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РЕДАКЦИОННАЯ КОЛЛЕГИЯ

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RECONSTRUCTION OF THE AREOLARICAL AREA IN THE SURGICAL TREATMENT OF BREAST CANCER
(reconstruction of the nipple using the areola's own tissues)

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Abstract. Extensive operations with lymph node dissection often lead to the development of a number of physical defects, as well as to the development of persistent mental maladaptation of those operated on. Therefore, in modern oncology, doctors pay special attention to plastic, reconstructive types of surgery that improve the quality of life of patients.

By performing a single-stage mammoplasty operation on a breast resected with the nipple due to cancer, the nipple is created from the residual areola. Achieving a radical operation and a good cosmetic and psychological result at the same time. We give an example of a case where a single-stage breast reconstruction mammoplasty was performed in conjunction with a mastectomy for breast cancer. A 64-year-old patient was diagnosed with "Breast cancer, nodular type St Ia T1N0M0. Luminal type A" on 02.10.2024. MDT No. 2736 and was recommended surgical treatment. The areola is sutured to the nipple shape through a subcutaneous suture and sutured to the skin is cosmetically and psychologically effective and contributes to rapid wound healing. Although the size is somewhat reduced, the shape of the breast is preserved. 6 operations were performed with this method in the Oncology Center of Shymkent. In conclusion, one-stage breast reconstruction surgery for breast cancer is currently a unique cosmetically convenient and effective method. The rapid wound healing and psycho-emotional effectiveness of the surgery allow for an increase in the number of such surgeries.

Key words: oncology, breast cancer, reconstruction, areola, nipple.

Сүт безі обырының оперативті емінде емізік ареолярлы аймақтың (ареоланың өзіндік тіндері арқылы емізік түзу) реконструкциясы (клиникалық жағдай)

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ДСБ ШЖҚ "Онкологиялық орталығы бар көпбейінді қалалық аурухана",
МКК Шымкент қ, Қазақстан

Аңдатпа. Кең ауқымды лимфодиссекциясымен жасалатын радикальды операциялар, отадан кейінгі кезеңде науқас өмірінің сапасын күрт нашарлатып, психоэмоциональды дезадаптацияға алып келетіндігі мәлім. Сондықтан да заманауи хирургияда реконструктивті, пластикалық оталар жасау үлкен қажеттілікке ие.

Обыр бойынша емізігімен бірге резекцияланған сүт безіне бір моменттік маммопластика отасын жасау арқылы, қалдық ареоладан емізік түзу. Бір мезете радикальды ота мен косметикалық және психологиялық тұрғыда жақсы нәтижеге қол жеткізу. Сүт безі обырында мастэктомиямен қатар бір кезеңдік емізікті қалпына келтіру бойынша маммопластика жасалған жағдай туралы мысал келтіреміз. 64 ж науқас «Сүт безі обыры, түйінді түрі St Ia T1N0M0. Люминальды А типі» 02.10.2024ж.. №2736 МДТ –та қаралып, оталық ем ұсынылды. Ареоланы тері асты шелі арқылы бүре тігіп емізік формасына келтіріп, теріге тігу косметикалық, психологиялық тұрғыда тиімді және жараның тез жазылуына септігін тигізеді. Көлемі біршама кішірейгенімен, сүт безі формасы сақталған. Осы тәсілмен Шымкент қ. Онкологиялық орталықта 6 ота жасалынды. Сүт безі обырының бір кезеңдік емізікті қалпына келтіру отасы қазіргі таңда косметикалық тұрғыда ыңғайлы, тиімді бірегей

тәсіл. Жараның тез жазылуы мен отадан кейінгі психоэмоциональды тұрғыда тиімділігі аталған отаның санын арттыруға мүмкіндіктер береді.

Түйін сөздер: онкология, сүт безі обыры, реконструкция, ареола, емізік түзу.

Одномоментная реконструкция сосочно ареолярной зоны (формирование соска с использованием собственной ткани ареолы) при оперативном лечении рака молочной железы (клинические случаи)

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Аннотация. Обьемные операции с лимфодиссекцией, часто приводит к развитию ряда физических дефектов, а также к развитию стойкой психической дезадаптации оперированных. По этому в современной онкологии особое внимание врачей уделяется на пластические, реконструктивные виды операции которые улучшает качества жизни пациентов.

В условиях онкодиспансера демонстрация одномоментной маммопластики с восстановлением удаленного соска местным тканями, и добиться хорошего косметического результата, улучшая в последствии количество и качество жизни пациентов. Приведен клинический случай, удачного, одномоментного, оперативного восстановления соска после мастэктомии с использованием ареолы удаленной молочной железы. Реконструктивные операции по восстановлению соска при подкожной мастэктомии, секторальной резекции по поводу рака молочной железы уникален, не имеет аналогов, удобен в косметическом плане, и способствует быстрому заживлению послеоперационных ран. Аналогичным способом в онкологическом центре г. Шымкент произведены 6 операции с удовлетворительными результатами. Проведенные реконструктивные операции по восстановлению соска из оставшееся ареолы, техническая простота манипуляции и удовлетворительные результаты дают возможность думать о увеличении числа подобных операции.

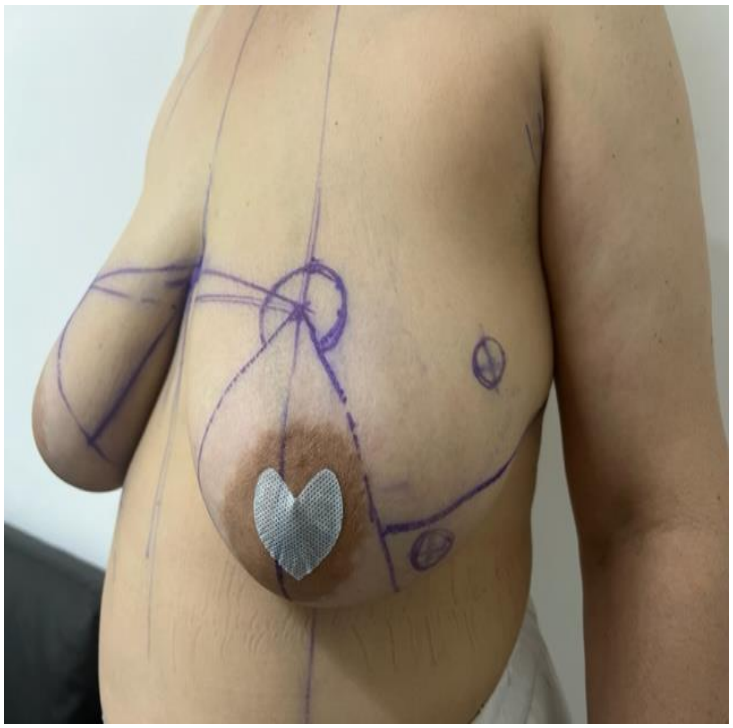
Ключевые слова: онкология, рак молочной железы, реконструкция, ареола, формирование соска.

Introduction. Simultaneous, primary mammoplasty allows you to simultaneously perform a radical operation from an oncological point of view, and achieve a good cosmetic result, subsequently improving the number and quality of life of patients. According to the literature, reconstructive breast surgery in cancer patients does not particularly affect the course of the disease and does not interfere with special treatment.

Duadze I.S. et al. Performed breast reconstruction using autologous flaps of the anterior abdominal wall and achieved good results. The authors recommend taking into account a number of factors such as the patient's age, the presence of concomitant diseases (diabetes mellitus, obesity, smoking, etc.), as well as the state of blood supply to the donor skin) [1].

After performing a number of reconstructive operations in breast cancer, the following authors indicate that good and satisfactory cosmetic results were obtained in every third woman. This is due to the peculiarities of the location of the tumor in the breast, as well as the stage of development (ratio of tumor size and breast) [2].

Tailor S.M. et al., having conducted randomized clinical trials with a long-term follow-up period in patients with stage I-II breast cancer, did not reveal differences in survival rates during mastectomy and organ-preserving operations, which made it possible to more widely use organ-preserving operations in the treatment of patients with breast cancer [3].



The following authors express the same opinion, comparing the long-term results of organ-preserving, oncoplastic operations with radical mastectomy, they do not find much difference in the survival rate of patients with breast cancer. It is recommended to use oncoplastic resections with a small tumor node, which give good aesthetic results, thereby improving the quality of life of patients in the postoperative period [4].

After conducting randomized studies of 101 breast cancer patients who underwent organ-preserving surgery and subcutaneous mastectomy, the authors found that in patients with subcutaneous mastectomy, the recurrence of the disease was approximately 2 times less than that of organ-preserving surgery [5].

Other authors described a successful skin-saving mastectomy with simultaneous reconstruction of the mammary gland with a flap of the broadest muscle of the back (TDL) with a good distant, disease-free result [6].

Purpose of the study: In the oncologic dispensary, demonstration of single-stage mammoplasty with restoration of the removed nipple with local tissues, and achieve a good cosmetic result, subsequently improving the number and quality of life of patients.

Material and methods: Performed surgical restoration of the nipple after mastectomy using areola, on the feeding pedicle, removed breast. Patient 64g. was admitted to operative treatment with complaints of a mass in the left breast.

Anamnesis morbi: Registered since 26.09.2024. diagnosed with C-r of the left breast, nodular form of St Ia T1N0M0. Luminal A subtype. According to the patient, the disease was detected by screening. Ultrasound of the m/glands from 07.08.2024. Focal lesions: for 12 hours, a hypoechosgenic lesion with a size of 0, 6x0.4 cm, the content is heterogeneous with CDK without blood flow. Conclusion: Glandular changes of both mammary glands. Left breast formation. BI-RADS RU2LU4

Trepan biopsy from the left breast was performed.

Histology of 16.09.2024. No. 14844-45 Histo: Invasive breast carcinoma G-2, nonspecific type, in the biopsy specimen. ICD-O:8500/3

IHC No. 14844-45 dated 01.10.2024 g-Her2- (0 +), RE-7b, RP-6b, Ki67-20%.

Discussed at MDG No. 2736 dated 02.10.2024-1. Recommended surgical treatment.

Hospitalized in the mammology department for surgical treatment.

The general condition of the patient is satisfactory, the position is active, the consciousness is clear, adequate. On the Karnovsky scale 80%. ECOG -1 point. There is no ARVI phenomenon. Somatic state corresponds to age, data from internal organs are not peculiar. HR 80 bpd in 1 min. BP 120/80 mm Hg Physiological findings are normal.

Status localis: On examination, the mammary glands are symmetrical. When palpating, the OWC of the left breast is determined by the formation of 1.0 * 1.0 cm times. Regional lymph nodes are not increased. (Fig. 1)

Methods and results: 16.10.2024 surgery was performed: resection of the quadrant of the left breast with lymphodissection, plastic surgery of the removed nipple with local tissues (areoles on the feeding pedicle).

After treatment of the surgical field, iodonate + alcohol 3 * fold produced two linear skin incisions around the central quadrant of the left breast. Hemostasis. Skin flaps are separated. The

central quadrant of the left breast was removed along with the nipple. Part of the areolar zone not affected by the tumor was left (Fig. 2).

