

COMPARISON OF THE QUALITY OF LIFE OF PATIENTS IN THE LOCALY ADVANCED BREAST CANCER FORMS AFTER SYSTEM AND INTRALYMPHATIC POLYCHEMOTHERAPY

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Abstract

In recent years, breast cancer (BC) is the most common cancer pathology and the most common cause of disability among women in developed countries. Finding the most effective ways of interaction between the patient and the doctor creates the preconditions for the necessary analysis of the treatment process from an objective and subjective point of view. Therefore, an important indicator to be taken into account is the quality of life of a patient.

To compare the indicators of a comprehensive assessment of the quality of life of patients to the adverse locally advanced forms (LA) of breast cancer before and after systemic intravenous polychemotherapy (SPCTx) and selective endolymphatic polychemotherapy (ELPCTx) in neoadjuvant mode.

The study was conducted on the basis of a random analysis of outpatient cards from 112 patients with LA BC T4A-DN0-3M0 who received a comprehensive antitumor treatment on the basis of the Donetsk regional antitumor center and the University Clinic of the Odessa National Medical University from 2000 to 2017, which was proposed a questionnaire at various stages of preoperative treatment. The first (control) group consisted of 65 patients (58 %) with inoperable forms of LA BC, which was performed in neoadjuvant mode by SPCTx. The second (study group) included 47 patients (42 %) with inoperable forms of LA BC, which was performed as a neoadjuvant course ELPCTx.

According to the integral indicators of quality of life and quality of health between patients in the control and study groups, there was no statistically significant difference. In a detailed analysis of the indicators of symptomatic scales, the difference between the groups did not exceed the critical. Based on the results of a study conducted among patients receiving endolymphatic chemotherapy in a neoadjuvant mode, the subjective evaluations of treatment in absolute numbers have better reference values without statistical superiority.

The study of the integrative indicator of quality of life and its discrete elements is an ergonomic and economical means of heuristic assessment of the health of patients in order to further develop more rational and convenient ways of solving urgent issues of modern oncology by increasing compliance and finding a compromise between the physician and the patient.

Keywords: locally advanced breast cancer, complex treatment, endolymphatic polychemotherapy, systemic polychemotherapy, quality of life.

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1. Introduction

Over the past decades, according to the registers of most countries of the world, breast cancer (BC) is the most widespread cancer and one of the most common causes of disability and mortality among women in the world. [1] As part of the development of the etiological profile for this pathology, a fairly wide range of factors has been formed, none of which has a statistically significant advantage over others, so each particular situation requires an individual approach to diagnosis. On the other hand, according to the pathogenetic and morphological characteristics of the breast cancer group, a wide variation of neoplasms, different from genotypic and phenotypic properties, is combined [2]. According to WHO, in the epidemiological mapping there is a clear tendency to a high prevalence among the population of the Western world, which is a consequence of their cultural-traditional and socio-demographic characteristics [3]. All this explains the increased costs of maintaining and improving diagnostic and therapeutic measures by public and private insurance institutions and the fairness of growing clinical and academic interest in understanding the key aspects of breast cancer [4, 5].

A weighted approach to each individual disease dictates to consider it through an individual prism for the optimal choice of appropriate therapy. In this very perspective, in cancer practice, targeted therapy in the widest possible sense of the term looks: from vector and monoclonal bio-engineering developments to direct mechanical targeting of necessary substances to the problem area by enriching the afferent vascular bed with active components of the drug. The most suitable for this method for obvious reasons are locally advanced forms of tumors, and in the context of the article, breast cancer (LA BC) [6, 7]. Despite the increasing interest of professionals and amateurs in addressing the problem of targeting this cancer, a wide range of treatments suggests that there is no statistically validated treatment for each individual case. The local problem of our country is a multicausal stagnation in the direction of conducting necessary research and accumulation of relevant information [8, 9].

The problem of finding an adequate route for delivery of chemotherapeutic agents and the composition of the drug panel itself for the selective complex treatment of LA BC is a topical issue, given the poor performance of systemic polychemotherapy (SPCTx).

Regular methods of CTx (intraarterial, intravenous, endolymphatic) are one of the modern surgical ways of solving the question of a selective approach to the treatment of malignant neoplasms. Lymphotropic therapy is based on the notion of the additivity of the lymphatic structure of a particular region with a clear direction of lymph movement from the periphery to the regional centres. The complicated and histotoxic method of intradermal injection with subsequent passive drainage on the principle of diffusion requires a combination of parallel intravenous administration and eliminates repeat CTx sessions. Therefore, the new and progressive stage of the evolution of the method was the manoeuvre of microsurgical high-precision catheterization of several major lymphatic vessels with saturation of the afferent bed of the target area for 3–5 days. The theoretical efficiency and reliability of endolymphatic infusion make the technique promising in the context of further study [10, 11]. The aim is to achieve common results for all targeting methods: increasing local exposure and reducing the systemic toxic response.

