ФГБУ "НМИЦ ОНКОЛОГИИ"
МИНЗДРАВА РОССИИ

ISSN 2686-9039 (Online)

South Russian Journal of Cancer

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

Южно-Российский онкологический журнал

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

vol. / том 6 № 3/2025

www.cancersp.com

ISSN 2686-9039 (Online)

PEER-REVIEWED SCIENTIFIC AND PRACTICAL JOURNAL

South Russian Journal of Cancer

The journal is included in the list of peer reviewed scientific journals and publications recommended by the Higher Attestation Commission of the Russian Federation for publishing the main scientific results of dissertations for the degree of candidate and Doctor of Sciences.

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- To promote the development of oncological medicine in the South of Russia and the implementation of its achievements in practice.
- High-quality published content that includes the latest and trustworthy scientific papers, research or work on oncology issues.

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- Informing readers about the results of major medical forums;
- Giving scientists the opportunity to publish the results of their research;
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- Expansion of the editorial board and reviewers by attracting well-known experts from Russia and other countries;
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Founder and Publisher:
Autonomous Non-profit Organization "Perspectives of Oncology"
(ANO "Perspectives of Oncology")

Editorial and publisher address:
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www.cancersp.com
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The journal is registered at the Roskomnadzor on 28.10.2019,
EL No. FS 77-80665 – online.
Frequency: 4 issues per year.

Accepted for publication 09.09.2025

ISSN 2686-9039 (Online)

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

Южно-Российский онкологический журнал

Журнал входит в рекомендованный ВАК РФ перечень рецензируемых научных журналов и изданий для опубликования основных научных результатов диссертаций на соискание учёной степени кандидата и доктора наук.

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- Расширение состава редакционной коллегии и рецензентов путем привлечения известных экспертов из России и других стран;
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- Повышение импакт-фактора журнала.

Журнал принимает к публикации: результаты оригинальных исследований, обзоры литературы, описание клинических случаев.

Издатель и учредитель:
Автономная некоммерческая организация «Перспективы онкологии» (АНО «Перспективы онкологии»)

Адрес редакции и издателя:
344037, Россия, Ростов-на-Дону, 14-я линия, д. 63, литер Г, комната 1
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Сайт: www.cancersp.com
Для корреспонденции: 111555, Москва, а/я 3

Журнал зарегистрирован в Роскомнадзоре 28.10.2019 г.,
ЭЛ № ФС 77-80665 – сетевое издание.
Периодичность: 4 номера в год.

Принят к публикации 09.09.2025

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https://doi.org/10.37748/2686-9039-2025-6-3-1
https://elibrary.ru/pskoqy
ORIGINAL ARTICLE

Prognostic significance of AKT/mTOR signaling pathway components, transcription factors, and growth factors in the development of skin melanoma recurrence

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ABSTRACT

Purpose of the study. Was to investigate the prognostic significance of the AKT/mTOR signaling pathway components, transcription, and growth factors in the development of skin melanoma recurrence.

Patients and methods. The study included 48 patients with a verified diagnosis of skin melanoma. All patients had a negative status for the $BRAF^{V600E}$ mutation.

The study material consisted of samples of tumor and unchanged skin located at a distance of at least 1 cm from the tumor border, obtained during surgical treatment, which were frozen and stored at a temperature of –80 °C after sampling. Gene expression was assessed by real-time PCR. The status of the BRAF gene was assessed using allele-specific PCR. Statistical processing was carried out using the Statistica 12.0 software package.

Results. Predicting the course of cancer is an important task in practical oncology. The unfavorable outcome of melanomas is largely due to the tendency to relapses and metastasis in both the short and long-term follow-up period. While analyzing the study results, we noted the association of AKT/mTOR signaling pathway components with the development of skin melanoma recurrence and disease progression. It was revealed that the expression level of AKT, c-RAF, GSK-3β and VEGFR2 is associated with an unfavorable outcome of the disease. A logistic regression model is presented that can accurately predict the risk of recurrence, taking into account the expression of protein kinase mTOR and the size of the tumor (T). The lack of significant indicators related to the biological features of the skin tumor does not allow to increase the effectiveness of treatment of such patients. Therefore, the attention of researchers is focused on finding optimal models for predicting the risk of an unfavorable outcome of the disease.

Conclusion. Molecular markers were identified that make it possible to predict an unfavorable outcome of the disease during the study. A logistic model based on the expression of the key mTOR kinase and the size of the T has been developed, which makes it possible to assess the risk of disease recurrence and change treatment tactics in a timely manner.

Keywords: AKT, c-RAF, GSK-3β, VEGFR2, mTOR, skin melanoma, prognosis

For citation: Bogdanova V. A., Spirina L. V., Chizhevskaya S. Yu., Kovaleva I. V., Nikulnikov K. V., Merkulov E. D. Prognostic significance of AKT/mTOR signaling pathway components, transcription factors, and growth factors in the development of skin melanoma recurrence. South Russian Journal of Cancer. 2025; 6(3): 6-15. https://doi.org/10.37748/2686-9039-2025-6-3-1, https://elibrary.ru/pskoqy

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Compliance with ethical standards: the study is carried out in compliance with the ethical principles set forth in the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the Scientific Research Institute of Oncology, Tomsk Scientific Research Medical Center (extract from the protocol of meeting No. 5 dated 11/26/2023). Informed consent was obtained from all participants of the study

Funding: this work was not funded

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 05.01.2025; approved after reviewing 07.04.2025; accepted for publication 05.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 6-15
https://doi.org/10.37748/2686-9039-2025-6-3-1
https://elibrary.ru/pskoqy
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Прогностическая значимость компонентов AKT/mTOR сигнального пути, транскрипционных и ростовых факторов в развитии рецидивов меланомы кожи