Plastic nipple with a particle of the left areola and skin on the feeding leg was produced. Hemostasis is achieved by electrocoagulation and vascular ligation. Wound drainage along the anterior axillary line along Redon. Operating wound toilet. Wound sutures. Alcohol. Aseptic dressing. The postoperative period proceeded smoothly. The wound healed with primary tension. Ultimately, the shape of the mammary gland is partially restored, a nipple is formed from the remaining areoles. The operated mammary gland is reduced in size, but the overall shape is preserved. If desired, the patient can increase the size of the breast using a silicone implant simultaneously with the removal of the tumor, as well as after a certain time, after the healing of the postoperative wound (Fig. 3).

There are no complaints at discharge. On the Karnovsky scale 90%. ECOG -0 point.

The general condition is satisfactory. There is no ARVI phenomenon. T body 36.5 C. Vesicular breathing in the lungs, no wheezing. Heart tones are clear, rhythmic. BP - 120/80 mm Hg

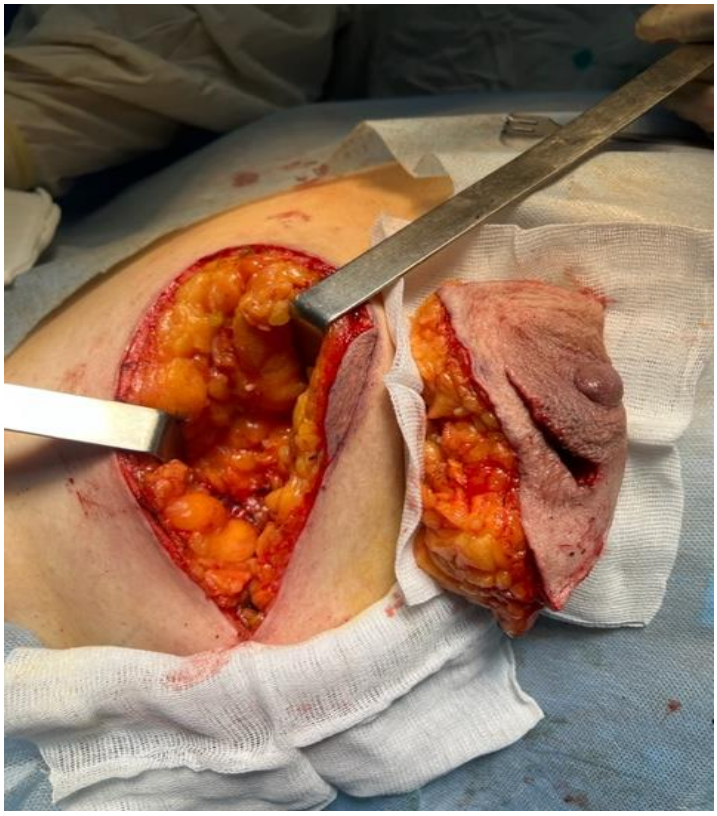
Pulse - 77 beats per minute, rhythmic, satisfactory filling. The tongue is moist, clean. The abdomen is soft, painless. The liver is not enlarged, painless. The spleen is not palpable. The swaying symptom is negative on both sides. The stool is normal. Urination is free, painless.

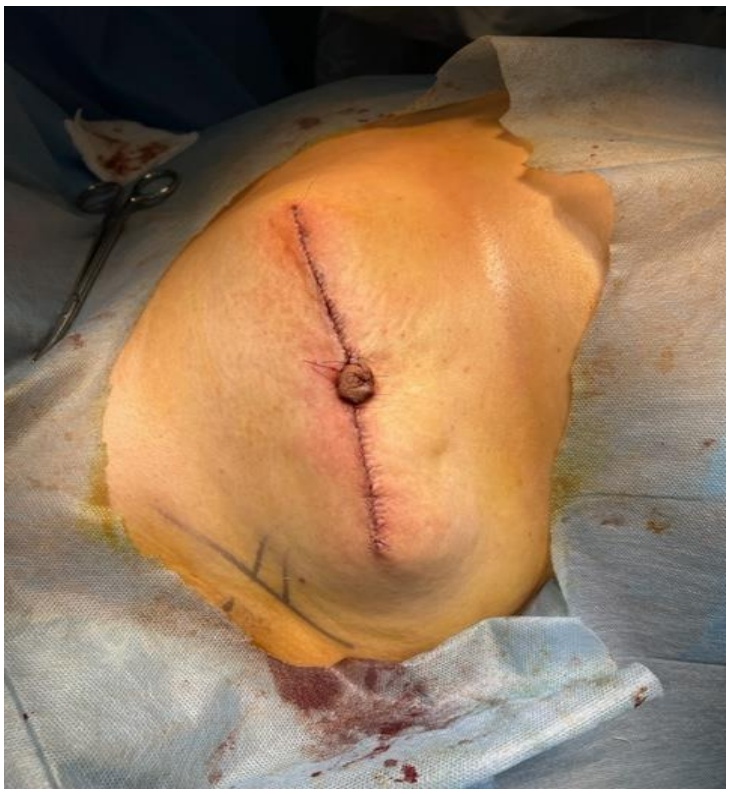
Status Localis: The seam is pure calm. Processed. Aseptic dressing.

Discharged in satisfactory condition.

Clinical diagnosis at discharge: C-r of the left breast, nodular form, OWC. StIIA T2N0M0 G2. Luminal type B. No HER 2 overexpression. SSW ShSR on the left with LD. Clinical group II.

Discussion of results; Reconstructive surgery to restore the nipple during subcutaneous mastectomy, sectoral resection for breast cancer is unique, has no analogues, is convenient in cosmetic terms, and contributes to the rapid healing of postoperative wounds. In a similar way, 6 operations were performed at the Shymkent Cancer Center with satisfactory results. The results after 4-6 months are satisfactory and good. There is no failure of sutures and no local recurrences.





Conclusions: Thus, the method used by surgeons and mammologists of the Shymkent Cancer Center to restore the nipple during subcutaneous mastectomy, sectoral resection for breast cancer is unique, has no analogues (studying the set of literature on breast plastic surgery, the authors did not find such a description), is cosmetically convenient, and contributes to the rapid healing of postoperative wounds. Supports patients psychologically, gives self-confidence and preservation of femininity. Convenient for use in Paget cancer.

Study transparency

The study had no sponsorship.

Declaration of Financial and Other Relationships

The authors did not receive study royalties.

Authors' contributions

All authors were equally involved in the conception and design of the study; data analysis and processing; writing the first version of the article; in the final approval of the article for printing.

Conflict of interest

The authors declare no conflict of interest.

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OSIMERTINIB-BASED COMBINATION THERAPY FOR EGFR-MUTANT NSCLC WITH BRAIN METASTASES: A CLINICAL CASE IN THE CONTEXT OF THE FLAURA2 STUDY

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Abstract. This article presents a clinical case of treating a female patient with EGFR-mutant non-small cell lung cancer (NSCLC) with brain metastases using osimertinib-based combination therapy. Following disease progression after afatinib therapy, third-generation tyrosine kinase inhibitor (osimertinib) targeted therapy was initiated, followed by combination treatment in accordance with the FLAURA2 study protocol. This included osimertinib, chemotherapy (carboplatin + pemetrexed), and bevacizumab. Significant regression of cerebral metastases and disease stabilization were observed. The article discusses practical aspects of applying FLAURA2 data in real-world clinical settings and explores the potential for implementing a personalized approach to oncology, even under budget constraints. The importance of molecular diagnostics and physicians' clinical awareness in making therapeutic decisions is emphasized.

Keywords: EGFR-mutant NSCLC, osimertinib, FLAURA2, brain metastases, targeted therapy, pemetrexed, carboplatin, bevacizumab, personalized oncology, clinical case.

EGFR-мутантты ұсақ жасушалы емес өкпе обыры мен ми метастаздарындағы осимертинибке негізделген біріктірілген терапия: FLAURA2 зерттеуінің контексіндегі клиникалық жағдай

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Аңдатпа. Мақалада миға метастаздары бар EGFR-мутантты ұсақ жасушалы емес өкпе обырын (ҰЖЕӨО) емдеу бойынша клиникалық жағдай ұсынылған. Осимертинибке негізделген біріктірілген терапия қолданылды. Афатинибпен емделгеннен кейін аурудың үдеуі байқалған соң, үшінші буын тирозинкиназа тежегішімен (осимертиниб) мақсатты терапия басталды, кейіннен - FLAURA2 зерттеуінің хаттамасына сәйкес біріктірілген ем жүргізілді. Бұл емге осимертиниб, химиотерапия (карбоплатин + пеметрексед) және бевацизумаб кірді. Нәтижесінде ми метастаздарының айқын регрессі мен үдерістің тұрақтануы байқалды. FLAURA2 деректерін нақты клиникалық тәжірибеде қолданудың практикалық аспектілері, сондай-ақ шектеулі бюджет жағдайында да онкологияда жекелендірілген тәсілді енгізу мүмкіндіктері талқыланады. Терапиялық шешім қабылдауда молекулалық диагностиканың және дәрігерлердің клиникалық хабардарлығының маңыздылығы атап өтіледі.

Түйін сөздер: EGFR-мутантты ҰЖЕӨО, осимертиниб, FLAURA2, ми метастаздары, мақсатты терапия, пеметрексед, карбоплатин, бевацизумаб, жекелендірілген онкология, клиникалық жағдай.

Комбинированная терапия на основе осимертиниба при EGFR-мутантном немелкоклеточном раке лёгкого с метастазами в головной мозг: клинический случай в контексте исследования FLAURA2

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Аннотация. В статье представлен клинический случай лечения пациентки с EGFR-мутантным немелкоклеточным раком лёгкого (НМРЛ) с метастазами в головной мозг, на фоне применения комбинированной терапии, основанной на осимертинибе. На фоне прогрессирования заболевания после терапии афатинибом была начата таргетная терапия ингибитором тирозинкиназы 3-го поколения (осимертиниб), а в дальнейшем — комбинированное лечение в соответствии с протоколом исследования FLAURA2, включающее осимертиниб, химиотерапию (карбоплатин + пеметрексед) и бевацизумаб. Наблюдался выраженный регресс церебральных метастазов и стабилизация процесса. Обсуждаются практические аспекты применения данных FLAURA2 в реальной клинической практике, а также возможности внедрения персонализированного подхода в онкологии даже в условиях ограниченного бюджета. Подчёркивается значимость молекулярной диагностики и клинической осведомлённости врачей в принятии терапевтических решений.

Ключевые слова: EGFR-мутантный НМРЛ; осимертиниб; FLAURA2; метастазы в головной мозг; таргетная терапия; пеметрексед; карбоплатин; бевацизумаб; персонализированная онкология; клинический случай.