2. Aim of the research

To compare the indicators of the integrated assessment of the quality of life of patients to locally advanced forms of breast cancer (LA BC) before and after systemic intravenous polychemotherapy (SPCTx) and selective endolymphatic polychemotherapy (ELPCTx) in a neoadjuvant mode.

3. Materials and methods

The study was conducted on the basis of a random analysis of outpatient cards from 112 patients with LA BC T4A-DN0-3M0 who received a comprehensive antitumor treatment on the basis of the Donetsk regional antitumor center and the University Clinic of the Odessa National Medical University from 2000 to 2017, which was proposed a questionnaire at various stages of preoperative treatment. Before entering the patient in the study protocol, a written voluntary consent to participate in the study was obtained in accordance with the WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects, 2013 form.

The sample was standardized according to age, gender, social and clinical parameters. Age range: 46.3 ± 12.4 years. Out of all patients, 85 (76 %) belonged to the active working age group. The first (control) group consisted of 65 patients (58 %) with inoperable forms of LA BC, which was performed in neoadjuvant mode by SPCTx. The second (study group) included 47 patients (42 %) with inoperable forms of LA BC, which was performed as a neoadjuvant course ELPCTx. The number of courses spent on preoperative PCTx was at most 4. The ultimate goal was to achieve the tumour of the operable state.

The study of the quality of life of patients was conducted within the framework of the International protocol of the European organization for the study and treatment of cancer, using questionnaires for the European organization for the research and treatment of cancer (EORTC QLQ-C30) questionnaire, which have been tested in numerous foreign studies and meet the criteria for reliability, validity and effectiveness.

The questionnaire has a protocol form and includes 30 standard questions: general questions (quality of life (QL) and quality of health (QH)), functional status scale (physical, emotional, role, social and cognitive) and the scale of key symptoms. In contrast to the proposed by the authors method of the evaluation, a linear analogue scale with a range from 1 to 100 points was applied. For functional scales, the worst indicator corresponded to an estimate of 0 points, the best one was 100 points. In the symptomatic scales, the weakest manifestation was estimated at 0 points, the strongest – 100 points.

Patient questionnaires were carried out within 1 week prior to the start of PCTx and 10–14 days after each course of PCTx. The most representative changes in functional and symptomatic scales occurred at these checkpoints. The questionnaire was conducted among 100 % of patients before the start of treatment and stopped after the end of therapy for any reason or at the patient's own request.

Total course doses of chemotherapy were calculated individually for each patient according to BSA criteria (**Table 1**).

Table 1

Protocols for conducting PCTx in the ELPCTx mode according to BSA criteria

CAF protocol:	Cyclophosphamide: from the second to the fourth day – 400 mg/m²; Fluorouracil: from the second to the fourth day – 500 mg/m²; Doxorubicin: on the first day IV – 50 mg/m².
CAMF protocol:	Cyclophosphamide: from the second to the fourth day – 400 mg/m ² ; Methotrexate: the first and fifth days – 30 mg/m ² ; Fluorouracil: from the second to the fourth day – 500 mg/m ² . Doxorubicin: on the first day IV – 30 mg/m ² .
CMF protocol:	Cyclophosphamide: from the second to the fourth day – 400 mg/m ² ; Methotrexate: the first and fifth days – 30 mg/m ² ; Fluorouracil: from the second to the fourth day – 500 mg/m ² .

Data processing was performed using standard statistical functions of the MSExcel program. When comparing the indicators of QL in the study groups, a nonparametric index is used – the Pearson coefficient χ^2 , for the study of dynamics - the indices of the study of dynamic series. Static comparison parameters: estimated value of degree of freedom=1; at p-level<0.05 $\chi^2=3.841$; at p<0.01 $\chi^2=6.635$).

5. Results

The general condition of patients at all stages is mainly formed due to objective (presence of tumour neoplasms, intoxication syndrome, asthenic syndrome, local and systemic manifestations of tumour lysis, the addition of secondary infection of compromised tissues) and subjective (psychological and emotional discomfort from physical condition, social disadaptation through oncological stigmatization and disability) of factors.

