

Assessment of the quality of patients' life with non-small cell lung cancer during the rehabilitation period

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Abstract

Today, in countries with a high level of medical development, one of the main criteria for selecting the optimal strategy for the introduction and treatment of cancer patients is the quality of life. The definition of life quality makes it possible to differentially determine the effect of the disease and the effectiveness of treatment, thereby objectively assessing the health status of the onco patient. In this regard, the relevance of studying the quality of life and adequate methods of recovery after chemotherapy is beyond doubt. The purpose of this study was to conduct a statistical analysis of the incidence of non-small cell lung cancer and to study the level of life quality in these cancer patients after receiving targeted therapy using controlled physical activity. Methods The study was conducted in the period from 2019-2022 on the basis of the oncological center of the Turkestan region in the Republic of Kazakhstan. During this period, we studied the effectiveness of targeted therapy in 48 patients with non-small cell lung cancer with a mutation of the EGFR gene at the oncology center. Anamnestic and clinical characteristics of patients were studied, as well as data from a sociological survey on the level of life quality using the QLQ-LC13 questionnaire. Results. As a result of histological features, adenocarcinoma was detected in 48 patients in 85% of cases, undifferentiated cancer in 3 patients (6%), squamous cell carcinoma in 4 patients (8%) and malignant neoplasm of lung cancer in 1 patient (2%). After receiving timely and personalized targeted therapy, in 77% of cases, the stabilization of the process lasted more than 12 months. Moreover, there is a statistically significant improvement in quality-of-life indicators ($p>0.05$) when regressing the oncological process after the rehabilitation period using controlled physical activity. Conclusion. The obtained data confirmed the diagnostic effect of physical exercise of 150 minutes per week, which led to a clinically significant reduction in pain syndrome in cancer patients and an improvement in their quality of life after receiving chemotherapy (targeted therapy). A comprehensive multidisciplinary approach in the treatment and rehabilitation of cancer patients is necessary to optimize diagnosis and reduce the risk of adverse outcomes in patients with metastatic non-small cell lung cancer at any stage of development.

Keywords: rehabilitation, quality of life, lung cancer, physical activity.

Introduction

Fundamental research shows that more than half of all cases of cancer in Russia could be prevented by following simple rules of a healthy lifestyle, simply increasing physical activity, controlling weight, improving diet and systematically undergoing medical screening (Stein & Colditz, 2004; Zhang, et al., 2020; Steinberg, et al., 2021). However, according to the international agency Globocan, lung cancer ranks second among all malignant neoplasms in prevalence, and it is the leading cause of death worldwide (Sung, et al., 2021). According to the statistical data of the Republic of Kazakhstan, 14.150 deaths from malignant neoplasms were registered in 2020. Lung cancer occupies the leading position out of all deaths from malignant neoplasms and accounts for 2.324 cases per year, which is one and a half times higher than the death rate from stomach cancer and two times from breast cancer (Kaidarova et al., 2020).

The high mortality rate of patients suffering from malignant diseases is undoubtedly associated with numerous adverse consequences as a result of the cancer patients' treatment. Constant psychological stress and concomitant immunological-metabolic disorders certainly lead to a violation of the oncopatient's life quality (Silver & Baima, 2013). In this regard, the relevance of medical rehabilitation of patients suffering from malignant diseases is beyond doubt, because an oncological patient is a special cohort of patients who undoubtedly need the selection of optimal treatment means and adequate recovery methods for a speedy approach to normal social and physiological living conditions.

Today, one of the main criteria for selecting the optimal strategy for the introduction and treatment of cancer patients is the quality of life (QOL) in countries with a high level of medical development. According to the definition of the World Health Organization, "quality of life is the perception by individuals of their position in life in the context of the culture and value system of the environment in which they live, in accordance with their goals, expectations, standards and concerns" (WHOQoL Group, 1993). According to the statement of the

US National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO), the QOL indicator is the second most important criterion for evaluating the results of antitumor treatment after survival and is more important than the primary "tumor response" to therapy (Lautz, et al., 2020). Thus, QL includes information about the main spheres of human activity and makes it possible to differentially determine the effect of disease and treatment on the patient's condition, thereby objectively assessing the health status of the onco patient (Sprangers, 2002; Holmes, 2005). To date, there are more than 20 questionnaires on the study of QOL problems. The questionnaire of the European Organization for Cancer Research EORTC QLQ-C30 and its module QLQ-LC13 (Quality of Life Questionnaire-Core 30 of European Organization for Research and Treatment Cancer) is the most suitable to assess the quality of life in our conditions, since this questionnaire has been tested in many international clinical trials and meets the criteria of reliability, validity and realizability (Musoro, et al., 2020; Davda et al., 2021). Moreover, the questionnaire is highly sensitive and applicable for assessing the quality of life in patients regardless of the cancer type (Liu, et al., 2009). The current global trend of rehabilitation measures among cancer patients is aimed at a multidisciplinary approach of providing rehabilitation and pre-rehabilitation measures in the interval between the moment of cancer diagnosis and the beginning of its treatment. Since 2018, oncological services with a multidisciplinary approach to the diagnosis and treatment of cancer have been operating at the national level in the Republic of Kazakhstan to improve the life quality of cancer patients.