Introduction. EGFR-mutant non-small cell lung cancer (NSCLC) is a subtype of NSCLC characterized by mutations in the epidermal growth factor receptor (EGFR) gene. The frequency of EGFR mutations varies but is typically:

- Approximately 10–15% among patients in the United States, more commonly in cases of adenocarcinoma [1]
- Up to 30–50% in Asian populations, including about 38% in China [2]
- Around 20% of all adenocarcinoma cases in NSCLC in Russia [3]

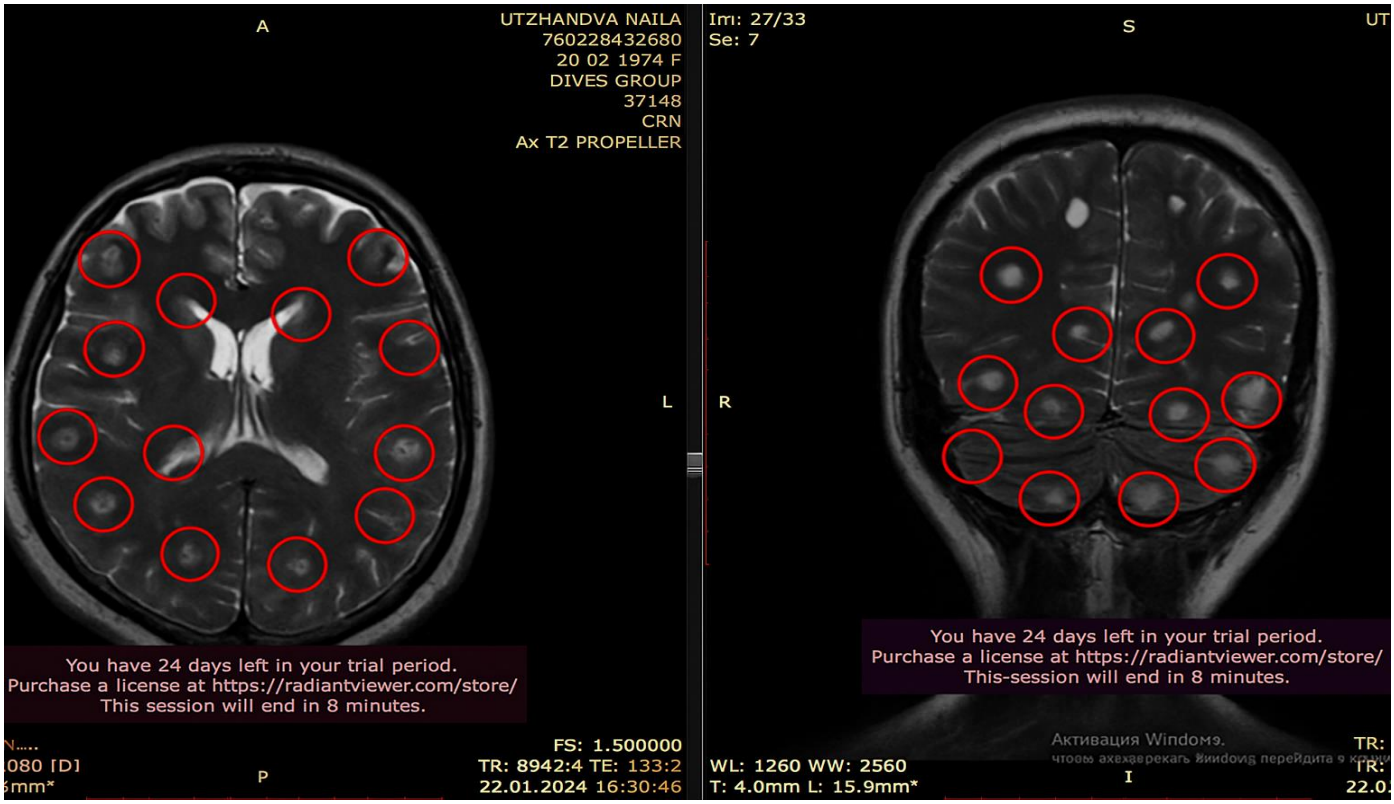
Thus, on average, EGFR mutations are found in approximately 20% of all NSCLC cases, particularly in the adenocarcinoma subtype, and more frequently among women and non-smokers [4].

Until recently, Osimertinib was the standard first-line therapy. However, results from the “FLAURA-2” study [5, 6] demonstrated a significant improvement in progression-free survival with the addition of chemotherapy to Osimertinib, especially in patients with brain metastases. Below is a clinical case illustrating the application of this treatment regimen.

Clinical Case. Patient U., 49 years old. Under follow-up at the Regional Clinical Hospital of Turkestan Region since July 20, 2022. Discussed at the Multidisciplinary Team (MDT) meeting on June 17, 2022. Recommendation: diagnostic thoracotomy. The patient was admitted to the City Oncology Center in Shymkent to the Thoracoabdominal Surgery Department for operative treatment. On July 12, 2022, the patient underwent a video-assisted thoracoscopic surgery (VATS) on the left side with a lung lesion biopsy. Postoperative histological report No. 11224-25 dated July 19, 2022: moderately differentiated adenocarcinoma, G-II. Discussed at MDT on July 20, 2022. Recommendation: EGFR mutation testing via molecular genetic analysis; dynamic PET/CT scan. From July 21 to July 29, 2022, the patient received courses of neoadjuvant chemotherapy. Molecular genetic analysis of EGFR (report No. 257 dated August 2, 2022): EGFR Exon 19 deletion mutation detected. Beginning in August 2022, the patient started targeted therapy with “Afatinib”. In August 2023, disease progression was noted in the form of brain metastases. As a

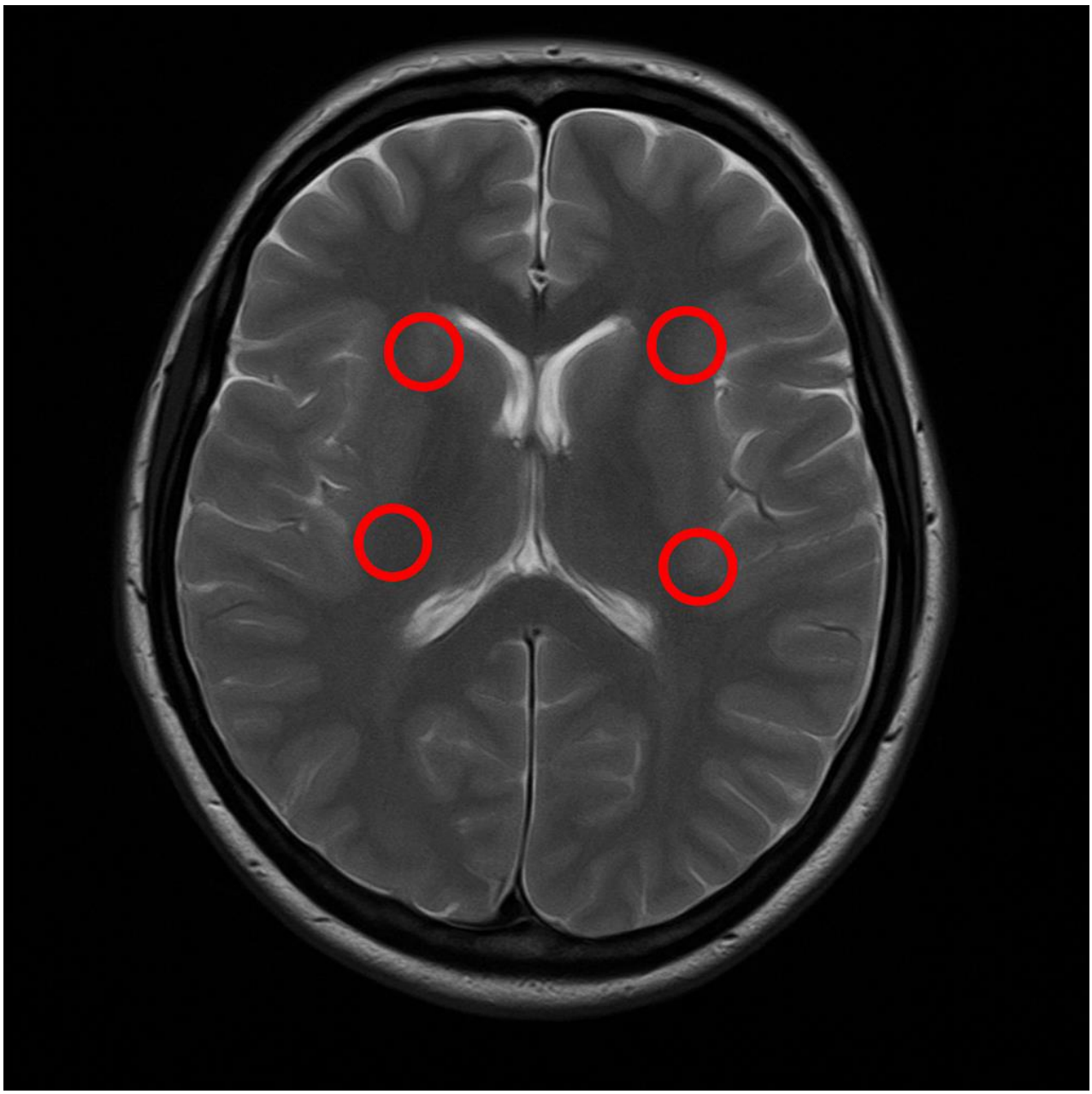
result, on August 11, 2023, the MDT recommended initiating targeted therapy with the EGFR inhibitor Osimertinib.

Protocol of Magnetic Resonance Imaging of the Brain and Intracranial Arteries dated 22.01.2024



In both cerebral hemispheres and cerebellar hemispheres, multiple lesions are observed - approximately 15 in total - round in shape, with a homogeneous structure, measuring up to 2.2 × 1.6 cm, surrounded by a perifocal zone of vasogenic edema. Conclusion**:** Multiple lesions in both cerebral hemispheres and cerebellar hemispheres (differential diagnosis: metastases).