After analyzing the QL index (**Fig. 1**), there were no statistically significant differences in the control group: the mean value was 54 ± 11.3 points in the control group, 57 ± 4.1 points in the study (at $p=0.67$ index=0.182). After completing 1 and 2 courses of chemotherapy, the QL index had a phase-out negative dynamics of the first (7.4 % and 8.0 %, respectively, with a final result of 46 ± 4.3 points), and in the second (5.3 % and 13.0 %, respectively, with a final result of 47 ± 3.1 points) in groups, retaining proportional statistical closeness of results. It is worth noting that because of the expressed intoxication syndrome and the psychological discomfort of participating in the trial, 3 patients (4.6 %) of group 1 and 2 patients (4.3 %) of the second group refused to further study their quality of life and continued treatment in the usual way. Such dynamics of indicators, according to the authors, is related to insufficiently established complications with patients and insufficient explanation of the essence of treatment: the persistence of the intoxication syndrome, the dissonance of the expected and actual changes in tumour size, the panic disappointment of treatment and the lack of improvement in well-being were interpreted by most patients as a negative result. The ultimate aim was achieved in 16 (25 %) patients in the first group and in 13 (28 %) patients in the second group. After completing the third course of chemotherapy, the reference values of the QL parameter were positive, increasing by 13 % (52 ± 2.3 points) in the control group and by 18 % (55 ± 4.9 points) in the study groups as a consequence of improving the general condition, becoming accustomed to the systematic wave-like dynamics of the symptoms toxicity to PCTx, improvement of local tumour status and achievement of the end result in most patients. However, statistically, the indices of both groups remained indispensable (at $p=0.671$, the index $\chi^2=0.181$). The regimen of the tumour was achieved in 30 (46 %) women in the first group and in 21 (45 %) women in the second group. After completion of 4 courses of PCTx, the indicators decreased by two or four points in both groups (50 ± 4.4 and 52 ± 2.3 points respectively), interpreted as the result of physical and moral deprivation of patients, lack of the same dynamics of clinical symptoms as in other patients, depression in the positive result and dissatisfaction with the symptoms of iatrogenic intoxication. There was no statistical difference in favour of one or another technique in the fact of holding 4 courses of PCTx ($\chi^2=0.08$ at $p=0.778$). Clinical effects appeared in 17 (26 %) women in the control group and in 11 (23 %) women in the study group. Unfortunately, the resectable state of La BC did not reach 2 (3 %) patients of the first group and 2 patients (4 %) of the second group; They were offered a system of professional assistance and support for cancer patients and symptomatic therapy in an oncologic dispensary.

Another indicator of the general character – the quality of health (**Fig. 2**) – was similar dynamics. Prior to conducting PCTx in patients of the first and second groups, the following results were obtained: the average score of good health in group 1 was 32 ± 4.1 points, and in the second – 35 ± 3.7 points, which had no statistically significant difference ($\chi^2=0.202$, $p=0.654$) According to patients, such a low estimate is due to the effect of the “depressed” state due to “incurable” disease and pessimistic predictions about the results of future treatment, formed through self-disinformation of patients when communicating with each other and studying unverified sources. Unfortunately, the conditions and format of the experiment did not allow a cleaner study to isolate patients and clarify their health and technical options for treating this pathology. Subsequently, after each course of chemotherapy, there was a stable difference of 3, 3 and 2 points, respectively,

insignificant by the Pearson coefficient ($\chi^2 < 3.841$), and with the fluctuations within the group of $5 \pm 1\%$, between the groups of indicators. In the phase of neoadjuvant therapy, the patient had no to evaluate the final result, however, with the help of explanatory work the doctor can correctly interpret the trends of the general state of the organism and local parameters (size and disintegration of the tumour).