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РЕЗЮМЕ

Цель исследования. Исследование прогностической значимости компонентов сигнального пути AKT/mTOR, а также транскрипционных и ростовых факторов в развитии рецидивов меланомы кожи.
Пациенты и методы. В исследование были включены 48 пациентов с верифицированным диагнозом меланома кожи. Все пациенты имели отрицательный статус по мутации $BRAF^{V600E}$.
Материал исследования – образцы опухолевой и неизмененной кожи, находящиеся на расстоянии не менее 1 см от границы опухолей, полученные при проведении оперативного лечения, которые после забора замораживались и хранились при температуре –80 °С. Экспрессия генов оценивалась методом ПЦР в реальном времени. Статус гена *BRAF* оценивали с помощью аллель-специфичной ПЦР. Статистическая обработка проводилась с помощью пакета программ Statistica 12.0
Результаты. Прогнозирование течения онкологических заболеваний является важной задачей в практической онкологии. Неблагоприятный исход меланом во многом обусловлен склонностью к возникновению рецидивов и метастазов как в ближайшем, так и в отдаленном периоде наблюдения. При анализе результатов исследования нами отмечена ассоциация компонентов AKT/mTOR сигнального пути с развитием рецидивов меланом кожи и прогрессированием заболевания. Выявлено, что уровень экспрессии AKT, c-RAF, GSK-3β и VEGFR2 связан с неблагоприятным исходом заболевания. Представлена модель логистической регрессии, которая с высокой точностью может дать прогноз риска развития рецидивов заболевания с учетом экспрессии протеинкиназы mTOR и размера опухоли (T). Отсутствие значимых показателей, связанных с биологическими особенностями опухоли кожи, не позволяет повысить эффективность лечения таких больных. Поэтому внимание исследователей сосредоточено на поиске оптимальных моделей прогноза риска неблагоприятного исхода заболевания.
Заключение. В ходе исследования были идентифицированы молекулярные маркеры, которые позволяют прогнозировать неблагоприятный исход заболевания. Разработана логистическая модель, основанная на экспрессии ключевой киназы mTOR и T, которая позволяет оценить риск возникновения рецидивов заболевания и своевременно изменить тактику лечения.

Ключевые слова: AKT, c-RAF, GSK-3β, VEGFR2, mTOR, меланома кожи, прогноз

Для цитирования: Богданова В. А., Спирина Л. В., Чижевская С. Ю., Ковалева И. В., Никульников К. В., Меркулов Е. Д. Прогностическая значимость компонентов AKT/mTOR сигнального пути, транскрипционных и ростовых факторов в развитии рецидивов меланомы кожи. Южно-Российский онкологический журнал. 2025; 6(3): 6-15. https://doi.org/10.37748/2686-9039-2025-6-3-1, https://elibrary.ru/pskoqy

Для корреспонденции: Спирина Людмила Викторовна – д.м.н., ведущий научный сотрудник лаборатории биохимии опухолей, Научно-исследовательский институт онкологии – филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Российская Федерация; заведующий кафедрой биохимии и молекулярной биологии с курсом клинической лабораторной диагностики, ФГБОУ ВО «Сибирский государственный медицинский университет» Министерства здравоохранения Российской Федерации, г. Томск, Российская Федерация
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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при Научно-исследовательском институте онкологии – филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук» (выписка из протокола заседания № 5 от 26.11.2023 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 05.01.2025; одобрена после рецензирования 07.04.2025; принята к публикации 05.08.2025

BACKGROUND

Melanoma is the most dangerous skin malignancy, which is characterized by an aggressive course. According to a study based on GLOBOCAN data, the rate of increase in the incidence of melanoma will remain unchanged from 2020, which may lead to an increase in the incidence by about 1.5 times by 2040 [1]. In 2020, about 14 % of cases of melanoma among all malignant skin tumors were recorded in Russia. At the same time, it caused the death of 70 % of patients suffering from this group of diseases [2, 3].

Melanoma occurs due to a few genetic transformations, while ultraviolet radiation often serves as a mutagenic risk factor [4]. A deep understanding of the diversity of molecular signaling pathways characteristic of different types of melanomas makes it possible to describe these pathologies more accurately and provides tools for creating treatment methods based on the effects on the signals generated by these cascades [5]. Among the key molecular genetic indicators, a mutation of the *BRAF* gene can be identified, which occurs in 60–80 % of cases of all skin malignancies [6, 7].

Modern treatments for skin melanoma are becoming increasingly available, which improves survival rates, but there are no tools available to predict the recurrence of skin melanoma. To predict the recurrence of skin melanoma in the early stages of development, the use of clinical and histological data in machine learning technologies is being considered [8]. In addition, predicting an unfavorable outcome of the disease is possible by examining molecular markers in the homogenates of tumor tissue samples and the visually unchanged tissue adjacent to it [9]. Great importance is attached to the study of genetic factors that can predict the risk of developing an unfavorable outcome of the disease [10, 11]. In general, the rationale for the use of a number of signaling cascades associated with the molecular features of tumor growth is an urgent problem in fundamental oncology [12].

Previous studies have shown the role of microRNAs in the regulation of these markers [13, 14], reflecting the intensity of oncogenesis processes. Their association with the presence of signs of invasive growth and metastasis was noted. However, in general, there are practically no approaches that allow predicting the development of an unfavorable outcome of the disease with high accuracy.

Purpose of the study: was to study the prognostic role of components of the AKT/mTOR signaling pathway, as well as transcription and growth factors in predicting skin melanoma recurrence.

PATIENTS AND METHODS

The study involved 48 patients with a confirmed diagnosis of skin melanoma. The age of the study participants ranged from 45 to 72 years, and the stages of the disease ranged from I to IV. All patients underwent surgical treatment, which included extensive excision of the skin tumor with a sentinel lymph node biopsy.

T1a N0M0 stage of the disease was detected in 10 patients (21 %), T1b N0M0 – in 12 (25 %), T2b N0M0 – in 2 (4 %), T3a N0M0 – in 11 (23 %), T3b N0M0 – in 2 (4 %), T4a N1M0 – in 9 (19 %), T4b N1M0 – in 2 (4 %).

Tumor ulceration was absent in 23 (47 %) patients, and the presence of tumor ulceration was noted in 25 (53 %) patients. The level of Clark invasion of the 1st degree was not recorded, the 2nd degree was noted in 17 (35 %); the 3rd degree – in 17 (35 %); the 4th degree – in 3 (6.5 %); the 5th degree – in 11 (23.5 %).

The Breslow tumor thickness of less than 0.75 mm was recorded in 6 (12 %), from 0.75 mm to 1.5 mm was observed in 20 (41 %), from 1.51 to 3.0 mm – in 2 (6 %), from 3.01 mm to 4.0 mm – in 6 (12 %), from 4.01 mm and more than 14 (29 %).

It is important to note that all patients lacked the $BRAF^{V600E}$ mutation. The study was approved by the Ethics Committee of the Scientific Research Institute of Oncology, a branch of the Tomsk National Research Medical Center of the Russian Academy of Sciences. 6 patients with melanocytic nevus were selected as a control group. All procedures involving patients were conducted in accordance with the Helsinki Declaration on Human Rights (1964). Before starting the study, all participants signed an informed consent. The material for the study was samples of tumor and healthy skin obtained during surgical treatment. The samples were taken at a distance of at least 1 cm from the tumor border and frozen for subsequent storage at a temperature of –80 °C.