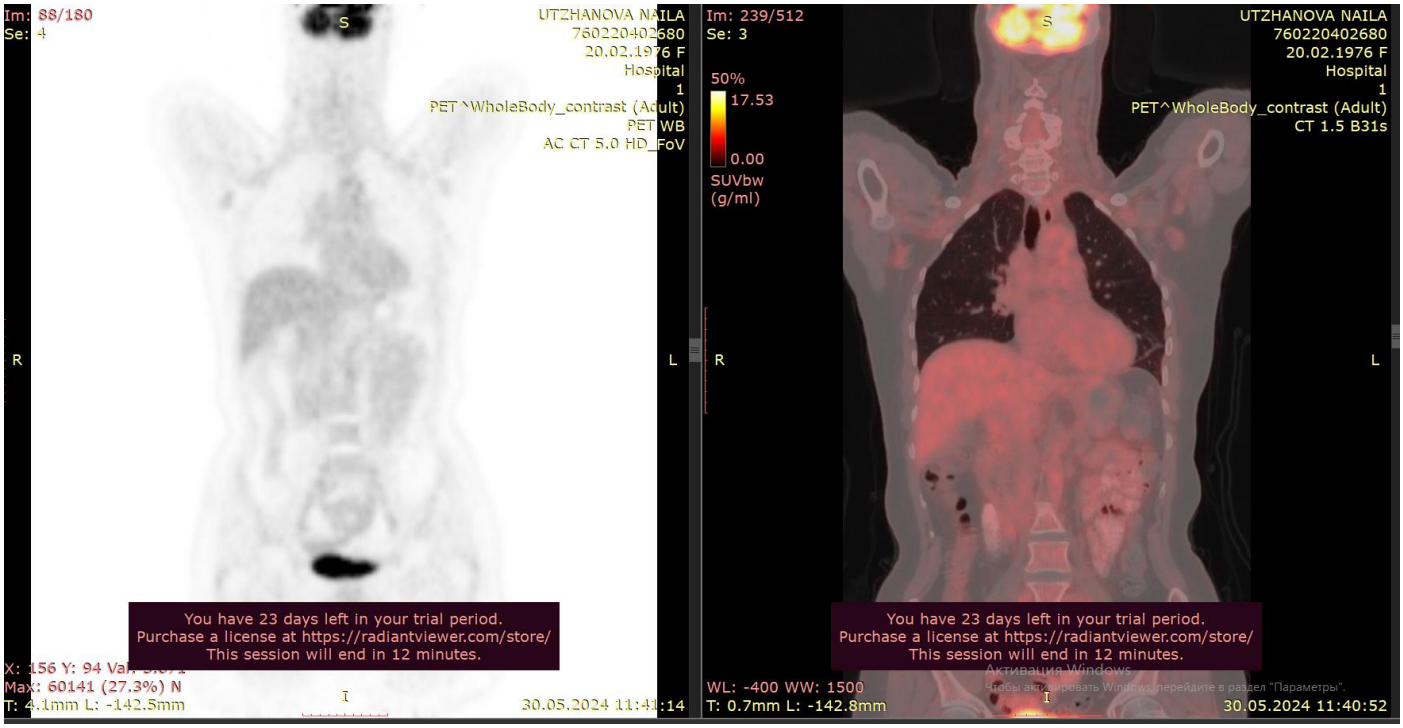
A follow-up magnetic resonance imaging (MRI) of the brain was performed. Protocol of Brain MRI dated 18/03/2024: on a series of MR images, hyperintense foci are identified on T2-weighted and FLAIR sequences in the frontal and parietal lobes of both cerebral hemispheres. The lesions are round to oval in shape, measuring up to 2.6 × 1.4 cm, with no signs of surrounding perifocal edema. (*Images not provided; visualization generated using artificial intelligence.*)



Until May 2024, the patient received targeted therapy with a third-generation tyrosine kinase inhibitor (TKI), Osimertinib.

In May 2024, difficulties arose with access to the medication. Given the presence of metastatic brain involvement, the patient was recommended to undergo Targeted therapy with a VEGF inhibitor (Bevacizumab) in combination with chemotherapy using the Pemetrexed + Carboplatin regimen. However, the patient declined chemotherapy courses, opting instead to continue with targeted therapy alone and wait for the availability of her original medication.

/CT Scan dated 30.05.2024:



PET/CT dated 30.05.2024: Conclusion: no convincing PET/CT evidence of a metabolically active ^{18}F-FDG-avid tumor process was detected. Axillary lymphadenopathy on the right side.

From May 13, 2024, to July 24, 2024, the patient received courses of targeted therapy with the VEGF inhibitor Bevacizumab.

Given the PET/CT findings showing no convincing evidence of a metabolically active ^{18}F-FDG-avid tumor process, and based on the published data from the “FLAURA-2” clinical trial, the case was reviewed by the MDT. By decision of the MDT on August 23, 2024, considering the patient’s young age and the presence of cerebral metastases, it was recommended that she undergo courses of TT with protein kinase inhibitors combined with VEGF inhibitors, along with 6 cycles of chemotherapy using the carboplatin + pemetrexed regimen, followed by maintenance therapy with pemetrexed.

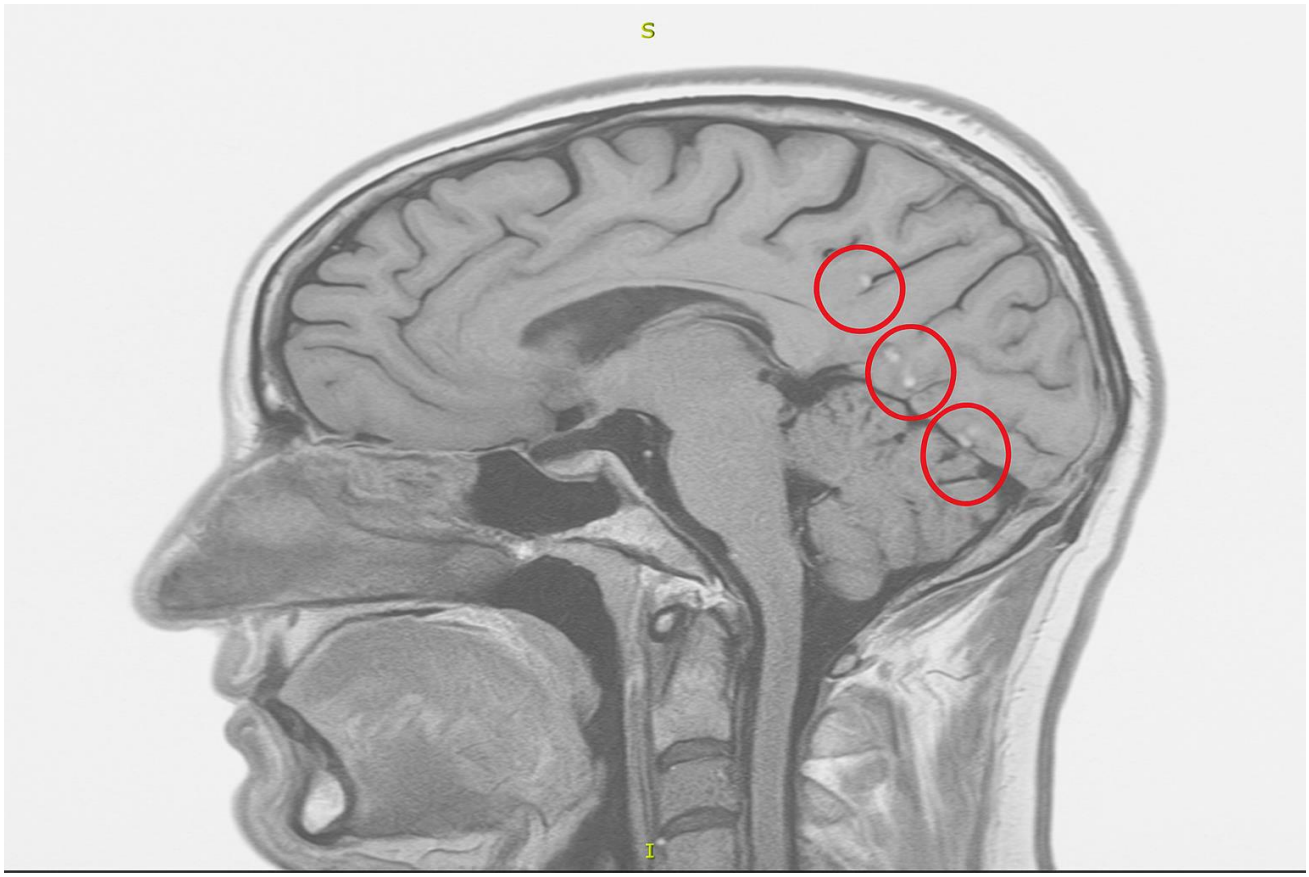
Considering the published data from the “FLAURA-2” study, the patient agreed to undergo chemotherapy. At that time, she also regained access to the third-generation tyrosine kinase inhibitor (TKI), Osimertinib.

From August 28, 2024, to December 30, 2024, the patient received 6 cycles of palliative polychemotherapy according to the “RR” regimen:

- **Pemetrexed** 500 mg/m² = 800 mg, administered intravenously (IV) by infusion
- **Carboplatin** AUC 4 = 450 mg, administered IV by infusion

The patient underwent regular follow-up examinations, with a particular focus on the brain.

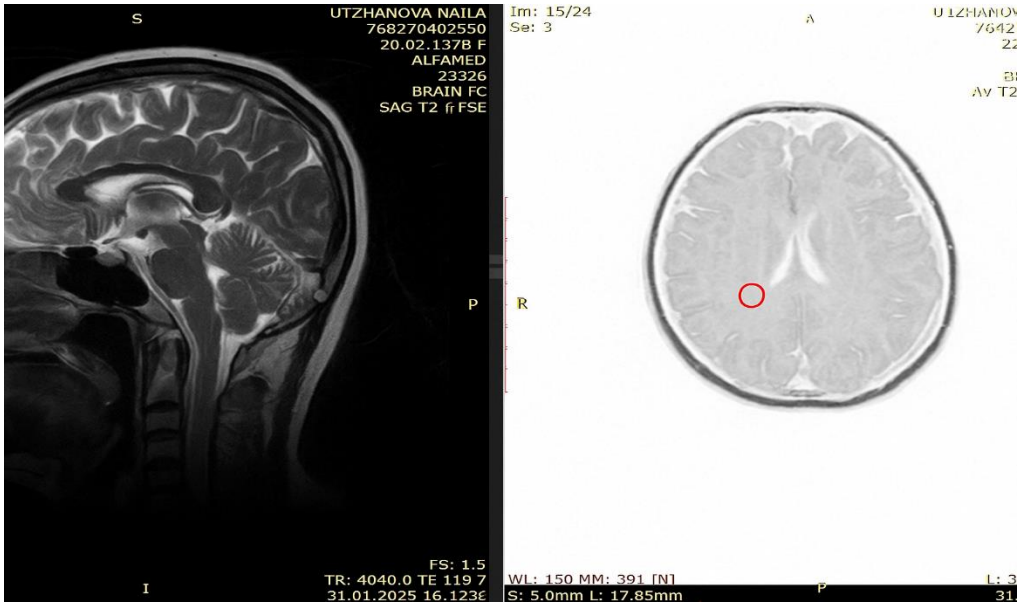
MRI of the Brain with Contrast — October 24, 2024:



Against the background of periventricular leucomalacia, hyperintense foci are observed on T2-weighted and FLAIR sequences in the parietal and occipital lobes of both cerebral hemispheres. The lesions are round to oval in shape, measuring up to 3.6 × 2.1 mm, with no signs of surrounding perifocal edema.