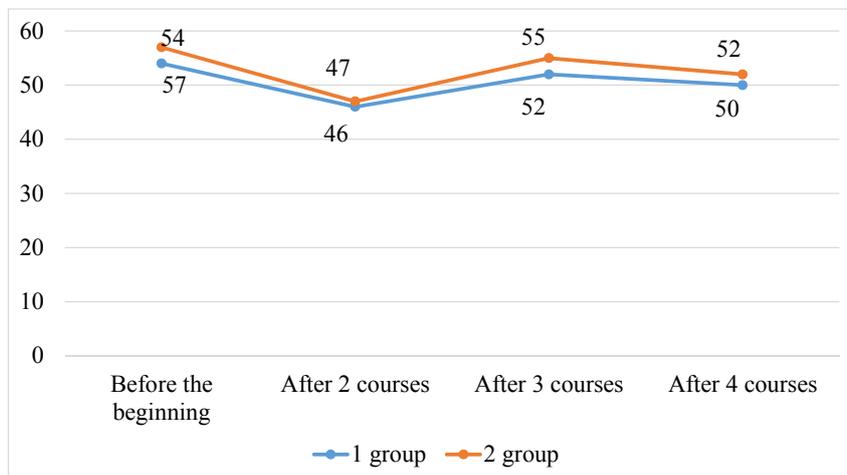


Fig. 1. QL patients before and after SPCTx and ELPCTx

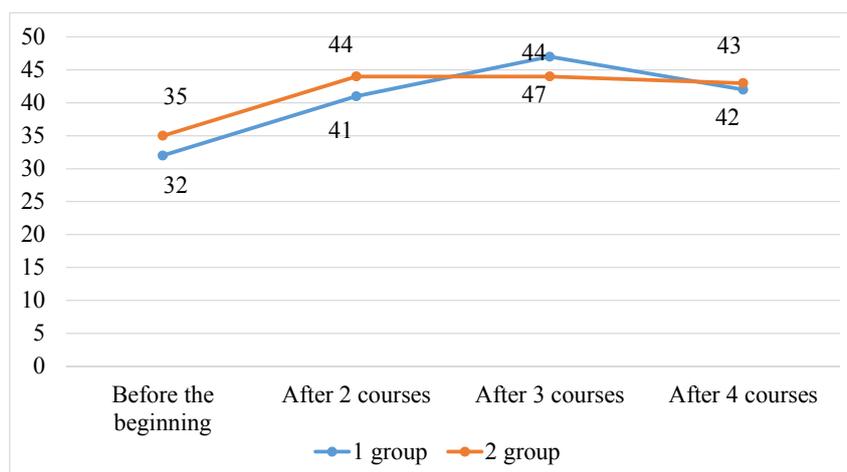


Fig. 2. QH patients before and after SPCTx and ELPCTx

In the structure of the questionnaire EORTC QLQ-C30, specific questions of the symptomatic scale are first and foremost, there are placed more general scales of functional, cognitive, emotional, psychological and social status, at the end there are two integral indicators – quality of life and quality of health, giving patients the opportunity move from solving more simple tasks to responding to global additive issues. Analyzing the questionnaires in reverse order, you can evaluate the components of these integral parameters.

The following changes were observed in the analysis of indicators on the general and physical health scales (Fig. 3, 4): a statistically insignificant difference before the start of chemotherapy (63 ± 6.4 and 81 ± 5.4 points in the first group, 65 ± 4.3 and 83 ± 9.6 points in the second, χ^2 , respectively, 0.087 and 0.136), followed by a negative dynamics of 5 points after 2 courses of chemotherapy and almost unchanged at the time of further treatment.

The smallest changes in response to chemotherapy were observed for the indicator of cognitive status: the intergroup and intragroup incomplete differentials stood in the range of 4 points and did not have statistical differences (Fig. 5).