The aim of the study is to conduct a statistical analysis of the incidence of metastatic non-small cell lung cancer and to evaluate the quality of life of these cancer patients after receiving targeted therapy and undergoing rehabilitation measures.

Materials and Methods

This study is aimed at assessing the quality of life and the effectiveness of pre-rehabilitation measures after receiving targeted therapy in patients with metastatic non-small cell lung cancer with an EGFR gene mutation in the Turkestan region over the past 4 years (2019-2022). Anamnestic and clinical characteristics of patients were studied, as well as data from a sociological survey on the level of life quality using the QLQ-LC13 questionnaire.

Data collection

The study was conducted in the period from 2019-2022 on the basis of the oncological center of the Turkestan region in the Republic of Kazakhstan. The study included patients with established lung cancer diagnoses. All protocols of the multidisciplinary group were reviewed to confirm histopathological data. The study was approved by the local Healthcare of the Republic of Kazakhstan for Data Protection (No. 47 dated 29.12.2018) and the local ethics Committee of the South Kazakhstan Medical Academy.

The study was approved by the Ethics Committee of JSC "South Kazakhstan Medical Academy", Shymkent, Republic of Kazakhstan (Protocol of the Local Ethics Commission No. 044-65\08-45 dated 03/16/2021).

We studied the effectiveness of targeted therapy in 48 patients with metastatic non-small cell lung cancer during this period in the oncology center. Physical rehabilitation was carried out daily for 20-25 minutes. Static and dynamic breathing exercises are performed with an elongated exhalation and a gradual deepening of the inhalation. The number of draining exercises increases. General developmental exercises for small, medium and large muscle groups. Drainage exercises, exercises for limbs and relaxation are carried out in a ratio of 2:1:1. The complex included aerobic exercise in the form of walking at the usual pace at least 3 times a week for 30-40 minutes. The Medical Research Council (MRC) dyspnea assessment scale was used to monitor and manage internal loads. All patients underwent a sociological survey before and after treatment according to the questionnaire EORTC QLQ-C30, created by the European Organization for Research on Cancer Treatment. It was consisted of 30 questions covering scales on the patient's quality of life and functional-symptomatic condition. The QLQ-LC13 module was additionally used to describe specific symptoms reflecting the life quality of lung cancer patients. It was consisted of one scale and nine separate questions. All scales and individual questions were linearly transformed and measured in the range from 0 to 100 to facilitate the interpretation of the data obtained on the questionnaires in accordance with the recommendations of the EORTC. A higher indicator represented a higher/better response level - for the five functional scales and for the general health status scale, but a high indicator for symptom scales and individual questions represented a high level of symptomatology/problems.

Protocol of the multidisciplinary group

Protocols on the decision of further treatment tactics in patients with lung cancer were available and analyzed by the joint efforts of the two authors. The data of laboratory and instrumental examination methods of each lung cancer patient were used. 3 copies of the multidisciplinary group conclusion were given to the patient, to the local oncologist at the place of residence and to the journal of the multidisciplinary group register.

Data analysis

All statistical calculations were performed using the SPSS program (version 25.0, IBM SPSS Inc., Chicago, USA), the value of $p < 0.05$ was considered statistically significant. All data were summarized using descriptive statistics methods. All parameters were visually checked for normality, and also tested using the Shapiro-Fork normality criterion. All data was tabulated in Microsoft Excel (office 2013, Microsoft Corp). The data included the patient's age, gender, histological data, final diagnosis, stages, types of treatment.

Results

To achieve this goal, statistical data on the incidence of lung cancer over the past decade in the Turkestan region in the Republic of Kazakhstan were studied. According to statistics, in 2011, 226 cases of lung cancer per 100,000 population were registered, 34 patients (15%) of which were identified at stage I-II, 152 (67.2%) at stage III and 40 (17.6%) patients at stage IV. According to chart – 1, there was a significant reduction in lung cancer in the number of 137 patients in 2020.