Isolation of RNA. RNA was isolated using the RNeasy mini-Kit containing DNAase I (Qiagen, Germany). To estimate the amount of isolated RNA, the concentration and purity of the isolated RNA were evaluated on a NanoDrop-2000 spectrophotometer (Thermo Scientific, USA). The RNA concentration ranged from 80 to 250 ng/ml, A260/A280 = 1.95–2.05; A260/A230 = 1.90–2.31. RNA integrity was assessed using capillary electrophoresis on a TapeStation device (Agilent Technologies, USA) and an R6K ScreenTape kit (Agilent Technologies, USA). The RIN was 5.6–7.8.

Real-time quantitative reverse transcription PCR. The level of gene expression was assessed using quantitative real-time reverse transcriptase PCR (RT-qPCR) using the SYBR Green dye on an iCycler amplifier (Bio-Rad, USA; CCP "Medical Genetics"). To obtain cDNA on an RNA template, a reverse transcription reaction was performed using the OT m-MuLV-RH kit (Biolabmix, Russia) with random hexanucleotide primers according to the kit instructions. PCR was performed in three replicas in a volume of 25 µl containing 12.5 µl of HS-qPCR SYBR Blue BioMaster (Biolabmix, Russia), 300 nM of direct and reverse primers and 50 ng of cDNA:
CAIX: F 5'-GTTGCTGTCTCGCTTGGAA-3',
R 5'-CAGGGTGTCAGAGAGGGTGT-3';
HIF-1α: F 5'- CAAGAACCTACTGCTAATGCCA-3',
R 5'- TTTGGTGAGGCTGTCCGA-3';
EPAS1: F 5'- TGGAGTATGAAGAGCAAGCCT-3',
R 5'-GGGAACCTGCTCTTGCTGT-3';
NFKB1: F 5'-CGTGTAAACCAAAGCCCTAAA-3',
R 5'-AACCAAGAAAGGAAGCCAAGT-3';
RELA: F 5'-GGAGCACAGATACCACCAAGA-3',
R 5'-GGGTTGTTGTTGGTCTGGAT-3';
VEGFA: F 5'-AGGGCAGAATCATCACGAA-3',
R 5'-TCTTGCTCTATCTTTCTTTGGTCT-3';
KDR: F 5'-AACACAGCAGGAATCAGTCA-3',
R 5'-GTGGTGTCTGTGTCATCGGA-3';
4E-BP1: F 5'- CAGCCCTTTCTCCCTCACT-3',
R 5'- TTCCCAAGCACATCAACCT-3';
AKT1: F 5'- CGAGGACGCCAAGGAGA-3',
R 5'- GTCATCTTGGTCAGGTGGTGT-3';
C-RAF: F 5'- TGGTGTGTCCTGCTCCCT-3',
R 5'- ACTGCCTGCTACCTTACTTCCT-3';
GSK-3β: F 5'- AGACAAGGACGGCAGCAA-3',
R 5'- TGGAGTAGAAGAAATAACGCAAT-3';
70S kinase alpha:
F 5'- CAGCACAGCAAATCCTCAGA-3',
R 5'- ACACATCTCCCTCTCCACCTT-3';
mTOR: F 5'- CCAAAGGCAACAAGCGAT-3',
R 5'- TTCACCAAACCGTCTCCAA-3';
PDK1: F 5'- TCACCAGGACAGCCAATACA-3',
R 5'- CTCCTCGGTCACTCATCTTCA-3';
VHL: F 5´ – GGCAGGCGAATCTCTTGA-3´,
R 5´-CTATTTCCTTTACTCAGCACCATT-3´;
PD-L2: F 5'-GTTCCACATACCTCAAGTCCAA-3',
R 5'-ATAGCACTGTTCACTTCCCTCTT-3';
PD-L1: F 5'-AGGGAGAATGATGGATGTGAA-3',
R 5'-ATCATTCACAACCACACTCACAT-3';
PD-1–1: F 5'-CTGGGCGGTGCTACAACT-3',
R 5'-CTTCTGCCCTTCTCTCTGTCA-3';
AMPK: F 5'- AAGATGTCCATTGGATGCACT-3',
R 5'- TGAGGTGTTGAGGAACCAGAT-3';
LC3B: F 5'- CCCAAACCGCAGACACAT-3',
R 5'-ATCCCACCAGCCAGCAC-3';
GAPDH: F 5'- GGAAGTCAGGTGGAGCGA-3',
R 5'-GCAACAATATCCACTTTACCAGA-3'.

The two-step amplification program included: preliminary denaturation of the reaction mixture at 94 °C, 10 minutes – 1 cycle; denaturation at 94 °C, 10 seconds and annealing/elongation at 60 °C, 20 seconds – 40 cycles. The primers were selected using the Vector NTI Advance 11.5 program and the NCBI database (https://www.ncbi.nlm.nih.gov/nuccore).

The "housekeeping" gene of the GAPDH enzyme (glyceraldehyde-3-phosphate dehydrogenase) was used as a reference gene, and the expression level of each target gene was normalized relative to GAPDH expression. Quantitative analysis of expression was performed using 2ΔΔCt in relation to the constitutively expressed referee gene of the GAPDH enzyme.

Statistical analysis

Statistical processing of the results was carried out using the Statistica 12.0 software package. Normality was checked using the Kolmogorov-Smirnov criterion. The results of the determination of gene expression are presented as Me (Q1; Q3). The significance of the differences in independent parameters was assessed by the Mann-Whitney criterion. The differences were considered significant at $p < 0.05$. When comparing the differences in more than two study groups, nonparametric analysis of variance (Kruskal-Wallis test) was used.

STUDY RESULTS

Predicting cancer treatment outcomes is one of the key tasks in oncology. An unfavorable prognosis for melanoma is associated with a high probability of recurrence and metastasis. As part of this study, we analyzed the accuracy of molecular markers of skin melanoma in predicting its development. To do this, we used the log-rank criterion and Kaplan-Meyer survival curves. As a result of the study, it was found that the expression of markers such as AKT, c-RAF, GSK-3β and VEGFR2 are of the greatest importance for predicting disease-free survival (Table 1).