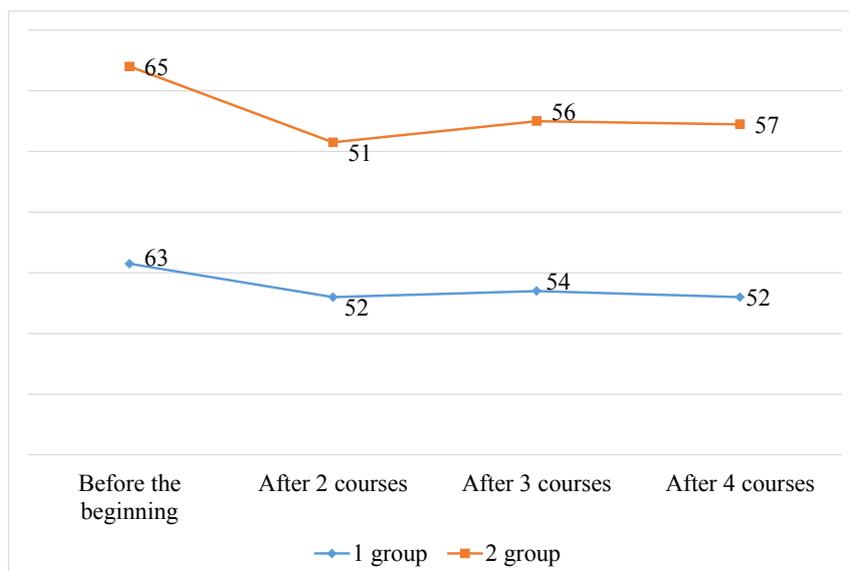


Fig. 3. The general condition of patients before and after the SPCTx and ELPCTx

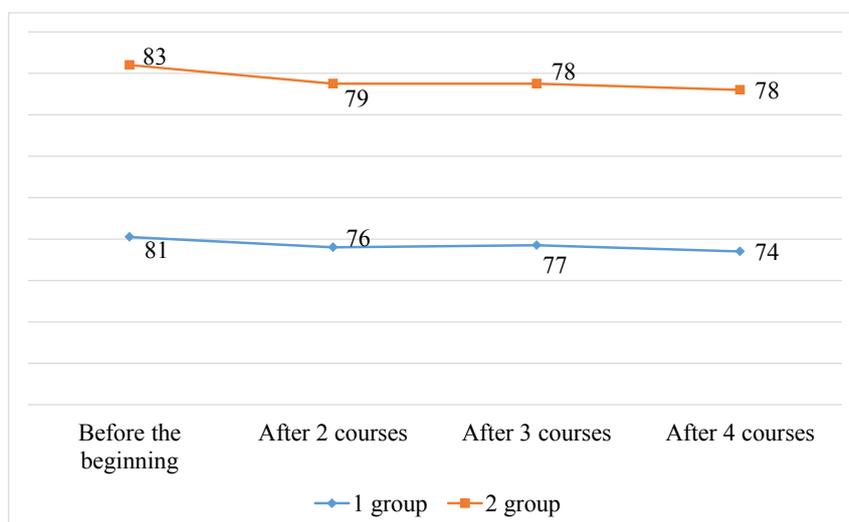


Fig. 4. Physical condition of patients before and after the SPCTx and ELPCTx

The most variability was naturally found in the results on the scales of psychological and emotional state and social adaptation. As expected, the indicators of the emotional background were extremely labile and the dynamics of the system was not traced; of course, this parameter is the most subjective and least reliable for discrete evaluation, however, as already noted, necessary for an integrated approach. During the analysis of the psychological state of women in both groups before and during the PCTx, fluctuations of wide amplitude that were not related to external factors (**Fig. 6**) were revealed, which is a serious consequence of insufficient professional psychotherapeutic assistance to patients.

On the other hand, the scale of social adaptation has shown a non-slip positive dynamics for both groups, though, again, without statistical discrepancies with intergroup differences of 5 points maximum. Yet, according to the authors, this parameter is a key component of the quality of life indicator, since it is social adaptation and self-determination that is the ultimate goal of integrated treatment and an intermediate for each of the stages.

Before the start of chemotherapy, the patients of both groups considered themselves equally low socially adapted (47 ± 3.7 points in the first group and 49 ± 3.9 in the second group). After two courses of PCTx in both groups, the indicators improved: 25.5 % in control patients, making

59 ± 7.2 points, and by 16 % in the studied cohort with 49 ± 4.3 points. Subsequently, the positive dynamics were maintained (Fig. 7): in the first group +8.5 % (64 ± 5.0 points) after 3 courses and +12.5 % (72 ± 5.2 points) after the fourth; in the second – +11 % (65 ± 4.7 points) in the third stage of the study +7.5 % (72 ± 3.1 points) in the fourth. At the same time, objectively, in patients, there was a marked reduction of local symptoms in both cohorts of patients.