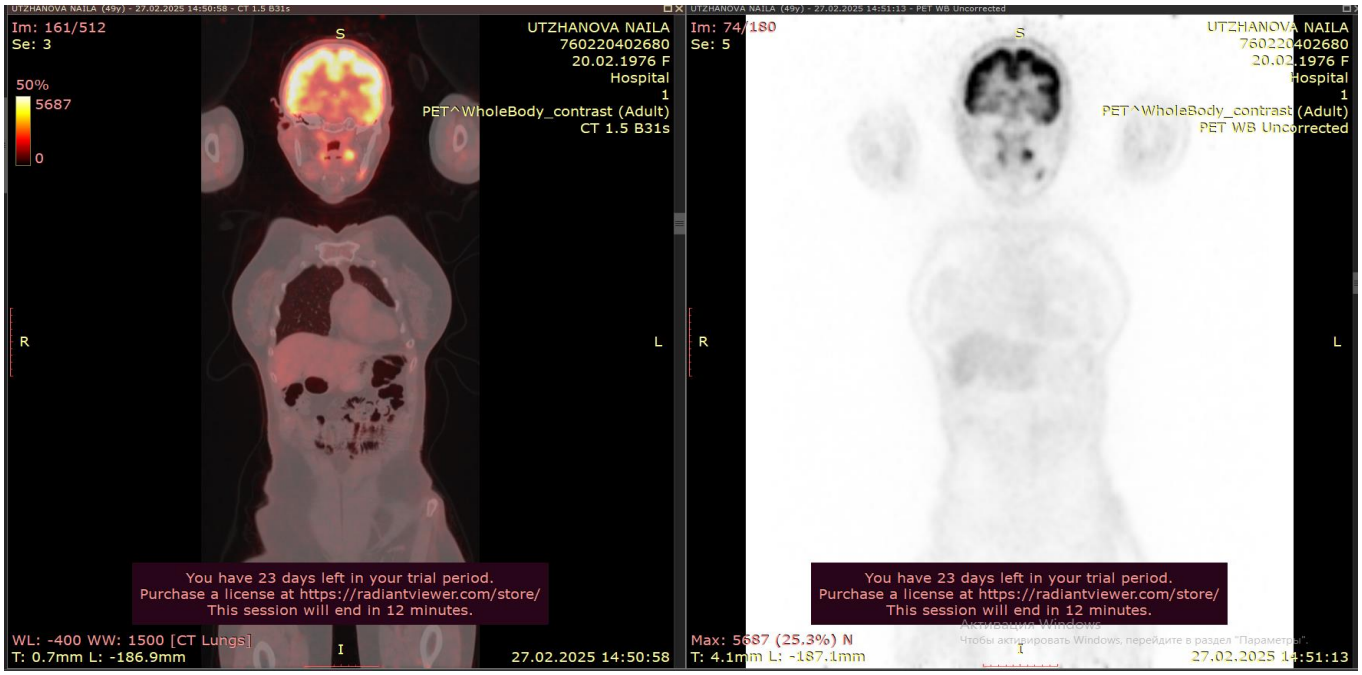
The patient completed chemotherapy courses in December 2024 and subsequently underwent follow-up examinations.

MRI of the Brain with Contrast – January 31, 2025.



In the subcortical and periventricular regions of both cerebral hemispheres, single hyperintense foci are observed on T2-weighted and T2 FLAIR images, measuring up to 0.55 mm. No diffusion restriction is noted on diffusion-weighted images, and no accumulation of paramagnetic contrast agent is seen on post-contrast scans. Conclusion**:** solitary foci, most likely of vascular origin, without accumulation of paramagnetic contrast agent, located in the subcortical and periventricular regions of both cerebral hemispheres.

PET/CT dated February 27, 2025. Conclusion:



- No definitive PET/CT evidence of a local recurrence of the primary oncological disease in the left lung with high metabolic activity was detected.
- PET/CT signs of symmetrical increased tracer uptake in the lymph nodes of the head, neck, and mediastinum (bronchopulmonary group on both sides), possibly corresponding to reactive changes, warrant dynamic observation.
- PET/CT findings of a nodular lesion in the left lobe of the thyroid gland (no significant changes compared to previous scans). Endocrinologist consultation and ultrasound follow-up are recommended.
- A hypervascular mass in the left lobe of the liver without metabolic activity, most consistent with a hemangioma (stable compared to previous scans).

Compared to the PET/CT results from May 30, 2024, there is newly observed increased metabolic activity in the lymph nodes of the retropharyngeal, submandibular, and bronchopulmonary groups on both sides. No isotope uptake is noted in the axillary lymph nodes in the current scan.

- As of February 2025, the primary lesion remains stable, and there is regression of the metastatic brain lesion.
- The patient continues on maintenance therapy with pemetrexed.

Discussion. The FLAURA2 study demonstrated that adding 4 cycles of chemotherapy (carboplatin + pemetrexed) to osimertinib:

- increases median progression-free survival (PFS) to 25.5 months compared to 16.7 months with monotherapy (Hazard Ratio [HR] 0.62),
- is particularly effective in cases with CNS metastases (24.9 months vs. 13.8 months, HR 0.47),

- has a manageable toxicity profile.

In patient U., a clinical response was observed that aligns with the findings of the study: significant regression of CNS metastatic lesions, disease control, and symptom improvement. The initiation of maintenance therapy with pemetrexed alongside ongoing osimertinib treatment is consistent with the FLAURA2 protocol.

Conclusion. The presented clinical case highlights not only the clinical significance of identifying an EGFR mutation in a patient with non-small cell lung cancer (NSCLC) and cerebral metastases, but also underscores the importance of increasing clinician awareness of contemporary clinical trials such as FLAURA and FLAURA2. These studies have fundamentally changed the treatment paradigm for EGFR-positive NSCLC, demonstrating the efficacy of third-generation tyrosine kinase inhibitors (e.g., osimertinib) and their combination with chemotherapy in improving progression-free survival and achieving effective control of cerebral lesions.

In resource-limited countries with strict financial constraints, the implementation of personalized medicine is often perceived as an unaffordable luxury. However, even a minimal level of molecular profiling (such as testing for EGFR, ALK, and ROS1 mutations) can fundamentally alter the therapeutic strategy, improve treatment effectiveness, and ultimately reduce overall costs by enabling more rational use of high-cost drugs and decreasing the number of hospitalizations.

It is important to emphasize that knowledge of, and active engagement with, the results of international clinical trials enables physicians to make well-informed decisions, adapting global standards to local realities. In this way, professional awareness and analytical competence among clinical oncology specialists become essential resources for implementing the principles of personalized care—even within the constraints of limited budgets.

The FLAURA2 study may serve as a basis for reconsidering first-line treatment standards for this category of patients.

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MONITORING THE DYNAMICS OF BREAST CANCER HETEROGENEITY THROUGH IMMUNOHISTOCHEMICAL PROFILING: CASE STUDIES FROM CLINICAL PRACTICE

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Abstract. Breast cancer is a biologically heterogeneous disease with variable responses to therapy. The aim of this study was to demonstrate the clinical importance of monitoring changes in the immunohistochemical profile.

A retrospective analysis of four patient cases treated at one oncology center was conducted. During therapy, changes in tumor subtypes were identified, including transitions from triple-negative to HER2-low or luminal types, as well as shifts from hormone receptor–positive to hormone receptor–negative disease. These alterations required substantial adjustments in therapeutic strategies, such as discontinuation of endocrine therapy, initiation of CDK4/6 inhibitors, or the addition of HER2/neu-targeted agents.

The results indicate that dynamic monitoring of the IHC profile is a practical and effective method that may enhance personalized therapy in the Republic of Kazakhstan.

Keywords: breast cancer, immunohistochemistry, subtype shift, HER2-low, personalized therapy

«Сүт безі қатерлі ісігінің гетрогенділігінің иммуногистохимиялық профиль арқылы динамикасын бақылау: клиникалық тәжірбиден жағдайлар»

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Аңдатпа: Сүт безі қатерлі ісігі - биологиялық тұрғыдан гетерогенді және терапияға әртүрлі жауап беретін ісіктердің бірі. Зерттеудің мақсаты - клиникалық тәжірибеде иммуногистохимиялық профиль динамикасын бақылаудың маңыздылығын көрсету. Біздің орталықта ем алған төрт пациенттің ИГХ профиліне ретроспективті талдау жүргізілді. Емдеу барысында ісік субтипінің өзгеруі анықталды: үштік теріс подтиптен HER2-low немесе люминальды түрге ауысу, сондай-ақ гормонға тәуелділіктен тәуелсіз түрге трансформация жағдайлары байқалды. Мұндай өзгерістер емдік тактиканы түбегейлі қайта қарауды талап етті (гормонотерапияны тоқтату, CDK4/6 тежегіштерін қосу, HER2/neu-ге бағытталған терапияны қолдану).

Зерттеу нәтижелері ИГХ-профильді динамикалық бақылаудың қолжетімді әрі тиімді әдіс екенін және Қазақстан Республикасында дербестендірілген терапияны жетілдіруге болатынын көрсетті.

Түйін сөздер: сүт безі қатерлі ісігі, иммуногистохимия, субтип өзгерісі, HER2-low, дербестендірілген терапия.

Мониторинг динамики гетерогенности рака молочной железы с помощью иммуногистохимического профилирования: изучения из клинической практики

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Аннотация. Рак молочной железы – биологически гетерогенное заболевание с вариабельным ответом на терапию. Целью данного исследования было продемонстрировать клиническую значимость мониторинга изменений иммуногистохимического профиля. Был проведен ретроспективный анализ четырех случаев пациентов, проходивших лечение в одном из онкологических центров. В ходе терапии были выявлены изменения подтипов опухоли, включая переходы от трижды негативного к HER2-низкому или люминальному типу, а также переходы от гормон-рецептор-позитивного к гормон-рецептор-негативному типу. Эти изменения потребовали существенной корректировки терапевтических стратегий, таких как прекращение эндокринной терапии, начало терапии ингибиторами CDK4/6 или добавление препаратов, таргетных на HER2/neu

Результаты показывают, что динамический мониторинг иммуногистохимического профиля является практичным и эффективным методом, который может улучшить персонализированную терапию в Республике Казахстан.

Ключевые слова: рак молочной железы, иммуногистохимия, смена подтипа, низкий уровень HER2, персонализированная терапия.

Introduction. Breast cancer (BC) remains one of the most significant challenges in oncology in the Republic of Kazakhstan. Despite the implementation of large-scale screening programs and nationwide initiatives aimed at raising cancer awareness, BC continues to rank first in both incidence and mortality. According to data from the Ministry of Health of the Republic of Kazakhstan (2022) [1], approximately 5,000 new cases are diagnosed annually, with around 1,200 women dying from the disease each year. Thus, regardless of sex-related differences, BC holds a leading position among oncological diseases in terms of both prevalence and mortality.

This trend is also observed globally. According to the Global Cancer Observatory (2022), BC ranks first in incidence and fourth in cancer-related mortality worldwide [2].

BC is a heterogeneous malignancy that encompasses several phenotypic variants, each with distinct clinical courses and varying sensitivity to antitumor therapy. Based on stepwise clinical protocols approved by the Ministry of Health of the Republic of Kazakhstan (2022), BC is classified into phenotypic subtypes according to immunohistochemical (IHC) results, reflecting the biological characteristics of the tumor.

Breast cancer is classified into phenotypic subtypes according to immunohistochemical (IHC) results, which reflect the biological features of the tumor (Ministry of Health of the Republic of Kazakhstan, 2022) [3].