Table 1. One-factor analysis of prognostic parameters in patients with skin melanoma using a log rank test

Parameter	Expression, RU/ml	Progression-free survival, *p*
4EBP1, RU/ml	< 1.00 > 1.00	0.57770
AKT, RU/ml	< 1.0 > 1.0	0.00548
c-RAF	< 0.5 > 0.5	0.04345
GSK-3β	< 0.85 > 0.85	0.04229
70S 6 kinase	< 0.03 > 0.03	0.99828
mTOR, RU/ml	< 0.97 > 0.97	0.11658
PDK1, RU/ml	< 1.53 > 1.53	0.47026
PTEN, RU/ml	< 0.01 > 0.01	0.68012
NF-kB p65, RU/ml	< 0.20 > 0.20	0.18567
NF-kB p50, RU/ml	< 0.05 > 0.05	0.36003
VEGFR2, RU/ml	< 1.00 > 1.00	0.00156
VEGF, RU/ml	< 1.00 > 1.00	0.36003
CAIX, RU/ml	< 0.13 > 0.13	0.51732
HIF-1, RU/ml	< 0.26 > 0.26	0.18567
HIF-2, RU/ml	< 0.81 > 0.81	0.92342
VHL, RU/ml	< 0.14 > 0.14	0.81110
PD-1, RU/ml	< 1.15 > 1.15	0.82655
PD-L1, RU/ml	< 0.60 > 0.60	0.22916
PD-L2, RU/ml	< 1.34 > 1.34	0.88087
AMPK, RU/ml	< 0.00 > 0.00	0.48182
LC3B expression, RU/ml	< 0.50 > 0.50	0.29877

In a study aimed at determining the prognostic value of the expression of transcription and growth factors, as well as components of the AKT/mTOR signaling cascade for assessing progression-free survival in patients with skin melanoma, it was found that the best results are achieved when the expression level of AKT genes is above 1.0 (Fig. 1); c-RAF is below 0.5 (Fig. 2); GSK-3β is below 0.85 (Fig. 3) and VEGFR2 is above 1.0 (Fig. 4) cont. units.

Based on the results of clinical and morphological studies, as well as the expression of certain molecular markers, a model has been developed that makes it possible to predict the recurrence of skin melanoma and an unfavorable outcome of the disease.

The method consists in evaluating the expression of the serine-threonine protein kinase mTOR and taking into account the size of the tumor (T). These data are used to calculate the risk of skin melanoma progression (P). If *p* is less than 0.8, then a high risk of disease progression is predicted, and if *p* is greater than or equal to 0.8, then a low risk of progression is predicted. The method is based on the analysis of laboratory and clinical research results, as well as on the calculation of a logistic regression model. The following

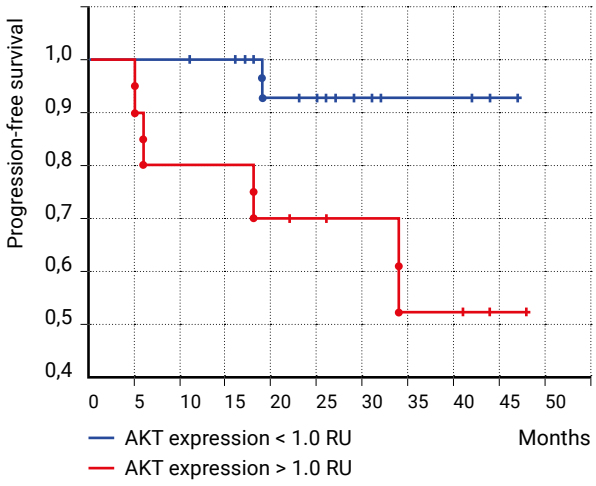

Fig. 1. Progression-free survival in patients with skin melanomas depending on AKT expression

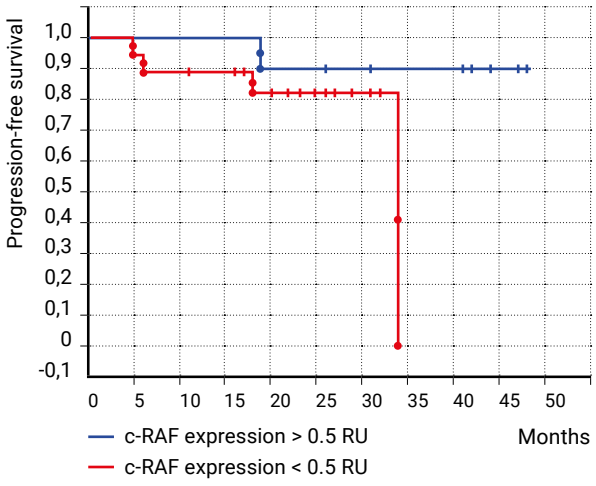

Fig. 2. Progression-free survival in patients with skin melanomas depending on c-RAF expression

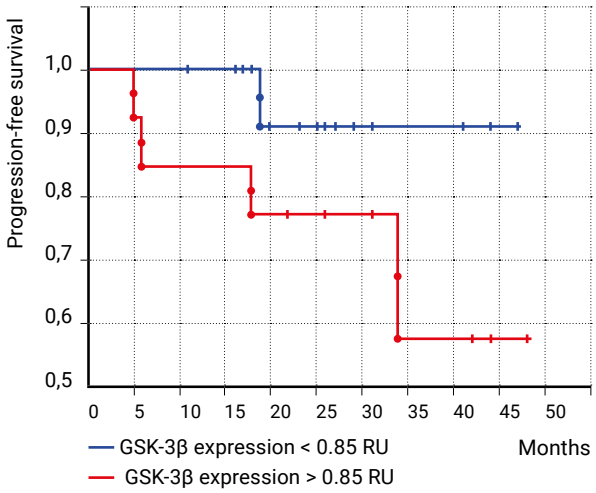

Fig. 3. Progression-free survival in patients with skin melanomas depending on the expression of GSK-3β

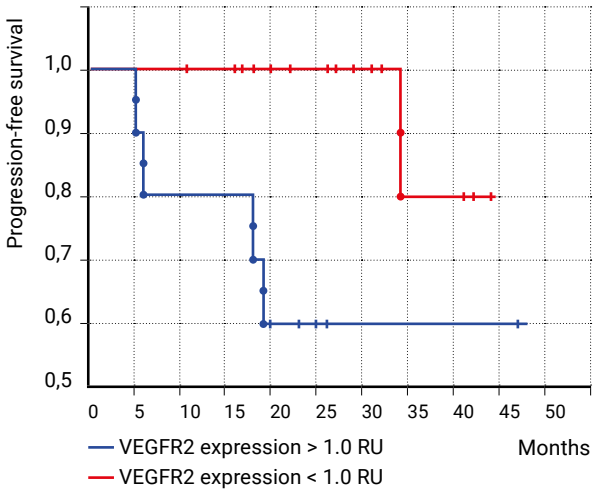

Fig. 4. Progression-free survival in patients with skin melanomas depending on VEGFR2 expression

parameters were included in the model: T and mTOR expression. A polynomial logistic regression was used to build the model. The analysis was performed using Statistica 12.0 software. Based on the optimal set of parameters with a significance level of $p < 0.05$, the regression function (F) was determined to calculate the risk of skin melanoma progression in patients.

