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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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