Table 1 - Phenotypic subtypes of breast cancer

Phenotype	Description
Luminal A	ER (+) and/or PR (+); HER2/neu-negative[1]; Low Ki-67 (<20%)
Luminal B (HER2/neu-negative)	ER (+) and/or PR (+); HER2/neu-negative; high Ki-67 (>20%)
Luminal B (HER2/neu-positive)	ER (+) and/or PR (+); HER2/neu-positive[2]; Ki-

	67-any level
Triple-negative[3]	ER (-), PR (-); HER2/neu-negative
HER2-positive (non-luminal)	ER (-), PR (-); HER2/neu- positive (non-luminal)

Notes:

1. HER2 (0, 1+) – negative: absence of expression and amplification.
2. HER2 (3+) – positive: overexpression and amplification.
3. HER2 (2+) – equivocal: borderline overexpression and amplification, requiring additional confirmation by fluorescence in situ hybridization (FISH).
4. In advanced or metastatic triple-negative breast cancer, additional assessment of PD-L1 expression in immune cells is recommended.

In addition to the phenotypic subtypes, a molecular classification has been proposed by Harbeck, Penault-Llorca, Cortes, and colleagues (2019). [4] This classification is based on molecular characteristics and is widely applied in clinical practice.

Table 1 - Molecular Classification of Breast Cancer

Subtype	Molecular Features	Clinical Characteristics	Frequency	Prognosis
Basal-like	TP53 mutations; genetic instability; BRCA mutations	Poor differentiation; aggressive course	~10–15%	Poor prognosis; high drug resistance; may respond to platinum-based chemotherapy and PARP inhibitors
Claudin-low (triple-negative)	ER–, PR–, HER2–; high grade of malignancy; high Ki-67	Very aggressive; limited options for targeted therapy; PD-L1 testing important	~10–15%	Among the least favorable subtypes; immunotherapy may be considered
HER2-positive (non-luminal)	HER2 amplification; GRB7 amplification; PIK3CA, TOP2A, MYC mutations	Aggressive course; high Ki-67; good response to HER2-targeted therapy	~13–15%	Prognosis improved with trastuzumab, pertuzumab, and other HER2-targeted agents
Luminal A	Activation of ESR1, GATA3, FOXA1, XBP1; ER+, PR+; HER2–	Low Ki-67; low malignancy	~60–70%	Favorable prognosis; good response to endocrine therapy
Luminal B	PIK3CA (~40%) mutations; ESR1 (30–40%) mutations; ERBB2, ERBB3 mutations	ER+; lower PR levels than Luminal A; may be HER2+ or HER2–; often high Ki-67	~10–20%	Less favorable than Luminal A; requires combined endocrine, chemo-, and targeted therapies

This classification enables a deeper understanding of tumor biology at the molecular level. It is considered valuable not only in research but also in clinical practice, as it allows treatment planning to be tailored according to the IHC or molecular profile of each patient.

In recent years, newly introduced targeted therapies and chemotherapeutic agents have brought renewed hope to patients with breast cancer. However, as our experience has shown, many patients rapidly develop drug resistance following an initial positive response. This phenomenon is particularly evident in hormone-dependent tumors. Such tumor heterogeneity is one of the main reasons for treatment resistance, significantly complicating disease management. Resistance mechanisms are among the most complex issues and may include mutations in the *ESR1* gene, activation of alternative signaling pathways (such as PI3K/AKT/mTOR and MAPK), expression of epithelial-mesenchymal transition (EMT) factors, as well as changes in the tumor microenvironment [5–13]

Materials and Methods. A retrospective analysis was conducted on the medical histories of four patients diagnosed with breast cancer. All cases demonstrated disease progression during therapy along with changes in immunohistochemical (IHC) characteristics. The analysis was based on clinical data, histopathological findings, and dynamic monitoring of IHC profiles.

Patient K, 47 years old. Diagnosis: left breast cancer, nodular form, grade III, stage IIb (pT2N1M0). Triple-negative subtype.

Anamnesis morbi: Registered at the Turkistan Regional Oncology Dispensary since August 28, 2019. On June 24, 2019, breast ultrasound revealed a mass in the left breast. Mammography performed on July 11, 2019, identified an irregular mass with indistinct margins, measuring 3.3 × 4.2 cm, suspicious for malignancy. Histology on July 19, 2019, confirmed invasive ductal carcinoma, grade III. Immunohistochemistry (August 13, 2019): ER 0, PR 0, HER2/neu 0, Ki-67 – 60%.

Multidisciplinary team (MDT) decision (August 27, 2019):

1. Four cycles of neoadjuvant chemotherapy (NACT).
2. Radical mastectomy according to Madden.
3. Four cycles of adjuvant chemotherapy (ACT).

The patient received four cycles of NACT (AC regimen), with documented regression of the disease. On January 23, 2020, radical mastectomy was performed. Postoperative histology: invasive ductal carcinoma, no lymph node metastases.

In June 2020, four cycles of ACT with docetaxel were completed. The patient was then placed under dynamic observation.

Recurrence and further treatment:

- PET-CT (October 15, 2021) revealed metabolically active lesions in the left anterior chest wall and parasternal area (recurrence), metastasis in parasternal lymph nodes, as well as comorbid findings (bilateral sinusitis, chronic bronchitis, pulmonary nodules, left arm lymphedema).
- Ultrasound (November 9, 2021): hypoechoic lesion in the surgical scar (recurrence suspected).
- Histology (November 11, 2021): invasive carcinoma, grade II.
- IHC (November 22, 2021): ER 0, PR 0, HER2/neu 0, Ki-67 – 40%.

Based on MDT decision, six cycles of paclitaxel + cisplatin were administered, resulting in complete regression and remission lasting 11 months.

Progression (2023):

- PET-CT and ultrasound (March 2023) revealed metabolically active recurrent lesions in the surgical area, polyp in the right maxillary sinus, non-metabolic lung consolidation, and inflammatory findings. Compared with the October 2021 PET-CT, the parasternal lesion increased in size and metabolic activity.
- Ultrasound (March 7, 2023): hypoechoic lesion at the scar (1.6 × 1.1 cm), possible recurrence; supraclavicular lymph node (0.5 × 0.4 cm).

- Histology (March 13, 2023): invasive carcinoma, grade II. Cytology (March 9, 2023): proliferation of atypical cells with mild atypia.
- IHC: ER 0, PR 0, HER2/neu 0, Ki-67 – 25%.
- Six cycles of palliative polychemotherapy (pPCT) were administered.
- On August 31, 2023, wide excision with resection of major and minor pectoral muscles was performed. Postoperative histology: metastatic invasive carcinoma. Three cycles of pPCT (AC regimen) were given.

Further progression (2024–2025):

- MDT (January 8, 2024) recommended continuation of pPCT and dynamic PET-CT monitoring. Six cycles of pPCT (GP regimen) were administered.
- PET-CT (September 28, 2024) showed continued growth of the chest wall tumor.
- Re-biopsy (October 16, 2024): invasive carcinoma, grade III. IHC: ER 4b, PR 0b, HER2/neu 1+, Ki-67 – 35%.

Considering the shift to a luminal type, the MDT (February 6, 2025) recommended endocrine therapy combined with CDK4/6 inhibitors. Between February 12 and May 13, 2025, the patient received three cycles of targeted therapy, but progression with tumor necrosis was documented. Primary hormone dependency was confirmed. Systemic chemotherapy was initiated.

Summary: Left breast cancer, nodular form, grade III, stage IIb (pT2N1M0), initially triple-negative subtype. During treatment, the tumor subtype transformed into luminal B (HER2-low) with primary hormone dependency.

Note: According to ESMO and ASCO guidelines, primary endocrine resistance is defined as relapse during the first two years of adjuvant endocrine therapy or progression within six months of first-line endocrine therapy for metastatic disease. Secondary resistance is defined as relapse occurring after two years of adjuvant therapy, or within 12 months after completing adjuvant therapy, as well as progression beyond six months of endocrine therapy in metastatic settings (Sledge et al., 2017[14]).

Patient T, 70 years old. Diagnosis: right breast cancer, nodular form, stage IIA (T2N0M0, G2), luminal B subtype, HER2/neu-low status.

Anamnesis morbi: Registered at the Regional Clinical Hospital since December 4, 2024. The patient presented with complaints of a palpable mass. Breast ultrasound on October 29, 2024, revealed a lesion measuring 3.2 × 2.1 cm with echographic features classified as BI-RADS 4c. Core biopsy was performed.

Histology (November 21, 2024): invasive ductal carcinoma of the breast, grade 2. Cytology: tissue fluid with moderate atypia, erythrocytes, and cuboidal epithelial cells.

Immunohistochemistry (IHC): HER2/neu 1+, PR 0b, ER 3b, Ki-67 – 30%.

Multidisciplinary team (MDT) decision (December 2, 2024): neoadjuvant chemotherapy (NACT) was recommended. From December 4, 2024, to February 12, 2025, four cycles of NACT (AC regimen) were administered.

PET-CT (February 26, 2025): metabolically active mass in the right breast, located in the anterior chest wall, showing invasive growth, with no evidence of regional or distant metastases. Fluid formation in the precardial area without isotope accumulation, suggestive of a pericardial cyst.

Between February 27 and April 1, 2025, the patient received four cycles of NACT (TR regimen), with no significant clinical effect. Oncological consultation at the Kazakh Institute of Oncology and Radiology (April 7, 2025) recommended continuation of NACT for two cycles, with assessment of dynamics. Subsequently, the patient sought care at a private medical center, where metronomic therapy with paclitaxel + carboplatin (four cycles) was advised. From April 10 to May 22, 2025, four cycles of paclitaxel + carboplatin were administered, achieving partial regression.

Surgery: On June 13, 2025, radical mastectomy according to Madden was performed.

Postoperative histology (July 2, 2025): residual invasive nonspecific carcinoma of the right breast, grade III (2 + 3 + 1), measuring 45 mm at maximum dimension. Solid-type intraductal

component accounted for 20% of the tumor. Tumor cellularity was 70%. No metastases were identified in the axillary tissue. Residual Cancer Burden (RCB): class II, RCB index – 2.315.

Postoperative IHC (July 22, 2025): ER 2b (negative expression), PR 0b, Ki-67 – 70%, HER2/neu 0, corresponding to triple-negative subtype.

MDT recommendation: adjuvant radiotherapy and follow-up with dynamic PET-CT.

Summary: Right breast cancer, nodular form, stage IIA (T2N0M0, G2), initially luminal B subtype without HER2 overexpression. During treatment, the tumor subtype shifted to triple-negative.

Patient Zh, 42 years old. Diagnosis: right breast cancer, nodular form, T4N1M1, stage IV, grade II. Luminal B, HER2/neu-positive subtype.

Anamnesis morbi: Registered at the Turkistan Regional Oncology Dispensary since November 25, 2021. Breast ultrasound (November 11, 2021) revealed a hypoechoic lesion in the right breast (5.9 × 3.7 cm) and metastatic involvement of the left axillary lymph nodes.

Cytology (November 15, 2021): clusters of atypical tumor cells with polymorphic nuclei, coarse chromatin, and scant cytoplasm, on a background of erythrocytes and cellular debris. Conclusion: malignant tumor metastases.

Histology (November 6, 2021): invasive carcinoma of the breast, nonspecific type, grade II. ICD-O: 8500/3.