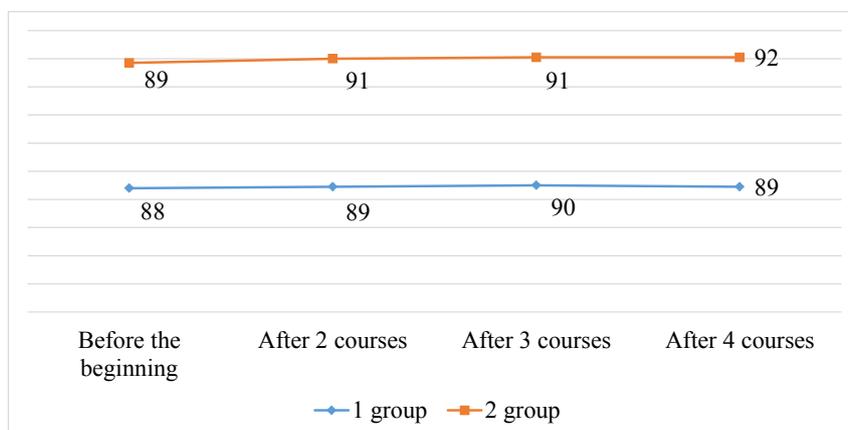


Fig. 5. Cognitive condition of patients before and after the SPCTx and ELPCTx

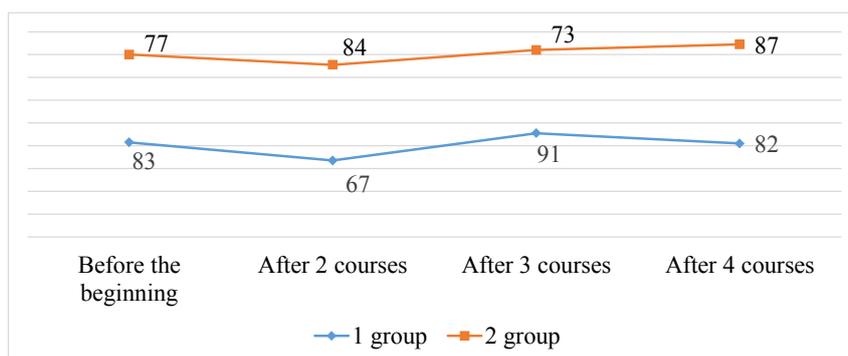


Fig. 6. Emotional condition of patients before and after the SPCTx and ELPCTx

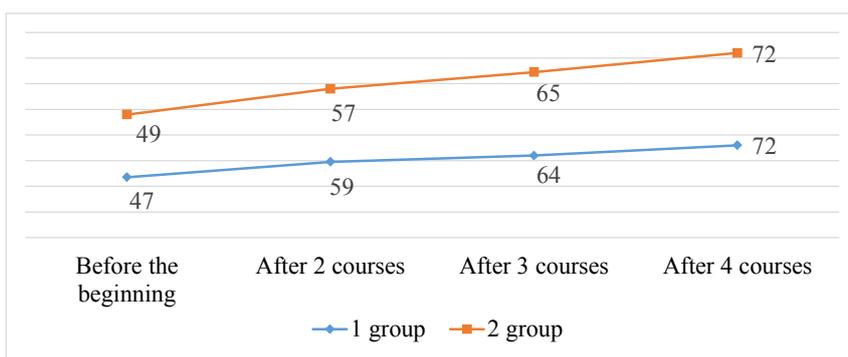


Fig. 7. Social condition of patients before and after the SPCTx and ELPCTx

During the analysis of the panel of symptomatic scales for publication only indicators with high reference values, statistically significant differences, and pathogenetic connection with the intervention: pain, nausea and loss of appetite – as parameters characterizing local and systemic changes in the body.

The intoxication syndrome is a major side effect of chemotherapeutic treatment. It is worth noting that objectively the symptoms of intoxication persist on average 5 ± 1 day after SPCTx and

4±1 day after ELPCTx. It is also important that the intoxication syndrome is generated both by the presence of the tumour itself and by therapeutic measures. It is advisable to explain this fact in detail to patients before conducting chemotherapy and to teach them to track the dynamics of new symptoms for a proper interpretation of their own condition.

The search for new drugs and their rational combination contribute to the reduction of the symptoms of iatrogenic poisoning of the body, regardless of the route of administration of drugs, therefore, the incidence of insomnia, apathy, depression and general fatigue will not change significantly. However, as can be seen from **Fig. 8, 9**, nausea and loss of appetite are observed in many patients with lysis syndrome before the treatment, which on average gives a low score (13±1.4 and 11±0.9 points respectively in the first group, 13±1.9 and 11±1.1 – in the second). At later stages, these symptoms were noted in typical terms in general, and were evaluated respectively [64±4.3 and 62±1.3] points in the first group and [59±4.1 and 63±2.0] points in the second to the second stage, [58±5.3 i57±1.1] and [57±3.2i59±1.7], respectively, on the third; [49±5.7 i51±1.3] and [49±4.0 and 49±2.1] in the fourth. The analysis did not reveal a significant difference between the parameters at any of the stages.