In patients, the following informative indicators with a significance level of $p < 0.05$ were included in the regression function: T, expression of serine threonine protein kinase mTOR. At the next stage, the value of the F is determined by the formula:

$F(x_1, x_2) = 4.551 + b_1x_1 + b_2x_2$,

where the coefficients of the regression function are: $b_1 = -1.693$, $b_2 = 0.508$; x_1 – T; x_2 – expression of serine threonine protein kinase mTOR.

Subsequently, using the value of the regression function and the base of the natural logarithm (e), a mathematical model was developed in the form of a formula for determining the risk of progression in patients.

General view of the mathematical model:

$$P = \frac{1}{1 + e^{-s}}$$

where P is the probability of melanoma progression, *e* (base of the natural logarithm) = 2.718, S is the regression function.

The effectiveness of the mathematical model was determined using ROC analysis (Receiver Operating Characteristic). The sensitivity of the model in patients with skin melanomas was 86.7 %, and the specificity was 90 %. To assess the quality of the constructed mathematical model, the characteristic of the area under the ROC curve, AUC (Area Under Curve), was used, the results are presented in Table 2.

For the variable or variables of the test result: Predicted probability there is at least one relationship between the positive current state group and the negative current state group. Statistics may be distorted.

The AUC parameter value for this model was 0.933, which makes it possible to characterize it as excellent according to the generally accepted criteria presented in Table 3.

The requirement of maximum overall sensitivity and specificity of the model was chosen as the optimal criterion for dividing the results into two categories.

optimal cut-off value = max|Se + Sp|,

Where Se is the sensitivity of the model, and Sp is the specificity of the model.

The threshold value was determined based on the results of calculations of the coordinates of the ROC curve (Table 4).

Table 2. Area under the curve

Validation result variables: Predicted probability				
Area	Standard error *	Asymptotic val.**	Asymptotic 95 % confidence interval	
			Lower border	Upper border
0.933	0.040	0.000	0.855	1.000

Note: * – according to a nonparametric assumption; ** – null hypothesis: = actual area = 0.5

Table 3. Characteristics of the logistic model

AUC parameter value	Quality of the model
0.9 – 1.0	great
0.8 – 0.89	very good
0.7 – 0.79	good
0.6 – 0.69	average
0.5 – 0.59	unsatisfactory

The maximum total value of sensitivity and specificity was 1.867, which corresponds to the cut-off threshold of 0.803. The results of constructing the ROC curve for this model are shown in Figure 5.

DISCUSSION

The study revealed a link between the components of the AKT/mTOR signaling pathway and the recurrence of skin melanoma, as well as the progression of the disease. It was found that the expression level of proteins such as AKT, c-RAF, GSK-3β and VEGFR2 in tumor tissue correlates with the intensity of oncogenesis processes and reflects key features of the biological behavior of the tumor. These results were confirmed in previous studies, which also indicated the involvement of these molecular markers in the processes of oncogenesis [11–14]. The presented data indicate activation of the processes of proliferation of transformed cells, invasive growth and neoangiogenesis.

Obviously, the lack of significant indicators related to the biological features of the skin tumor does not allow to increase the effectiveness of treatment of such patients. In this regard, the attention of researchers is focused on finding optimal models for predicting the risk of an adverse outcome of the disease. The study presents a logistic regression

Table 4. Coordinates of the curve

True if it is greater than or equal[a]	Sensitivity (Se)	1 – Specificity	Specificity (Sp)	Se + Sp
0.0000000	1.000	1.000	0.000	1.000
0.1420958	1.000	0.800	0.200	1.200
0.1553039	0.933	0.800	0.200	1.133
0.1675397	0.933	0.600	0.400	1.333
0.3685236	0.933	0.400	0.600	1.533
0.5837076	0.933	0.200	0.800	1.733
0.6749142	0.867	0.200	0.800	1.667
0.8027119	0.867	0.000	1.000	1.867
0.8809557	0.800	0.000	1.000	1.800
0.9220825	0.733	0.000	1.000	1.733
0.9456728	0.667	0.000	1.000	1.667
0.9460033	0.600	0.000	1.000	1.600
0.955173	0.533	0.000	1.000	1.533
0.9653566	0.467	0.000	1.000	1.467
0.9691635	0.400	0.000	1.000	1.400
0.977768	0.333	0.000	1.000	1.333
0.9877487	0.267	0.000	1.000	1.267
0.994264	0.200	0.000	1.000	1.200
0.9975519	0.133	0.000	1.000	1.133
0.9984705	0.067	0.000	1.000	1.067
1.0000000	0.000	0.000	1.000	1.000

Note: The lowest threshold value corresponds to the minimum observed test value minus 1, and the highest threshold value corresponds to the maximum observed test value plus 1. All other threshold values are the averages of two consecutive ordered observed test values.

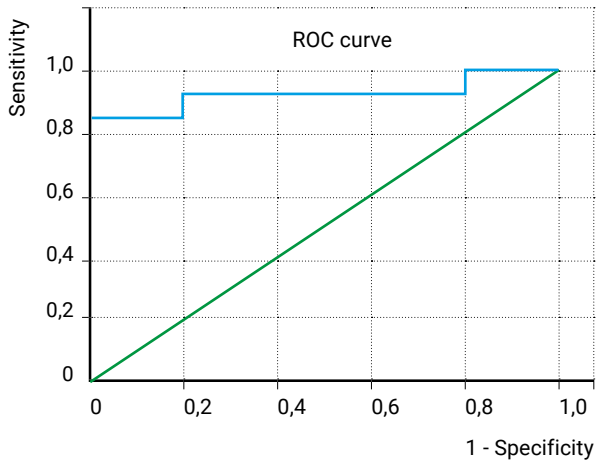

Fig. 5. ROC curve for the model determining the probability of progression of skin melanomas

model that can accurately predict the risk of disease recurrence, taking into account the expression of protein kinase mTOR and T. The value of this marker has been substantiated in many studies and mediates the effectiveness of treatment [15]. It is worth noting that the $BRAF^{V600E}$ mutation was not found in these patients, which indicates the presence of other molecular features in the mechanisms of tumor growth. At the same time, mTOR expression is essential, which is probably due to its involvement in the mechanisms of formation of resistance to treatment and, in particular, in the progression of the disease [16, 17].