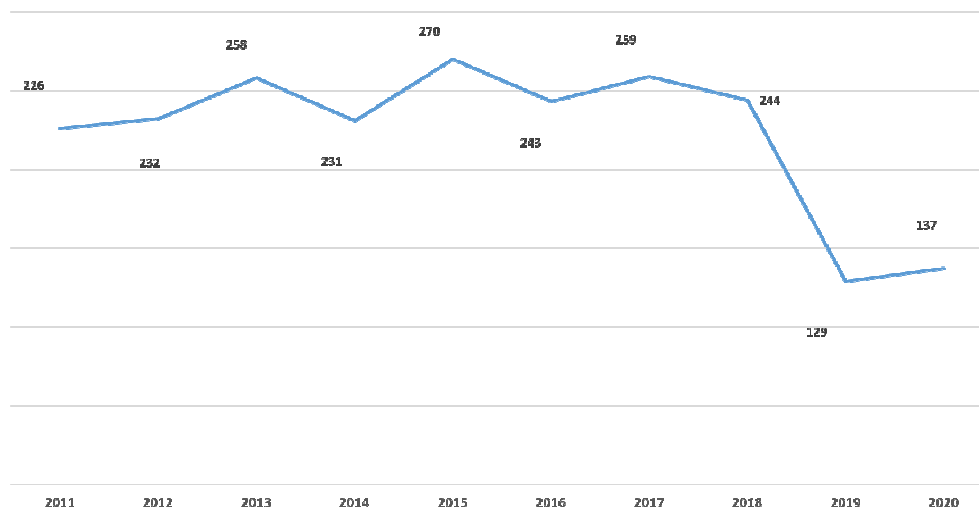


Diagram 1. Incidence of lung cancer in Turkestan region in the Republic of Kazakhstan for 2011-2020. (per 100 thousand population)

According to diagram – 2, the five-year survival rate of lung cancer in the Turkestan region in the Republic of Kazakhstan in 2011 was 163 cases (29.75), and in 2020 only 66 (33.7%) patients were recorded.

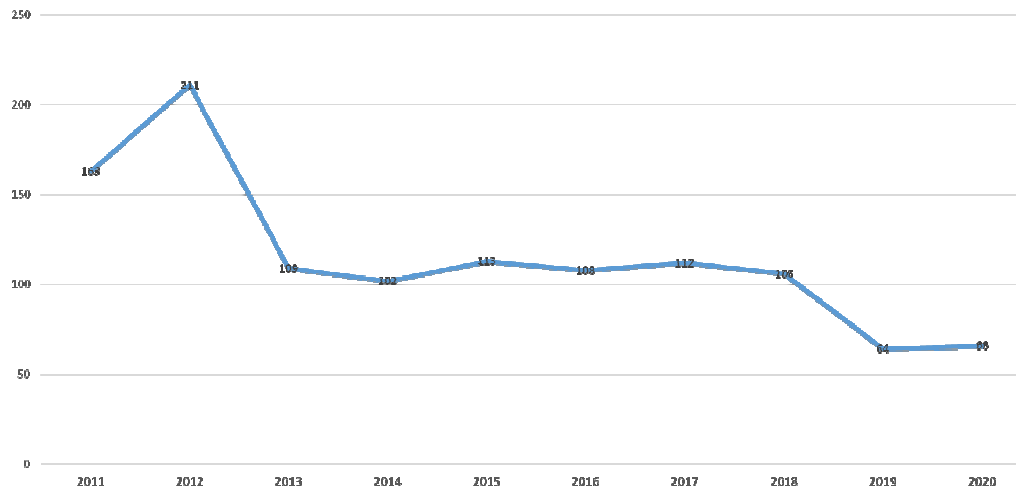


Diagram 2. Five-year survival rate of lung cancer in Turkestan region in the Republic of Kazakhstan for 2011-2020 (per 100 thousand population)

As a result of a search through the databases of the oncological center of the Turkestan region and protocols of multidisciplinary groups, including reference information of outpatient patient records and data from laboratory and instrumental examination methods, as well as the results of molecular genetic studies, it was revealed that 391 patients were referred for further treatment in the Turkestan region at the oncological center by the decision of the multidisciplinary group (since January 2019 until December 2020).

The average age of patients was 55 years (range: 30-75 years). In the course of studies, a total of 48 patients with metastatic non-small cell lung cancer revealed mutations of the EGFR gene. As a result, EGFR mutations were detected in the loci Ex19del, L858R, Ex20Ins and T790M (Figure 1).