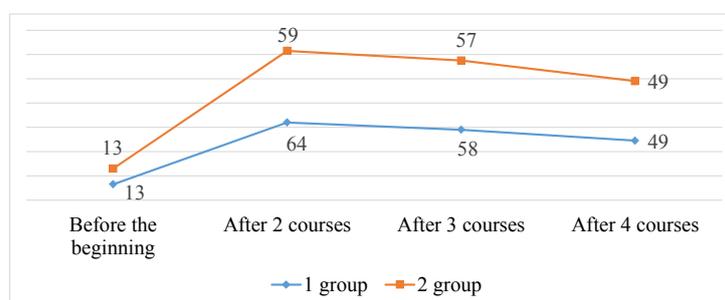


Fig. 8. Nausea of patients before and after the SPCTx and ELPCTx

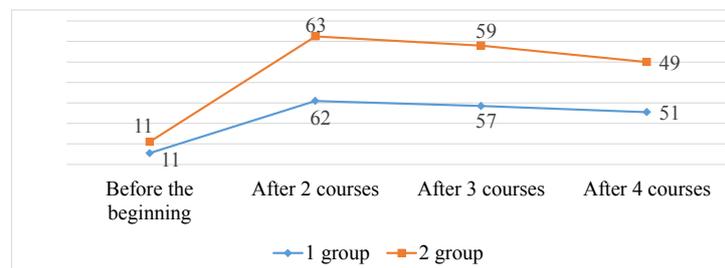


Fig. 9. Loss of appetite of patients before and after the SPCTx and ELPCTx

Separately, it is necessary to consider the parameter of pain syndrome. Unlike the others, it is an indicator of the dynamics of the local status. Interdependent control groups of reliable differences are not traced (**Fig. 10**).

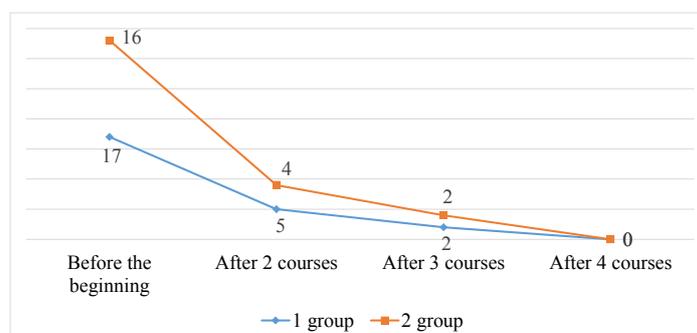


Fig. 10. Pain syndrome in patients before and after the SPCTx and ELPCTx

6. Discussion

Modern medicine is in the unbalanced conflict environment of the ideas of the past and the present. Formed at the beginning of the last century, patterns of thinking and implementation of approaches to working with patients were characterized by profound personalization and unreasonably radical actions, and now phase-by-stage processes of viewing and comparing are underway [11, 12]. With the advent of evidence-based medicine and the beginning of the formation of international information bases in the global medical community comes the conclusion about the irrationality of many classical methods of treatment, and the methods used to assess the results achieved [13]. However, despite the constant progress of medicine, new advances in the development of general and special directions, as well as the tireless and close attention of the public to the problems of medicine, statistical data on a scale of decades do not show convincing qualitative changes in the dynamics of morbidity and mortality [14, 15]. A rational approach to the organization of work posits that the achievement of the absolute result is a strategically false course, and a competent program of development envisages, first of all, the right choice of purpose and the correct statement of the problem before discipline in the person of each individual participant. Therefore, at the end of the last century, medicine completely changed the concept of its approach to the patient, turning it from the object to the subject of the medical process. The aim of achieving maximum clinical effect at the cost of limiting comfort was no longer a self-image, and the new balanced way of medicine became patient oriented, on its needs, interests and experiences [16]. The total vector of human impact in the health care system has changed the direction from quantitative intensive and extensive statistical indicators of overall survival, duration of a non-recurrent period and disability to compromise qualitative indicators of comfort and health. In this context, the question arises of the need to develop and use measures to evaluate not only the quantitative but also qualitative component of a comprehensive conclusion on the results of therapy. Therefore, an important indicator to be taken into account is the quality of life of a patient [17, 18].

In the original IndexMedicus (1977), QL is defined as the physical, emotional, financial and spiritual well-being of man [19]. According to the decision of the American Society of Clinical Oncology (ASCO), QL is more important than the level of non-recurrent survival in assessing the results of antitumor therapy [20].

The main advantage of the QL index is its integrative ability: the ideal QL index is an objective assessment of subjective data. In the future it will provide an opportunity to unite and coordinate a number of nonparametric additive characteristics such as overall health, emotional, cognitive, psychological and social aspects, i.e. implementing strategic objective to assess the condition of the patient before and after treatment in terms of the patient, then it will become possible to rationalize further therapeutic tactics more effectively. The main drawback of the QL index is idempotence its synthetic nature and lack immanence parameters, which create prerequisites for the approximability of any mathematical function for its modelling and quantitative and qualitative terms.

Modern integrated assessment questionnaire QL reflect these positive and negative aspects, but still allow you to “compare what is comparable.” The widespread introduction of standardized forms surveys as a routine cancer research and regular large-scale meta-analyzes will accumulate and structure the material to further a more advanced scientific and methodological materials.