CONCLUSION

As a result of the study, molecular markers were identified that can predict the unfavorable course of the disease associated with tumor recurrence. A logistic model was proposed that takes into account the expression of the key kinase mTOR and T, which allows predicting the risk of disease recurrence. The data obtained indicate the prospects of this model as a tool for predicting the progression of the disease.

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Spirina L. V. – scientific management, research concept, methodology development;
Chizhevskaya S. Yu. – participation in development of curricula and their implementation;
Kovaleva I. V. – participation in development of curricula and their implementation;
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Merkulov E. D. – statistical data processing.

South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 16-25
https://doi.org/10.37748/2686-9039-2025-6-3-2
https://elibrary.ru/aenylo
ORIGINAL ARTICLE

Clinical use of xenon-oxygen therapy to restore neuropsychological and adaptive status in young women with hormone-dependent breast cancer after total ovarian suppression

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ABSTRACT

Purpose of the study. The objective of this study is to evaluate the clinical effectiveness of activation xenon-oxygen therapy (XOT) in correcting neuropsychological and adaptive status in patients diagnosed with hormone-dependent breast cancer who have undergone total ovariectomy.

Patients and methods. We analyzed data on the intensity of clinical symptoms, the dynamics and intensity of adaptive responses (AR) with calculation of the anti-stress/stress ratio, as well as the bioelectric brain activity of 36 young patients diagnosed with hormone-dependent breast cancer, presenting with clinical signs of post-mastectomy syndrome (PMES) and early signs of post-ovariectomy syndrome (POES).

Results. In determining the distribution of stress and anti-stress reactions, a postoperative phase transition from a physiological to a pathological state was reliably established. In the postoperative period following ovariectomy, normal reaction types were observed in 11.3 % of cases. The predominant response was the stress reaction. Analysis of AR structure in patients with PMES and POES manifestations demonstrated a clear advantage for XOT. During rehabilitation, patients in the non-XOT group did not achieve full restoration of AR structure to baseline values, with the stress response persisting in 58.7 % of cases. In contrast, the XOT group demonstrated anti-stress reactions, with no stress reactions detected. Furthermore, analysis of the bioelectric activity of the brain in patients after two hormone-reducing surgeries revealed significant alterations in the spectral power of the electroencephalogram (EEG). These changes were indicative of a balanced state of excitation and inhibition, suggesting an equilibrium in neural processes underlying cognitive function.

Conclusion. Xenon, as a biologically active factor, functions as a catalyst for complex functional transformations within the body's regulatory systems. Xenon-based therapy induces a substantial reduction in stress reactions, highlighting the pronounced biotropic effect of xenon in restoring the adaptive status of the female body.

Keywords: xenon-oxygen therapy, hormone-dependent breast cancer, post-mastectomy syndrome, postovariectomy syndrome

For citation: Popova H. N., Shikhlyarova A. I., Rozenko D. A., Vashchenko L. N., Ardzha A. Yu., Marykov E. A. Clinical use of xenon-oxygen therapy to restore neuropsychological and adaptive status in young women with hormone-dependent breast cancer after total ovarian suppression. South Russian Journal of Cancer. 2025; 6(3): 16-25. https://doi.org/10.37748/2686-9039-2025-6-3-2, https://elibrary.ru/aenylo

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set forth in the World Medical Association Declaration of Helsinki, 1964, ed. 2013. Approval was obtained from the Ethics Committee of the National Medical Research Centre for Oncology (Protocol No. 5, September 14, 2019). Informed consent was obtained from all participants of the study

Funding: the work was supported by National Medical Research Centre for Oncology

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 23.01.2025; approved after reviewing 03.07.2025; accepted for publication 12.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 16-25
https://doi.org/10.37748/2686-9039-2025-6-3-2
https://elibrary.ru/aenylo
3.1.6. Онкология, лучевая терапия.
ОРИГИНАЛЬНАЯ СТАТЬЯ

Клиническое применение ксенон-кислородной терапии в коррекции нарушений нейропсихологического и адаптационного статуса молодых пациенток с диагнозом гормонозависимый рак молочной железы в условиях тотальной овариальной супрессии

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РЕЗЮМЕ

Цель исследования. Оценить клиническую эффективность применения активационной ксенон-кислородной терапии (ККТ) в коррекции нейропсихологического и адаптационного статуса у пациенток с диагнозом гормонозависимый рак молочной железы (РМЖ) в условиях овариоэктомии.

Пациенты и методы. Проанализировали данные интенсивности клинических симптомов, динамику адаптационных реакций (АР) с расчетом коэффициента соотношения антистресс/стресс, а также биоэлектрическую активность мозга 36 пациенток молодого возраста с диагнозом гормонозависимый РМЖ с клиническими признаками постмастэктомического (ПМЭС) и ранними признаками постовариоэктомического синдрома (ПОЭС).

Результаты. При определении структуры частоты встречаемости стресса и антистрессорных реакций достоверно установлено, что после овариоэктомии, нормотипы наблюдались в 11,3 % случаях. Основная выборка представлена реакцией стресс. Анализ структуры АР у пациенток с проявлениями ПМЭС и ПОЭС продемонстрировал явное преимущество применения ККТ. На этапе реабилитации у пациенток в группе без ККТ не выявлено полного восстановления структуры АР до исходных цифр. Реакция стресс составляла 58,7 % случаев. В группе с ККТ в эти же сроки преобладали антистрессорные реакции. Реакция стресс не зафиксирована вовсе. При анализе биоэлектрической активности мозга у больных РМЖ после двух гормонредуцирующих операций отмечали значительные изменения спектральной мощности электроэнцефалографии (ЭЭГ) с формированием сбалансированного состояния процессов возбуждения и торможения мозга.

Заключение. Несомненно, ксенон в качестве биологически активного фактора служит триггером запуска каскада сложных функциональных преобразований на уровне регуляторных систем организма. Сформированный после терапии пул антистрессорных реакций ярко демонстрировал высокую значимость биотропного действия ксенона в нормализации адаптационного статуса организма женщин.