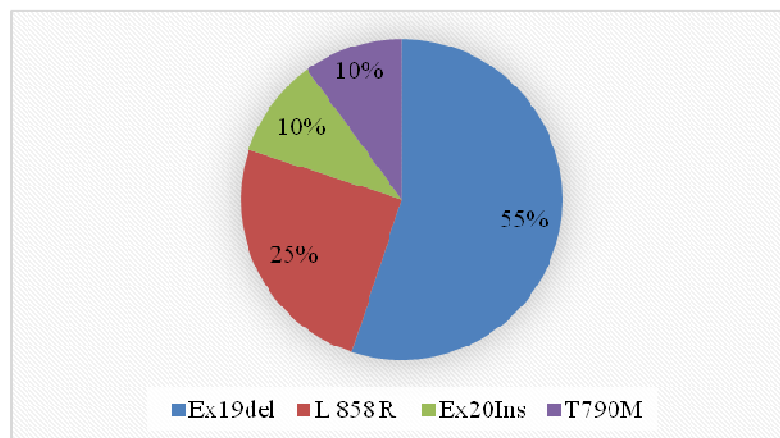


Fig. 1. Percentage ratio of histological features of non-small cell lung cancer mutation in Turkestan region

As a result of histological features, adenocarcinoma was detected in 41 patients (85%), undifferentiated cancer in 3 patients (6%), squamous cell carcinoma in 4 patients (8%), and malignant neoplasm of lung cancer in 1 patient (2%). Thus, adenocarcinoma is the most common histological subtype of non-small cell lung cancer. After verification of the diagnosis, all patients underwent a sociological survey according to the questionnaire QLQ-LC13 reflecting the life quality of patients with lung cancer (Gümüş, et al., 2023; Konstantinidis, et al., 2023). Analysis of the data obtained before receiving targeted therapy showed high values of the symptomatic scale and with high scores for cough, shortness of breath, loss of appetite and chest pain (more than 80 points). Undoubtedly, this is due to the general pathological effect on the body of the developing tumor and the accompanying inflammatory complications (Ning, et al., 2023; Watanabe, & Oshima, 2023).

Moreover, depressive disorders such as anxiety, irritability and tearfulness were recorded in patients. Correspondents were also concerned about asthenic manifestations in the form of malaise, constant general weakness, increased fatigue and decreased ability to work.

Based on the obtained histological data of lung cancer mutation, all patients were prescribed biomarker-controlled therapy (Chao, et al., 2023) and appropriate targeted therapy using afatinib, erlotinib, gefitinib and osimertinib (Liu, et al., 2018; Xiong, et al., 2022).

The analysis of the survival of patients with metastatic non-small cell lung cancer with EGFR, ALK+ mutation in the Turkestan region of the Republic of Kazakhstan for the period 2019-2020, shows 5 (25%) patients - partial regression, 12 (60%) patients - stabilization of the process and 3 (15%) patients - the progression of the process.

Further prospective observation revealed 60% of patients had a process stabilization for 12-24 months. The median overall survival was 10.9 months (5.92-9.41; 95% CI), moreover, one-year survival was 60%, and two-year survival varied within 30% (Figure 2).

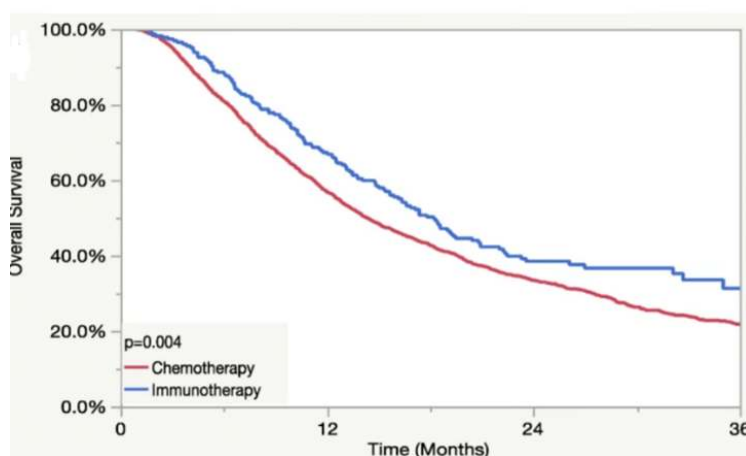


Fig.2. Kaplan-Meier curve shows overall survival depending on the therapy type (standard and targeted).

Thus, the targeted therapy (erlotinib, afatinib, osimertinib, brigatinib) showed a significant increase in overall and disease-free survival compared with standard therapy in patients, regardless of the histological tumor subtype, line of therapy, gender, age.

