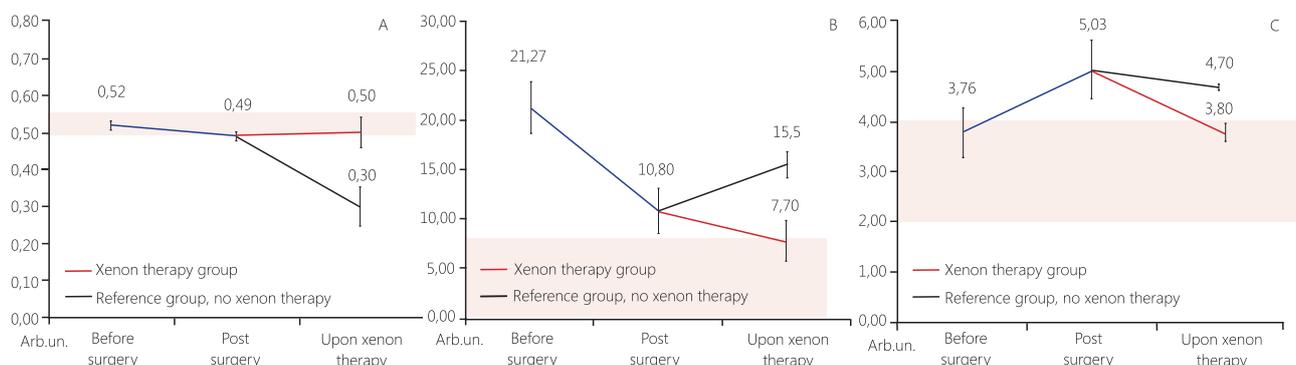


Figure 1. Metabolic processes in the myocardium at three stages of examination: A – oxygen concentration, B – lactate concentration, C – phosphocreatine concentration. Note: Beige background indicates the limits of the norm for each parameter.

Table 1. The main characteristics of heart hemodynamics at three stages of experimental studies

Parameters	SV	MV	PV1	PV2	PV3	PV4
Before surgical treatment	47,8±7,6	4,1±0,7	30,1±2,4	24,0±2,9	32,1±2,9	22,0±1,9
Postsurgery period	58,3±4,9	5,3±0,4	34,9±3,1	30,6±4,2	34,6±2,9	23,7±0,1
Upon completion of the xenon therapy	56,7±7,1	4,7±0,6	32,4±6,3	24,3±4,1	33,7±4,2	23,1±2,9
Upon completion of treatment without xenon therapy	48,6±1,4	4,3±0,2	27,5*±3,3	25,2±3,4	28,8±0,9	19,7*±0,6

Note: \* reliably significant variances at  $p < 0,013$

In this case, the xenon therapy has resulted in a stable maintenance of the oxygen concentration at its normal level (0.5 arbitrary units), which has exceeded its reduced level in the reference group by 1.6 times. As compared with the reference group patients, we have observed a decrease in the lactate concentration by 2.0 times, the values of which have been found to be reduced in the postsurgery period reaching the normal level of 7.7 arbitrary units. The same case is with the phosphocreatine level, which has reached the value of 3.8 arbitrary units (see Figure 1 herein). An essential feature of the above cases is that against the background of the xenon therapy, we have succeeded in full mitigation of the neurovegetative and psychoemotional manifestations of the castration syndrome in the patients under study.

As opposed to the main test group, in the reference group upon the completion of the standard therapy without using xenon-oxygen inhalations, a significant hemodynamic disorder has been diagnosed, mainly due to a decrease in cardiac cycle phase volumes PV1 (from  $34.9 \pm 3.1$  to  $27.5 \pm 3.3$  ml,  $p < 0.013$ ) and PV4 (from  $23.7 \pm 0.11$  to  $9.7 \pm 0.6$  ml,  $p < 0.013$ ). This has been confirmed by a reduction in the volume of blood entering the ventricle in the early diastole and ejected by the left ventricle during the slow ejection phase (see Table 1 herein). The TI value has demonstrated even a greater increase and has reached the value of  $693.6 \pm 15.7$  arbitrary units that is in correspondence with the stable state of uncompensated distress. The oxygen concentration has been recorded to be much lower than the norm: 0.30 arbitrary units ( $p < 0.013$ ), the lactate level has reliably exceeded the norm reaching values significantly higher than those identified after the surgical treatment: 15.5 arbitrary units ( $p < 0.013$ ), and the level of phosphocreatine has remained much above the norm, demonstrating an imbalance in the processes of the cellular energy supply and the predominance of anaerobic energy exchange (see Figure 1 herein).