Ключевые слова: ксенон-кислородная терапия, гормонозависимый рак молочной железы, постмастэктомический синдром, постовариоэктомический синдром

Для цитирования: Попова Н. Н., Шихлярова А. И., Розенко Д. А., Ващенко Л. Н., Арджа А. Ю., Марыков Е. А. Клиническое применение ксенон-кислородной терапии в коррекции нарушений нейропсихологического и адаптационного статуса молодых пациенток с диагнозом гормонозависимый рак молочной железы в условиях тотальной овариальной супрессии. Южно-Российский онкологический журнал. 2025; 6(3): 16-25. https://doi.org/10.37748/2686-9039-2025-6-3-2, https://elibrary.ru/aenylo

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование проведено с разрешения Комитета по Этике ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (протокол № 5 от 14.09.2019). Информированное согласие получено от всех участников исследования

Финансирование: работа проведена при поддержке ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 23.01.2025; одобрена после рецензирования 03.07.2025; принята к публикации 12.08.2025

BACKGROUND

In Russia, as worldwide, breast cancer (BC) ranks first in incidence and mortality among malignant tumors in women. It is evident that providing comprehensive specialized care plays a crucial role in increasing survival and improving the quality of life of cancer patients. According to standard treatment protocols, antitumor therapy for BC includes surgery, chemotherapy, and hormone therapy, the latter being determined by the tumor's surrogate phenotype and the expression of estrogen and progesterone receptors. In premenopausal patients, hormone therapy is aimed at complete or partial suppression of ovarian function. Methods include the use of tamoxifen, aromatase inhibitors, surgical castration, radiation ablation, and luteinizing hormone–releasing hormone agonists [1].

In clinical situations where hormone-dependent BC is combined with genital pathology, bilateral ovariectomy remains the method of choice. However, despite full-scale antitumor treatment, these patients often experience significant psychological and functional disturbances. Several factors contribute to this: it is known that women with BC and/or pelvic tumors often exhibit a so-called "feminine factor," characterized by negative reactions in the intimate sphere and family relationships [2]. Furthermore, after undergoing a mutilating and often aesthetically unsatisfactory mastectomy, patients must face castration surgery. Ovariectomy causes abrupt hormonal deprivation, provoking severe cardiovascular and neurovegetative disorders. According to V. A. Kulavsky (2016), post-ovariectomy syndrome (POES) develops in 75–90 % of patients, manifesting as maladaptive functional disorders and intense psychoemotional stress, with marked suppression of the body's protective reactions to internal and external stressors [3]. Consequently, many women develop a negative psychological pattern with impaired communication, inadequate responses to therapy, and heightened pain perception.

The main hormone replacement therapy (HRT) capable of correcting hormonal deficiency involves agents with estrogenic, androgenic, and progestogenic activity. However, in patients with estrogen-dependent malignant breast tumors, HRT is essentially contraindicated [4]. This creates a dilemma: how to provide safe rehabilitation therapy for women with hormone-dependent BC under conditions of total ovarian suppression.

Given current possibilities in oncological care, it is important to introduce concomitant therapies with predominantly protective mechanisms of action, aimed at correcting stress reactions, normalizing neuroendocrine and cardiovascular function, and providing psychosocial rehabilitation [2]. Russian research continues to prioritize the theoretical foundation and practical implementation of activation therapy technologies based on the patterns of nonspecific antistress adaptive reactions.

In this context, the inert gas xenon should be considered a promising component of rehabilitation therapy. Due to its diverse biological properties and unique clinical effects, xenon is increasingly used in medicine as both a preventive and therapeutic agent. Depending on the composition of the gas mixture, xenon-oxygen therapy (XOT) can normalize the psychoemotional state, attenuate the emotional component of pain, and exert anti-inflammatory, immunostimulatory, antihypoxic, and nootropic effects [5]. In oncology, xenon-based concomitant therapy has demonstrated its effectiveness in improving functional status at various stages of antitumor treatment, as well as in advanced disease with severe pain syndrome [6, 7].

However, the dynamics of neuropsychological and adaptive changes in reproductive-age patients with hormone-dependent BC under conditions of total ovarian suppression and the potential to mitigate negative symptoms through XOT require further investigation.

Purpose of the study was to evaluate the clinical effectiveness of activated XOT in correcting neuropsychological and adaptive status in patients with hormone-dependent BC following total ovarian suppression and surgical menopause.

PATIENTS AND METHODS

This study was carried out in compliance with the ethics protocol of the National Medical Research Center for Oncology (Protocol No. 5, dated September 14, 2019). All participants were informed about the procedure, potential benefits, and contraindications of XOT, after which they provided written

informed consent for rehabilitation therapy and personal data processing in accordance with generally accepted ethical standards.

Neuropsychological and adaptive status was assessed in 36 patients aged 36–45 years with a primary diagnosis of hormone-dependent breast cancer (BC) and concomitant genital pathology, all undergoing surgical treatment at the National Medical Research Center of Oncology. All participants had clinical signs of post-mastectomy syndrome (PMES) and early signs of post-ovariectomy syndrome (POES). Given the combination of hormone-dependent BC and genital pathology, as well as the desire for early termination of fertility, all patients underwent bilateral ovariectomy.

The XOT group included 19 patients with hormone-dependent breast cancer (BC), post-mastectomy syndrome (PMES), and post-ovariectomy syndrome (POES) who received XOT as part of early postoperative rehabilitation. The median age in this group was 37 years, with a mean age of 39.7 ± 1.3 years. The comparison group consisted of 17 patients with similar diagnoses who received standard postoperative care without XOT. The median age in this group was 36 years, with a mean age of 37.1 ± 1.7 years.

Exclusion criteria were respiratory center disorders, mental illness, decompensated comorbidities, and ongoing chemotherapy. According to the TNM-8 classification (2015), tumor stage distribution was as follows: XOT group: pT1N1M0–3 patients (15.7 %), pT2N1M0–11 (57.9 %), pT3N0M0–5 (26.4 %). Comparison group: pT1N1M0–2 patients (11.8 %), pT2N1M0–10 (58.7 %), pT3N0M0–5 (29.5 %).

The groups were comparable in age and clinical parameters; differences were not statistically significant ($p < 0.2$). The XOT procedure consisted of five sequential inhalation sessions starting on postoperative day 3 after ovariectomy, using a mixture of oxygen and Xemed® (xenon medical device No. LS-000121). The initial inert gas concentration was determined based on the patient's minimum clinical perception threshold. Each subsequent session was characterized by a gradual decrease in exposure time from 25 minutes (first session) to 10 minutes (final session). At the same time, in accordance with an exponential dependence and a coefficient of 0.8, the calculated xenon concentration was increased from 15 % to 25 %. All XOT procedures were performed by anesthesiologists under active monitoring of cardiovascular and respiratory parameters.