IHC: HER2/neu – 3+, ER – 5b, PR – 1b, Ki-67 – 25%.

MDT decision (November 25, 2021): initiation of palliative polychemotherapy (pPCT) combined with targeted therapy (trastuzumab + pertuzumab) and bone resorption inhibitors.

Chemotherapy regimens:

- November 25, 2021 – April 11, 2022: six cycles of docetaxel + carboplatin + targeted therapy (pertuzumab + trastuzumab) + bisphosphonates.

CT scan demonstrated signs of disease progression.

MDT decision (September 22, 2023): continuation of systemic chemotherapy (SCT), bone resorption inhibitors, and gonadotropin-releasing hormone (GnRH) agonists.

MDT decision (October 7, 2024): targeted therapy with trastuzumab emtansine, hormone therapy with fulvestrant, bisphosphonates, and GnRH agonists.

Between October 16, 2024, and June 9, 2025, the patient received targeted therapy with trastuzumab emtansine.

PET-CT (June 11, 2025): compared with results from September 24, 2024, negative dynamics were observed:

- increase in size and metabolic activity of lesions in the right breast and bone destruction foci, indicating tumor progression,
- increased isotope uptake (20% higher) in the right thyroid lobe lesion.

Re-biopsy (July 22, 2025): sample taken from metastatic site and sent for IHC.

IHC results: HER2/neu – 3+, ER – 0b, PR – 0b, Ki-67 – 30%. Loss of hormone receptor expression was documented.

Summary: Right breast cancer, nodular form, T4N1M1, stage IV, grade II. Initially luminal B, HER2/neu-positive subtype. During treatment, the tumor transformed into a hormone receptor–negative, HER2/neu-positive subtype.

Patient A, 46 years old. Diagnosis: left breast cancer, nodular form, stage IIIC (pT2N3M0), luminal A subtype.

Anamnesis morbi: Registered at the Turkistan Regional Oncology Dispensary since January 14, 2019. According to medical history, the breast lump had been present for a long period, with self-treatment attempted and no medical consultation until tumor growth prompted physician evaluation.

Ultrasound (November 21, 2018): right breast – hypoechoic lesion with indistinct margins, measuring 26 × 14 × 25 mm, containing calcifications and intranodular blood flow. Left axillary lymph nodes clustered with diameters ranging from 6 mm to 12 × 8 mm.

Histology (December 4, 2018): breast tissue biopsy showed infiltrative growth of small atypical cells, suspicious for malignancy.

Cytology (November 22, 2018): trephine biopsy revealed clusters of glandular epithelial cells with moderate to marked atypia.

MDT decision (December 13, 2018):

1. Wide sectoral resection with rapid cytology/histology.
2. If malignant, proceed to radical mastectomy (RM).
3. Repeat MDT after IHC results.

Surgery (December 21, 2018): radical mastectomy of the left breast according to Madden.

- Express cytology: suspicious for malignancy.
- Express histology: invasive ductal carcinoma.
- Final histology (January 3, 2019): invasive carcinoma, grade II. Metastases in 13 of 14 lymph nodes.

IHC (January 28, 2019): ER – 6b, PR – 5b, HER2/neu – 0, Ki-67 – 10%.

MDT decision (January 28, 2019): four cycles of adjuvant chemotherapy (AC regimen), four cycles of taxane-based chemotherapy, radiotherapy, and hormone therapy.

The patient completed six cycles of chemotherapy (AC regimen) by 2021. Hormone therapy was initiated but discontinued after eight months in 2021, as the patient declined continuation.

Recurrence: Scar formation was later noticed in the postoperative area.

Ultrasound (August 16, 2024): hypoechoic lesion 2 cm above the scar, measuring 1.2 × 0.6 cm, containing a hyperechoic component, avascular, irregular, with well-defined margins. Left supraclavicular lymphadenopathy was also documented.

Biopsy (August 23, 2024): cytology showed cell elements with marked dystrophic changes and moderate dysplasia, against a background of stained tissue fluid, erythrocytes, and cuboidal epithelial cells.

Histology (August 27, 2024): invasive carcinoma of the breast, nonspecific type, grade II. ICD-O: 8500/3.

IHC (September 17, 2024): HER2/neu – 2+, ER – 0b, PR – 0b, Ki-67 – 20%.

MDT decision (September 19, 2024): recommended systemic chemotherapy and FISH analysis to clarify HER2 status.

Treatment: October 1, 2024 – one cycle of chemotherapy (TR regimen). A treatment break of 10 months followed, during which disease progression occurred. The patient resumed systemic chemotherapy (AC regimen).

Summary: Left breast cancer, nodular form, stage IIIC (pT2N3M0), initially luminal A subtype. During treatment, the tumor subtype transformed into hormone receptor–negative, HER2/neu-low status

Discussion. The four clinical cases presented in this study illustrate the pronounced heterogeneity of breast cancer. During treatment, changes in phenotypic and molecular tumor profiles required reconsideration of therapeutic strategies. This phenomenon reflects both the biological variability of breast cancer and the complexity of resistance mechanisms.

Based on dynamic monitoring of the immunohistochemical (IHC) profile, some patients demonstrated transformation from hormone receptor–positive to hormone receptor–negative status, while others showed a switch from triple-negative subtype to HER2-low or luminal subtype. Such transformations necessitated major modifications in treatment strategy, including discontinuation of hormone therapy, introduction of CDK4/6 inhibitors, or implementation of HER2-targeted therapies.

According to published data, subtype switching occurs in 10–30% of patients, which is consistent with the present findings. The clinical importance of the HER2-low phenotype is particularly increasing. In recent years, the development of novel targeted agents for this group, such as trastuzumab deruxtecan, has offered additional therapeutic opportunities for patients in Kazakhstan.

Several practical challenges remain, however. Repeat biopsy is not always feasible, laboratory capabilities are sometimes limited, and financial constraints may influence therapeutic decision-making. Despite these limitations, systematic application of dynamic monitoring allows more accurate patient stratification and reduces the risk of unnecessary treatment.

Conclusion. The identified factors highlight the molecular complexity of breast cancer. Therefore, in Kazakhstan, the search for personalized treatment strategies represents not only a scientific question but also a practical necessity. As demonstrated by four clinical cases analyzed within one department, timely monitoring of immunohistochemistry (IHC) profile dynamics enabled more accurate therapeutic decisions.

Furthermore, under conditions of limited resources and budget constraints, the course of breast cancer can be effectively monitored through IHC. This method is relatively affordable and cost-efficient, as the use of 5–10 markers amounts to approximately 27,076.76 KZT (Ministry of Health of the Republic of Kazakhstan, 2020) [15]. IHC profiling can serve as a surrogate marker for the molecular classification of breast cancer. Although national clinical protocols recommend repeating IHC testing in cases of disease progression or the emergence of resistance, in practice, performing repeat biopsies or submitting postoperative material for analysis is not always feasible. These limitations reduce the ability to stratify patients accurately and to optimize the choice of personalized therapy.

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ESTIMATING THE PREDICTIVE VALUE OF THE CARDIOVASCULAR DISEASE RISK MODEL “SCORE” AMONG THE KAZAKH PEOPLE

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Abstract. Kazakhstan is the country with a high risk of cardiovascular diseases (CVDs) and one of the main reasons for this is the lack of early detection of the risk of CVDs. In this regard, the purpose of our study is to show the reliable CVD risk scale “SCORE” for determining the risk of CVDs, which are widely used in the world.

660 patients participated in the cohort study from 2012 to 2014 and 2019-2020. The diagnostic value and accuracy of SCORE was assessed using ROC/AUC analysis and Pearson correlation test. From these researchers, the main indicators of the scales for determining the risk of CVDs and changes in other risk factors based on 10-year dynamics were analyzed. AUC of SCORE risk score increased. Namely, AUC of SCORE model elevated from 0.88 in 2012 to 0.92 in 2020. The Pearson correlation rate was in the range 0.996 for following model with a p-value≤0.05. The proportion of the high-risk group was increased from 2.5% in 2012 to 4.4% in 2020. Predictive value of SCORE was investigated, and their accuracy was increased.

Keywords: SCORE, cardiovascular disease, risk score, predictive value, Kazakh population.

Қазақтар арасында жүрек-қан тамыр ауруларының қауіптілігін анықтаушы модел “SCORE”-нің диагностикалық құндылығына баға беру

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Аңдатпа. Қазақстан жүрек-қан тамыр ауруларының (ЖҚА) даму қаупі жоғары ел болып табылады, және оның негізгі себептерінің бірі – ЖҚА қаупінің ерте анықталмауы. Осыған байланысты біздің зерттеуіміздің мақсаты – әлемде кеңінен қолданылатын ЖҚА қаупін анықтау үшін қолданылатын «SCORE» қауіптілік шкаласының диагностикалық құндылығына баға беру.

2012-2014 және 2019-2020 жылдар аралығында когорттық зерттеуге 660 респондент қатысты. SCORE диагностикалық мәні мен дәлдігі ROC/AUC талдауы және Пирсон корреляция сынағы арқылы бағаланды. Осы зерттеушілерден 10 жылдық динамикаға негізделген ЖҚА қаупін және басқа қауіп факторларының өзгеруін анықтауға арналған шкалалардың негізгі көрсеткіштері талданды. SCORE қауіптілік шкаласының AUC көрсеткіші жоғарылады. Атап айтқанда, SCORE моделінің AUC мәні 2012 жылы 0,88-ден 2020 жылы 0,92-ге дейін көтерілді. Пирсон корреляция коэффициенті көрсеткішінің p-мәні≤0,05-ке тең, және берілген үлгі үшін 0,996 диапазонында болды. Тәуекел тобының үлесі 2012 жылғы 2,5%-дан 2020 жылы 4,4%-ға дейін өсті. SCORE қауіптілік шкаласының болжамдық мәндері зерттеліп, олардың дәлдігі айқындалды.

Түйін сөздер: SCORE, жүрек-қан тамыр жүйесі аурулары, қауіптілік шкаласы, диагностикалық құндылығы, қазақ популяциясы.

Оценка прогностической ценности модели риска сердечно-сосудистых заболеваний "SCORE" среди казахов

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Аннотация. Казахстан относится к странам с высоким риском сердечно-сосудистых заболеваний (ССЗ), и одной из основных причин этого является отсутствие раннего выявления риска ССЗ. В связи с этим, цель нашего исследования – продемонстрировать надежность шкалы риска ССЗ «SCORE» для определения риска ССЗ.

В когортном исследовании приняли участие 660 пациентов в период с 2012 по 2014 и с 2019 по 2020 годы. Диагностическая ценность и точность шкалы SCORE оценивались с помощью ROC/AUC-анализа и корреляционного теста Пирсона. По данным исследований, были проанализированы основные показатели шкал определения риска ССЗ и динамика других факторов риска на основе 10-летней динамики. AUC шкалы риска SCORE увеличилась. А именно, AUC модели SCORE увеличилась с 0,88 в 2012 году до 0,92 в 2020 году. Коэффициент корреляции Пирсона для данной модели находился в диапазоне 0,996 при p-значении ≤ 0,05. Доля группы высокого риска увеличилась с 2,5% в 2012 году до 4,4% в 2020 году. Прогностическая ценность SCORE была исследована, и ее повышенная точность была определена.