In addition to the direct response to targeted therapy, we assessed the patient's life quality. Aggressive treatment course of lung cancer following by a large number of side effects needs the studies of the patient's quality of life.

The physical rehabilitation effectiveness study shows the correlation between therapy effect and a subjective assessment of the quality of life. The results of physical rehabilitation and assessment of the severity of dyspnea allowed us to assess the actual level of stress and the degree of its impact on the body of a lung cancer patient, as well as to correct rehabilitation. Thus, at the beginning of training, the MRC scale 3-4 indicator is recommended, as it is trained, it can decrease to 1-2. To date, the breathing exercises are known as effective methods to reduce postoperative complications of lung cancer, including shortness of breath, and thus improve lung function and quality of life by strengthening the respiratory muscles.

According to a study conducted by the Duke Cancer Institute (DCI) on the effects of exercise on cancer progression, it was found that physical activity led to an increase in the number of capillaries and a positive response to chemotherapy (Betof, et al., 2015).

According to the results of a randomized clinical trial (RCT) using the EORTC-QLQ-C30 questionnaire, it was found that aerobic exercise and resistance training led to a reduction in pain syndrome in patients with cancer (Nakano, et al., 2018). Thus, the RCT has shown that 150 minutes per week of aerobic and strength training can lead to clinically significant pain reduction in cancer patients (Irwin, et al., 2015).

In our study, patients who received targeted therapy and structured physical activity showed a clinically significant reduction in chest pain and improvement in their quality of life. During the observation period, patients showed improvement in indicators related to breathlessness, fatigue, increased scores in overall health status, physical and professional functioning scales ($p > 0.05$) (Keilani, et al., 2019) [15]. Moreover, the duration of stabilization of the process was maintained for 12 months. These data correspond to the results of Lux-Lung 6 (Yang, et al., 2015; Herbst, et al., 2016; Soria, et al., 2018).

Discussion

To date, the 5-year survival rate for non-small cell lung cancer is one of the lowest among cancers, and varies at the level of 5%-15% for different countries (Detterbeck, Postmus, & Tanoue, 2013).

In recent years, platinum doublets have been the main method of treatment for non-small cell lung cancer. However, it is not able to provide long-term control of the disease in most patients (median overall survival varies from 8 to 10 months, one-year survival does not exceed 40%) (Argiris, 2004; Delbaldo, et al., 2004).

To date, non-small cell lung cancer is a genetically complex disease characterized by the presence of therapeutically significant genetic mutations. Application molecular genetic testing is an integral part of the diagnosis of non-small cell lung cancer, in order to select adequate therapy and personalize the treatment and rehabilitation of cancer patients.

Targeted therapy has improved the disease prognosis and increased the treatment effectiveness (Bansal, Yendluri, & Wenham, 2009).

Properly selected modern targeted or immunotherapy based on the results of molecular genetic testing can improve the immediate and long-term results of treatment of a complex category of patients with non-small cell lung cancer. All of the above certainly increases the survival rate of patients without disease progression, which proves high indicators of the life quality.

Thus, a multidisciplinary approach in the diagnosis and treatment of cancer patients, using combined targeted therapy and controlled physical exercise, undoubtedly leads to an improvement in quality of life and a reduction in fatigue and stress after exercise in cancer patients. Numerous studies conducted in Russia, Europe, and the USA have shown that cancer patients who underwent comprehensive restorative correction of postoperative disorders through the use of medical rehabilitation methods are able not only to improve their social status and quality of life, but also to reduce the risk of tumor recurrence and metastasis.

According to the results of the rehabilitation program "Healthy and Active Living After Cancer" developed by Canadian rehabilitation specialists, personalized physical exercises improve the functional abilities of the cancer patient's body, as well as quality of life indicators for up to 6 to 48 weeks (Santa Mina, et al., 2019).

The US National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO) underlined the quality of life is the second most important criterion in evaluation the anticancer therapy results after survival, and is more important than the tumor primary response to the treatment.

The physical rehabilitation effectiveness study shows the correlation between therapy effect and a subjective assessment of the quality of life. To date, the breathing exercises are known as effective methods to reduce postoperative complications of lung cancer, including shortness of breath, and thus improve lung function and quality of life by strengthening the respiratory muscles.

The personal social function indicators increase in comparison with initial data: satisfaction in social communication, satisfaction in taking leisure and recreation, not significantly, an increase of activity satisfaction ($p>0.05$).