Using the EORTC QLQ-C30 questionnaire as one of the most common forms in our research is largely dictated by these considerations. In the future, the systematization of the data of each individual medical unit will create the opportunity to form the axis of academic and clinical experience in a particular direction and develop an effective system of vertical and horizontal feedback on the local, regional, state and international levels. Taking into account the difference in the structure of patterns of health care organization between the countries of Eastern and Western Europe, as well as their greater practice in the study of quality of life indicators in the framework of an expanded individual approach to patient treatment, it is promising to create national information bases on discrete issues with further versatile comparisons and definitions of the most competitive options in the context of the evolution of methods and their artificial selection.

The quality of life study as an indicator is not a competitor to classical methods for evaluating the quality of treatment and can not be considered an alternative to extensive and intensive statistical parameters. However, parallel study of objective and subjective treatment outcomes allows using the second as a tuning cart the adequate effectiveness of the patient care program and facilitates the process of understanding between the physician and the patient, allowing the latter to actively participate in their own treatment. Investigating the correlation between clinical, morphological, laboratory and instrumental effects of intervention and a comprehensive indicator of patient's quality of life will take place in the future.

7. Conclusions

1. After the study identified beyond the range of quality of life in patients with inoperable form of LA BC before and after neoadjuvant systemic chemotherapy courses (SPCTx) and endolymphatic polychemotherapy (ELPCTx).
2. Clarified value including assessment of quality of life to the complex characteristics of the final treatment results, allowing to accumulate experience and information in this area and increase the practical sense of scientific work.
3. Research the integrative quality of life and its discrete elements are ergonomic and economical means of heuristic evaluation of the health status of patients to further develop the most efficient and convenient way to address pressing issues of modern oncology by improving compliance and compromise between doctor and patient.

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THE EFFICIENCY OF GLUCOCORTICOID THERAPY IN SECONDARY-PROGRESSIVE COURSE OF MULTIPLE SCLEROSIS

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Abstract

We have investigated the efficacy of pulse-therapy with glucocorticoids (GC) at different time stages (in debuts, at the recurrent stage and at the stage of progression) of secondary progressive course (SPC) of multiple sclerosis (MS) in 70 patients (57 women and 13 men) at the ages from 28 to 67 years (mean age 45 ± 2.5 years). The duration of the disease accounted for 7 up to 34 years (average duration was 19.8 ± 2.3 years). We have conducted 438 courses of GC therapy: at the onsets – 11, at the recurrent stage (RS) – 178 and at the stage of secondary progression-249.

The efficacy of hormonal therapy was assessed taking into account the following criteria: the dynamics of regression of neurological symptoms under the influence of the first course of GC therapy at the stage of onsets; a comparative evaluation of remission's duration after admission and without taking GC at the onsets; duration of RS depending on the duration of remissions after the first course of GC therapy; a comparative evaluation of remissions' duration after the 1st (at the stage of onset and/or on the RS), and the period of stabilization on the SPS before the last courses of GC; the variants of secondary progression under the influence of GC courses; scores according the EDSS disability scale after the 1st and before the last course of GC therapy; the rate of progression under the influence of the repeated courses of GC therapy.

We have defined the three categories of efficacy at the repeated courses of pulse therapy with GC: the moderate efficacy, the low efficacy, the lack of efficacy. We have not observed the high efficacy in patients with SPC.

The patients with MFR < 1.0 , among which the pulse therapy with GC promoted the prolongation of RS, relieved the severe (less often) and moderate (more often) relapses, the outcome of which was accompanied by a moderate and stable neurologic deficit, were subsumed under the subgroup with moderate efficacy (21 individuals). The most favorable progressive variant of progression prevailed in these patients after transformation of RS into SPS.

The patients with different rate of MFR (9 – with MFR < 1.0 and 12 – with MFR > 1.0), with short (more often) and moderate (less often) RS, during which the accumulation of neurological deficit due to the frequent and heavy relapses had occurred, were subsumed under the subgroup with low efficiency (21 individuals). After transformation into SPS, the recurrent variant of progression prevailed in these patients.

The patients who were characterized by short RS, by predominance of severe and prolonged relapses, the MFR value greater than 1.0, the steady accumulation of a pronounced and persistent neurologic deficit, a high rate of progression and high scores on the EDSS disability scale more than 6.5 points) were subsumed under the subgroup with the lack of efficacy (28 individuals). After transformation in the SPC, the most unfavorable variant of progression prevailed (21 patients); significantly less frequent were the recurrent (5 patients) and a combination of a steady and recurrent (2 patients) progression. The persistent lack of efficacy of the hormonal therapy in this subgroup of patients was most likely associated with the genetically determined low individual sensitivity to GC.