Ключевые слова: SCORE, сердечно-сосудистые заболевания, оценка риска, прогностическая ценность, казахская популяция.

Introduction. The social significance of cardiovascular diseases (CVDs) in population health is undoubtedly huge and they occupy first place among all other diseases globally [1]. Traditionally, in order to make an accurate diagnosis and treatment, patients must undergo a series of procedures and tests. However, conventional tests aimed at detecting the disease at an early stage may reduce the number of procedures in the assessment of the risk of CVDs.

Evaluation of the risk of cardiovascular events is challenging for clinicians due to multiple factors. Without risk calculators, physicians have been shown to overestimate risk by a factor of 2-6 [2]. However, more recent studies show that doctors working without a risk calculator assign patients to the appropriate risk categories in 59-71% of cases [3,4]. It is also difficult for patients to assess the degree of risk of cardiovascular pathology. If we define a high 10-year CVD risk above 20% and a low risk below 20%, then about four out of five high-risk patients underestimate their risk, and one in five low-risk patients overestimate their risks [5].

Current guidelines for primary prevention of CVD prioritize risk identification, mainly through traditional CVD risk factors, and risk stratification using clinical scores and risk assessments [6-10]. Researchers in the field have developed, and validated, multivariate risk prediction tools that synthesize information on CVD risk factors to predict future cardiovascular complications in various populations [10,11]. Since CVD is a long asymptomatic phase, from its clinical form to subclinical manifestations, the expansion of predictive studies of cardiovascular pathology has been supported [12]. The synergistic effect of several risk factors is greater than the effect of each risk factor in increasing overall cardiovascular risk. Therefore, calculating the overall risk of CVD is more important than identifying risk factors one at a time [13].

As a result, several clinical tools for predicting CVD have been developed, and the most commonly used are the SCORE risk score for European countries [6].

The use of risk assessments in clinical practice varies widely and often falls short of expectations [14-16]. The impact of applying these risk assessments in clinical practice is almost completely unknown, although their use is recommended in various national guidelines. The validation and impact of most predictive models have not been evaluated and there is a great need for such studies [17]. Similar studies assessing the risks of CVD using the SCORE model for the

Kazakh population were not conducted. Although the SCORE scale is recommended in national guidelines and introduced as a standard by order of the Ministry of Health of Kazakhstan for the use of the second stage of preventive medical examinations. Thus, the purpose of this study is to determine the diagnostic value and accuracy of CVD risk scales in the Kazakh population in accordance with the SCORE scale. This study also aims to evaluate the accuracy of the cardiovascular disease risk model of SCORE among the Kazakh population in the 8-year period. Moreover, the correlation of risk groups (low, medium and high) in the beginning and end of study timeframes was investigated.

Methods. The study was conducted at the Clinical Diagnostic Center of the Khoja Akhmet Yassawi International Kazakh-Turkish University (Turkistan city, Kazakhstan) in the period of 2012-2014 and 2019-2020. Due to the death of 28 participants, the final sample for this study included 632 participants (Figure 1). The age variable was divided into five categories: under 40 years old, 40-49 years old, 50-59 years old and 60-69 years old. The inclusion criteria for the study were age 18-69 years and written informed consent to participate in the study, whereas the participants of age over 69 years were excluded.

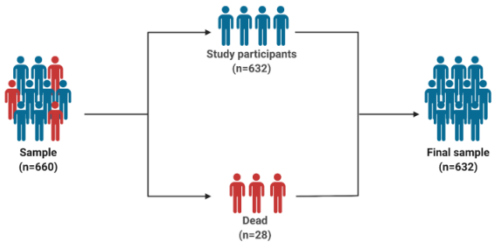

Figure 1. Formation of the final sample (Created with BioRender.com)

Data on study participants were collected in a patient survey card that contained a summary of the study, a written voluntary informed consent form, passport and demographic data, questionnaires on smoking, alcohol consumption, physical activity and stress, as well as anthropometric and laboratory studies.

The Fagerstrom test was used as a questionnaire to determine smoking status, and the Alcohol Use Disorders Identification Test (AUDIT) questionnaire was used for alcohol. The level of physical activity was determined according to the International Physical Activity Questionnaire (IPAQ), and patients were divided into three groups – with low, medium and high physical activity. According to the results of the Perceived Stress Questionnaire (PSQ) to determine the level of stress, among the study participants, were identified individuals with low, moderate and significant levels of stress.

The anthropometric study determining height, weight for which BMI was calculated. Laboratory research methods included the determination of total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Blood sampling was carried out from the cubital vein after a 12-hour fast. Biochemical studies were determined in the biochemical analyzer Cobas Integra-400 from Roche (Germany). The listed laboratory studies were carried out in the laboratory of the Clinical Diagnostic Center of Khoja Akhmet Yassawi International Kazakh-Turkish University.

Assessment of the accuracy of all risk score models was achieved using the values of the receiver operating characteristic (ROC) curve and calculating the area under the ROC curve (AUC). Pearson correlation coefficient was used to test the association between the risk scores in 2012 and 2020 for SCORE, significant if p-value$\leq$0.05.

This study was approved by the Commission on Clinical Ethics of the Faculty of Medicine of Khoja Akhmet Yassawi International Kazakh-Turkish University. Before attending the study, participants were provided with personal explanations regarding the purpose and method of the study, as well as information regarding the processing of the results. The written consent was achieved.

Results. The socio-demographic characteristics of the subjects are depicted in Table 1. The age of the respondents ranges from 27 to 69 years with a mean age of 51.2 ± 11.7 years. The study sample was dominated by women (69.9%), persons of Kazakh nationality (89.2%), patients with higher/incomplete higher education (64.8%), civil servants (72.7%), and married (89.3%) participants. Among patients, 13.4% smoked, 25.8% drank alcohol, 17.7% engaged in an average level of physical activity, 59.7% had a moderate degree of stress, 34.4% and 39.8% were overweight and obese, respectively.

Table 1. Social and demographic characteristics of the study participants (n=632)

No	Parameters		Number	Proportion, %
1	Gender	males	190	30.1
		females	442	69.9
2	Age	under 40	125	19.8
		40-49 years	152	24.1
		50-59 years	190	30.1
		60-69 years	165	26.0
3	Nationality	Kazakhs	564	89.2
		Others	68	10.8
4	Education	higher/incomplete higher	409	64.8
		average/below average	223	35.2
5	Occupation	civil servants/students	459	72.7
		private sector worker/entrepreneur	166	26.2
		unemployed (able or unable to work) / housewife / retired	7	1.1
6	Marital status	married	564	89.3
		single/divorced/widower	68	10.7
7	Smoking	yes	85	13.4
		no	547	86.6
8	Alcohol consumption	yes	163	25.8
		no	469	74.2
9	Physical activity	low	465	73.6
		average	112	17.7
		high	55	8.7
10	BMI	normal BMI	163	25.8
		overweight	218	34.4
		obese (I, II, III degrees)	251	39.8
11	Degree of stress	low	128	20.3
		average	377	59.7
		high	127	20.0

The accuracy of risk score model was assessed using the values of ROC and calculating the area under the curve. So, for the SCORE CODE at the beginning of the study period, AUC was 0.88 (95% CI, 0.22 – 0.94), whereas this value increased to 0.92 (95% CI, 0.19 – 0.94) in 2020 (Figure 2).

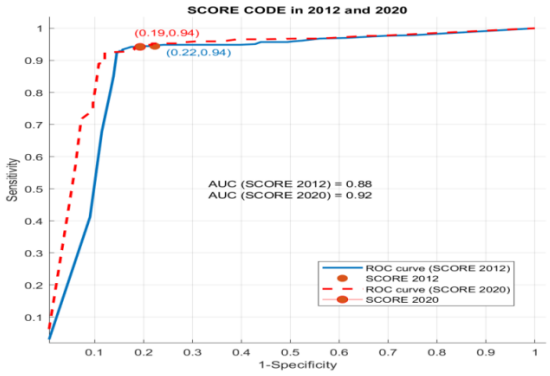

Figure 2. ROC curves and AUC values of risk score "SCORE" in 2012 and 2020

The Pearson correlation coefficients between the SCORE risk scores scales are displayed in Table 3. All risk scales correlated significantly with each other. The correlation rate was 0.996 for all scales with a p-value≤0.05. Also, it should be noted that the transition from low risk to medium risk and medium risk to high risk was observed from 2012 to 2020. Namely, in the SCORE scale, the proportion of high risk was increased from 2.5% in 2012 to 4.4% in 2020.

Table 3. Pearson correlation coefficients between SCORE risk score scales

Scales	2012	2020	correlation	p-value
SCORE	*n* (%)	*n* (%)		
Low risk (0-4%)	516 (81.6)	466 (73.7)		
Medium risk (4-9%)	100 (15.8)	138 (21.8)	0.996	0.054
High risk (≥10%)	16 (2.5)	28 (4.4)		

Discussion. In this study, we assessed the accuracy of the most common cardiovascular disease risk score model among the Kazakh ethnicities. SCORE model accuracy increased slightly from 2012 to 2020.

Nonetheless, according to the values of the area under the ROC curve, the most accurate result in 2020 was observed in the SCORE model. Also, in the SCORE scale, low-, medium- and high-risk groups outcomes in 2012 correlated significantly with the results of cardiovascular disease risk scores in 2020. The use of ROC/AUC for the evaluation of the accuracy of risk scores was demonstrated in the studies of Cooper et al. [18] and Versteylen et al. [19].

There are multiple contributing risk factors to the progression of cardiovascular diseases, and alcohol consumption [20], smoking [21] and body mass index [22] are not the exception. Especially, alcohol intake had the strongest relationship to the outcomes of all risk models. Based on our findings, the presence of cardiovascular diseases did also affect the values of the regression model of the scoring scales. Among the CVD parameters, BMI had the weakest relationship to the results of SCORE model in this study.

Among the limitations of the study, it should be noted that the predisposing risk factors for cardiovascular diseases were not investigated in terms of gender, although it was out of the scope of this study. Moreover, the predictive value of risk score models was irrespective of gender in the study of Hence et al. [23]. Also, long-term follow-up will be needed to identify the best predictive value among the compared risk models.

The study was limited by the application of SCORE risk model, and other risk scores such as SMART and Diamond-Forrester (DF) were not used. They could also provide the variability for doctors in the prediction of cardiovascular events, especially in patients with atherosclerosis, which

was assessed by SMART score in the study of Uthoff et al. [24], whereas the performance of updated DF was compared in the predicting obstructive coronary artery disease by Baskaran et al. [25].

Recent studies have shown that the compared risk models are effective across various populations in predicting relative and absolute risks of cardiovascular events [18,19,23]. Similarly, the accuracy of the predictive values of SCORE model among the Kazakh population in the risk of CVDs was increased. A strong correlation of low- to high-risk groups was observed at the beginning and end of the study period.

Conclusion: The predictive value of the SCORE risk scale were investigated and their accuracy was determined for Kazakh population.

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