It is noted that quality of life improves in social functioning (communication, family relations, activity, rest) and in emotional functioning (mood, satisfaction with appearance) during lung cancer patient's therapy. The data obtained from our study indicates that dynamic control and regular monitoring of exercise programs contribute to a lasting change in patient behavior, as well as an increase in adherence to treatment and compliance with recommendations.

Furthermore, a multidisciplinary approach to the diagnosis and treatment of lung cancer may be an excellent and intelligent system for determining the further tactics of rehabilitation for oncology patients.

To date, there is still no standardized rehabilitation program for cancer patients, although rehabilitation undoubtedly helps cancer survivors maintain their maximum physical, social, psychological, and professional functioning (Stubblefield, Kendig, & Khanna, 2019).

Patients with cancer at any stage of the disease require assessment of their quality of life before and after treatment to determine their physical potential and the need for corrective rehabilitation measures. Although the effectiveness of rehabilitation physical therapy is evident, further research is needed regarding its safety for patients with chemotherapy-induced heart failure. The study does not claim to be an exhaustive for all aspects of physical rehabilitation of after surgical treatment in postoperative period. Further clarification and improvement is needed to improve the lung cancer patient's rehabilitation assessment, also in studies of the physical rehabilitation influence on the development of respiratory system functional compensation and restoration state. Subsequent studies will be performed to assess the long-term effects of physical rehabilitation after lung cancer surgery.

Conclusions

1. According to statistical data in the Republic of Kazakhstan, there were 226 cases of lung cancer per 100,000 population in 2011, with 34 patients (15%) detected at stages I-II, 152 (67.2%) at stage III, and 40 (17.6%) at stage IV. Diagram 1 shows a significant decrease of 137 lung cancer patients in 2020.

2. The five-year survival rate for lung cancer in the Turkestan region of Kazakhstan was 29.75% in 2011 and only 33.7% in 2020, with a total of 66 recorded survivors.

3. These changes are attributed to appropriately tailored targeted therapy based on molecular-genetic testing, which has improved both immediate and long-term treatment outcomes for patients with non-small cell lung cancer (NSCLC).

4. Among the group of oncology patients who received targeted therapy with afatinib, erlotinib, gefitinib, and osimertinib, tumor control was achieved in 85% of cases, and the disease stabilization rate was 60% over a period of 12-24 months.

5. The median overall survival was 10.9 months (5.92-9.41, 95% CI), with one-year survival at 60% and two-year survival varying within 30%.

6. The study evaluated the "Recovery and Exercises for Cancer Survivors" rehabilitation program developed by Canadian rehabilitologists. Personalized physical exercises were found to improve the functional abilities and quality of life indicators of oncology patients for a period ranging from 6 to 48 weeks. The application of physical rehabilitation methods extended life expectancy by more than 48 weeks.

7. In this research, the greatest effectiveness of targeted therapy was observed when physical rehabilitation methods, such as controlled physical exercises and breathing gymnastics, were applied early. The analysis of physical rehabilitation results and the assessment of dyspnea severity using the MRC (1-4) scale allowed for the evaluation of the actual level of exertion and its impact on the patients' well-being.

8. According to data from the National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO), the quality of life is a significant criterion for assessing the outcomes of anticancer therapy. The conducted study evaluated the effectiveness of both anticancer therapy and physical rehabilitation, which allowed tracking the correlation between the therapy's effects and the subjective assessment of the patients' quality of life using the QLQ-LC13 questionnaire. The analysis of the data obtained after receiving targeted therapy showed satisfactory values on the symptomatic scale, indicating reduced symptoms related to cough, dyspnea, and chest pain.

9. Compared to the initial data, there is a significant increase in the indicators of scales reflecting social functioning of the individuals: satisfaction with communication with others, satisfaction with opportunities for leisure and recreation ($p>0.05$).

10. Currently, there is still no standardized rehabilitation program for patients with oncological diseases. However, the proposed multidisciplinary approach in the diagnosis and treatment of oncology patients, incorporating combined anticancer therapy and physical rehabilitation methods, significantly improves the quality of life and reduces fatigue and stress levels among oncology patients.

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Conflict of interest

The authors state that there are no conflicts of interest related to this study.