At the same time, complaints about increased arterial blood pressure (59%), headaches and dizziness (48%), sweating (52%), sleep disturbances (48%), increased fatigue (100%), pessimistic attitude to life (94%), apathy, poor sleep and low working capacity (75%), aggressiveness (66%), depression (50%) and anxiety (63%) have been observed to remain and even intensify in the reference group.

## Discussion

In modern clinical oncology, the practical application of therapy and rehabilitation measures targeted at improving the quality of life of patients at all stages of their antitumor treatment is given the highest priority [18]. Females of reproductive age with malignant tumors in the reproductive system are considered to be one of the most vulnerable categories among the cancer patients. The severity of their recovery in the postsurgery period can be explained by development of disorders and abnormalities at the different systemic levels in the organism, and they are primarily associated with the postovariectomy syndrome. Their cardiovascular performance disorders, caused by estrogen deficit, are attributed to delayed changes manifested in epicardial obesity and coronary calcinosis [19]. The study by Mitkovskaya et al. [19] shows that in females with the postovariectomy syndrome the myocardial hypertrophy and remodeling of left ventricle with abnormalities of its diastolic function often develop, and they have a high risk of cardiovascular diseases, having an unfavorable outcome in 46.4% of the cases.

The present study confirms the possibility of development of unfavorable pathogenic conditions responsible for the appearance of cardiac performance disorders in the early period after the nerve-sparing extirpation of the uterus and appendages with the upper third of the vagina in the cervical cancer patients. First of all, the high TI values recorded in the said cohort of the patients indicate that we deal with

a stable tension state of the uncompensated distress dominating in the organism. This contributes to the appearance of the cardiovascular system performance disorders and abnormalities that is clearly reflected in suppression of the hemodynamic processes, accompanied by an enhancement of neurovegetative reactions such as high blood pressure, complaints about hot flashes, headaches, dizziness, etc. In addition, the tension in the myocardial metabolic processes, associated with the dominance of the anaerobic character of the energy-forming processes, is noted. The given alterations without an appropriate corrective therapy may result in a high risk of cardiovascular diseases.

The use of the low-dose xenon therapy in the patients in the main test group has produced normalization of the myocardial metabolism, the recovery of the aerobic metabolism, as well as elimination of neurovegetative and psychoemotional abnormalities associated with the postovariectomy syndrome. This approach should be treated as a valuable alternative which may be offered the above mentioned female patients, whose quality of life against the background of uncompensated distress after the surgical stage of their treatment is seriously deteriorated. The obtained data bear witness to the necessity of the above method for rehabilitation of patients with postovariectomy syndrome already in the early postsurgery period in order to reduce the risk of cardiovascular disorders and recover their neurovegetative and psychoemotional state as criteria for increasing the functional and social status and quality of life in the reproductive age female patients.

## Conclusions

1. Against the background of the early manifested postovariectomy syndrome in the postsurgery period, in the patients of the reference and main test group, noted are a decrease in the cardiovascular system adaptive resources due to their transition to a stable state of uncompensated distress, accompanied by a reduction in the coronary vessel blood circulation, a decrease in the oxygen level and an imbalance of the bioenergetic processes with the dominance of the anaerobic energy exchange, pronounced neurovegetative and psychoemotional disorders and abnormalities.
2. The use of the low-dose xenon therapy for the above test cohort of the patients contributes to normalization of the myocardial metabolism, the recovery of the aerobic energy exchange, as well as elimination of

neurovegetative and psychoemotional disorders and abnormalities of the postovariectomy syndrome that significantly improves the quality of life of the reproductive age patients of this category.

*Editor's note:* The Baevsky adaptive tension index is also known in English reference literature as “the Baevsky index” or “the Baevsky stress index”

## Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

## Conflict of interest

None declared.

## Author contributions

All the authors read the ICMJE criteria for authorship and approved the final manuscript.

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