Reference

- Argiris, A., & Schiller, J. H. (2004). Can Current Treatments for Advanced Non-Small-Cell Lung Cancer Be Improved?. *Jama*, 292(4), 499-500. doi:10.1001/jama.292.4.499.
- Bansal, N., Yendluri, V., & Wenham, R. M. (2009). The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. *Cancer control*, 16(1), 8-13. doi:10.1177/107327480901600102.
- Betof, A.S., Lascola, C.D., Weitzel, D., Landon, C., Scarbrough, P.M., Devi, G.R., Palmer, G., Jones, L.W., & Dewhirst, M.W. (2015). Modulation of Murine Breast Tumor Vascularity, Hypoxia, and Chemotherapeutic Response by Exercise. *Journal of the National Cancer Institute*, 107(5), djv040. DOI:10.1093/jnci/djv040.
- Chao, Q., Zhang, Y., Li, Q., Jiao, L., Sun, X., Chen, X., ... & Luo, X. (2023). Compute-and-Release Logic-Gated DNA Cascade Circuit for Accurate Cancer Cell Imaging. *Analytical Chemistry*, 95, 19, 7723–7734. DOI:10.1021/acs.analchem.3c00898.
- Davda, J., Kibet, H., Achieng, E., Atundo, L., & Komen, T. (2021). Assessing the acceptability, reliability, and validity of the EORTC Quality of Life Questionnaire (QLQ-C30) in Kenyan cancer patients: a cross-sectional study. *Journal of Patient-Reported Outcomes*, 5(1), 1-8. DOI:10.1186/s41687-020-00275-w
- Delbaldo, C., Michiels, S., Syz, N., Soria, J. C., Le Chevalier, T., & Pignon, J. P. (2004). Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. *Jama*, 292(4), 470-484. doi: 10.1001/jama.292.4.470.
- Detterbeck, F. C., Postmus, P. E., & Tanoue, L. T. (2013). The stage classification of lung cancer: Diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 143(5), e191S-e210S. DOI: 10.1378/chest.12-2354.
- Gümüş, M., Chen, C. I., Ivanescu, C., Kilickap, S., Bondarenko, I., Özgüroğlu, M., ... & Sezer, A. (2023). Patient-reported outcomes with cemiplimab monotherapy for first-line treatment of advanced non-small cell lung cancer with PD-L1 of $\geq 50\%$: The EMPOWER-Lung 1 study. *Cancer*, 129(1), 118-129. DOI:10.1002/cncr.34477.
- Herbst, R. S., Baas, P., Kim, D. W., Felip, E., Pérez-Gracia, J. L., Han, J. Y., ... & Garon, E. B. (2016). Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet*, 387(10027), 1540-1550. DOI:10.1016/S0140-6736(15)01281-7.
- Holmes, S. (2005). Assessing the quality of life—reality or impossible dream?: A discussion paper. *International journal of nursing studies*, 42(4), 493-501. DOI:10.1016/j.ijnurstu.2004.06.014.
- Irwin, M. L., Cartmel, B., Gross, C. P., Ercolano, E., Li, F., Yao, X., ... & Ligibel, J. (2015). Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *Journal of Clinical Oncology*, 33(10), 1104-1111. DOI: 10.1200/JCO.2014.57.1547
- Kaydarova, D. R., Baltabekov, N. T., Dushimova, Z. D., Shatkovskaya, O. V., Seisenbaeyva, G. T., & Azhmagambetova, A. E. (2020). Indicators of the Oncological Service of the Republic of Kazakhstan for 2019 (statistical and analytical materials). *JSC" Kazakh Institute of Oncology and Radiology" of the Ministry of Health of the Republic of Kazakhstan*. Almaty.
- Keilani, M., Kainberger, F., Patariaia, A., Hasenöhrl, T., Wagner, B., Palma, S., ... & Crevenna, R. (2019). Typical aspects in the rehabilitation of cancer patients suffering from metastatic bone disease or multiple myeloma. *Wiener Klinische Wochenschrift*, 131, 567-575. DOI: 10.1007/s00508-019-1524-3.
- Konstantinidis, T., Fragkioudaki, C., Patelarou, E., Zografakis-Sfakianakis, M., Naoum, S., Tsatsou, I., ... & Govina, O. (2023). Nutritional assessment and quality of life in patients with non-small cell lung cancer undergoing immunotherapy. *International Journal of Palliative Nursing*, 29(3), 118-128. DOI:10.12968/ijpn.2023.29.3.118.
- Lautz, T. B., Chi, Y. Y., Tian, J., Gupta, A. A., Wolden, S. L., Routh, J. C., ... & Rodeberg, D. A. (2020). Relationship between tumor response at therapy completion and prognosis in patients with group III rhabdomyosarcoma: a report from the Children's Oncology Group. *International journal of cancer*, 147(5), 1419-1426.
- Liu, R., Page, M., Solheim, K., Fox, S., & Chang, S. M. (2009). Quality of life in adults with brain tumors: current knowledge and future directions. *Neuro-oncology*, 11(3), 330-339. DOI: 10.1215/15228517-2008-093.
- Liu, Y., Li, Y., Ou, Q., Wu, X., Wang, X., Shao, Y. W., & Ying, J. (2018). Acquired EGFR L718V mutation mediates resistance to osimertinib in non-small cell lung cancer but retains sensitivity to afatinib. *Lung Cancer*, 118, 1-5. DOI:10.1016/j.lungcan.2018.01.015.
- Musoro, J. Z., Sodergren, S. C., Coens, C., Pochesci, A., Terada, M., King, M. T., ... & EORTC Quality of Life, Gastro-intestinal Groups. (2020). Minimally important differences for interpreting the EORTC QLQ-C30 in patients with advanced colorectal cancer treated with chemotherapy. *Colorectal Disease*, 22(12), 2278-2287. DOI:10.1111/codi.15295

- Nakano, J., Hashizume, K., Fukushima, T., Ueno, K., Matsuura, E., Ikio, Y., ... & Kusuba, Y. (2018). Effects of aerobic and resistance exercises on physical symptoms in cancer patients: a meta-analysis. *Integrative cancer therapies*, 17(4), 1048-1058. DOI:10.1177/1534735418807555
- Ning, X., Ni, Y., Cao, J., & Zhang, H. (2023). Liquiritigenin Attenuated Collagen-Induced Arthritis and Cardiac Complication via Inflammation and Fibrosis Inhibition in Mice. *Chemical and Pharmaceutical Bulletin*, 71(4), 269-276. DOI: 10.4240/wjgs.v7.i12.370.
- Santa Mina, D., Au, D., Auger, L. E., Alibhai, S. M., Matthew, A. G., Sabiston, C. M., ... & Jones, J. M. (2019). Development, implementation, and effects of a cancer center's exercise-oncology program. *Cancer*, 125(19), 3437-3447. DOI: 10.1002/cncr.32297.
- Silver, J. K., & Baima, J. (2013). Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *American journal of physical medicine & rehabilitation*, 92(8), 715-727. DOI:10.1097/PHM.0b013e31829b4af.
- Soria, J. C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K. H., ... & Ramalingam, S. S. (2018). Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *New England journal of medicine*, 378(2), 113-125. DOI: 10.1056/NEJMoal713137.
- Sprangers, M. A. (2002). Quality-of-life assessment in oncology. *Acta Oncologica*, 41(3), 229-237. DOI:10.1002/jclp.1029
- Stein, C. J., & Colditz, G. A. (2004). Modifiable risk factors for cancer. *British journal of cancer*, 90(2), 299-303. DOI:10.1038/sj.bjc.6601509.
- Steinberg, J., Yap, S., Goldsbury, D., Nair-Shalliker, V., Banks, E., Canfell, K., & O'Connell, D. L. (2021). Large-scale systematic analysis of exposure to multiple cancer risk factors and the associations between exposure patterns and cancer incidence. *Scientific Reports*, 11(1), 2343. DOI:10.1038/s41598-021-81463-6.
- Stubblefield, M.D., Kendig, T.D., & Khanna, A. (2019). Revitalizing cancer survivors — making cancer rehabilitation the standard of care. *MD Advis. Spring*, 12 (2): 30–33. DOI: 10.1200/JCO.2011.37.1674.
- Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 71(3), 209-249. DOI:10.3322/caac.21660
- Watanabe, H., & Oshima, T. (2023). The latest treatments for cancer cachexia: an overview. *Anticancer Research*, 43(2), 511-521. DOI: 10.21873/anticancer.16188.
- WHOQoL Group. (1993). Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). *Quality of life Research*, 2, 153-159.
- Xiong, X., Zhang, Y., Wang, Z., Zhou, C., Yang, P., Du, X., ... & Liu, W. (2022). Simultaneous quantitative detection of afatinib, erlotinib, gefitinib, icotinib, osimertinib and their metabolites in plasma samples of patients with non-small cell lung cancer using liquid chromatography-tandem mass spectrometry. *Clinica Chimica Acta*, 527, 1-10. DOI:10.1016/j.cca.2021.12.028.
- Yang, J. C., Sequist, L. V., Geater, S. L., Tsai, C. M., Mok, T. S. K., Schuler, M., ... & Wu, Y. L. (2015). Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *The lancet oncology*, 16(7), 830-838. DOI:10.1016/S1470-2045(15)00026-1
- Zhang, Y. B., Pan, X. F., Chen, J., Cao, A., Zhang, Y. G., Xia, L., ... & Pan, A. (2020). Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. *British journal of cancer*, 122(7), 1085-1093. DOI:10.1038/s41416-020-0741-x.