To assess the neuropsychological and adaptive status of patients before ovariectomy, and on the 3rd and 9th postoperative days, the following parameters were determined:

1. Menopausal Index (MPI) (Kupperman N), which accounts for various neurovegetative manifestations on a point scale. A mild form (12–34 points) was characterized by a satisfactory condition; a moderate form (35–58 points) by decreased work capacity and deterioration in general condition; and a severe form (> 58 points) by pronounced neurovegetative and emotional symptoms [8].
2. Dynamics of clinical symptom intensity were assessed using the standardized Edmonton Symptom Assessment System (ESAS), recommended for evaluating the functional state of cancer patients. The following symptoms were scored from 1 to 10: impaired general condition, sleep disturbance, appetite loss, nausea, weakness, depression, anxiety, dyspnea, and pain [9].
3. Type of general nonspecific adaptive reactions (AR) was determined by evaluating the Schilling leukogram with lymphocyte (Lph) percentage as the key indicator: stress – < 20 %, training reaction – 21–27 %, calm activation – 28–33 %, increased activation – 33–40 %, and reactivation – > 40 %. The counts of monocytes, eosinophils, neutrophils, and total leukocytes were used to assess AR tension and to calculate the antistress/stress ratio [10].
4. Functional state of the central nervous system (CNS) was assessed in patients with hormone-dependent BC before and after total ovarian suppression using electroencephalography (EEG) with an Encephalan EEGR 19/26 multichannel device in 19 standard monopolar leads. The spectral power of the EEG was calculated using Fourier transform in the frequency range 0.5–18.0 Hz during calm wakefulness with eyes closed. Spectral power data were logarithmized and analyzed using repeated-measures ANOVA (rANOVA).

Statistical analysis

Statistical data processing was performed using SPSS Statistics version 10.0 for Windows. Differences were considered statistically significant at $p < 0.05$.

STUDY RESULTS

When analyzing subjective data using the MPI questionnaire, it was found that on the 3rd day after ovariectomy, depressive symptoms prevailed in all 36 patients. Anxiety was observed in 35 patients (95.4 %), apathy in 32 (86.5 %), and sleep disorders in 32 (86.5 %) cases. Vegetative symptoms were pronounced, including a transient increase in blood pressure in 22 patients (61.6 %), sweating and hot flashes in 24 (67.2 %), and headache or dizziness in 28 (78.4 %) patients.

At the same time, mild POES occurred with the lowest frequency (7.4 %), while severe POES predominated, accounting for 72.8 % of cases. After XOT, there was a statistically significant decrease in moderate and severe MPI scores (by 4.8 and 2.4 times, respectively), with noticeable reductions in numerical values ($p < 0.05$) (Table 1).

It was determined that the change in the MPI coefficient showed a clear dependence on the use of XOT, as observed in comparison with the group that underwent standard treatment.

According to the results of the standardized Edmonton Symptom Assessment System (ESAS) questionnaire for cancer patients, women diagnosed with hormone-dependent breast cancer (BC) who had undergone ovariectomy demonstrated various clinical manifestations depending on the treatment method, including XOT (Table 2).

According to the results, there was a 3.2-fold decrease in symptoms of poor health, a 5.8-fold decrease in weakness, and a 2.8-fold decrease in the frequency of anxiety, depression, and sleep disorders ($p < 0.05$) compared with the group without XOT.

Analysis of the AR structure in patients with hormone-dependent breast cancer (BC) and clinical manifestations of PMES and POES demonstrated a clear advantage of using XOT. When determining the initial (pre-ovariectomy) adaptive status in patients with BC, it was found that reactions of increased activation and calm activation accounted for 33.4 % and 22.4 %, respectively. The training reaction was detected in 33.4 % of patients, and the acute stress reaction was detected in 11.2 % of patients. The group-wide integral antistress/stress coefficient was 8 units. Thus, the preoperative condition of patients who had already undergone radical breast surgery had a relatively balanced functional character. With further determination of the frequency structure of stress and antistress reactions, a postoperative phase transition from a physiological state to a pathological one was reliably established. Immediately after surgery, such normotypes as calm and increased activation were absent, and the training reaction was observed in only 11.3 % of cases. The main pattern was a stress reaction cluster – 88.7 % of cases – with a correspondingly low antistress/stress coefficient of 0.12 reference units. On the 9th postoperative day, patients in the group with-

Table 1. Indicators of POES severity in the postoperative period in patients with hormone-dependent breast cancer, depending on the therapy used

POES severity	3rd day after ovariectomy, *n* = 36		XOT group 9th day after ovariectomy, *n* = 19		No XOT group 9th day after ovariectomy, *n* = 17	
	%	score	%	score	%	score
Mild	7.4	22.5 ± 3.4	74.5	19.2 ± 2.6	11.9	24.3 ± 2.8 *p* = 0.8
Moderate	19.8	41.1 ± 3.1	12.9	37.1 ± 1.2	58.6	48.7 ± 1.3* *p* = 0.02
Severe	72.8	61.2 ± 4.1	12.6	54.0 ± 1.1	29.5	68.1 ± 2.2* *p* = 0.001

Note: * – statistically significant difference between indicators in the study groups ($p < 0.05$); XOT – xenon-oxygen therapy

out XOT did not show complete restoration of the AR structure to baseline values. The stress reaction accounted for 58.7 % of cases, while 40 % of cases demonstrated antistress reactions (increased activation and training). The antistress/stress coefficient remained very low – 0.68 units – which is 12.2 times lower than the initial level.

In the group receiving rehabilitation treatment in the XOT regimen, antistress reactions of calm activation predominated (52.7 % of cases), followed by the training reaction (26.3 %) and increased activation (21.1 %). The stress reaction was not recorded at all (Fig. 1). The antistress/stress coefficient was high, reaching 10 units, its maximum value, and exceeding the indicators in the group without XOT by 15.2 times.

These changes in AR structure and the magnitude of the antistress/stress coefficient reflected both the dynamics of pathological process development within the integral stress response and the normalization of functional changes, with the formation of stable antistress reactions under the influence of XOT.

Evaluation of the transformation of EEG frequency parameters under the influence of negative factors during antitumor therapy and the active restorative effects of XOT showed a systemic response of the patient's body to the correction of two pathological syndromes. In previous studies, Rozenko LYa, et al. (2017) found that, in patients with removed cerebral metastases at the stage of radiation therapy, xenon exposure improved the functional state of the central nervous system (CNS) and reduced the pronounced adverse reactions of antitumor therapy [7].

According to the results of our study, in patients with breast cancer who underwent ovariectomy, a significant decrease in the power of theta and delta rhythms was noted on EEG, along with a moderate increase in beta rhythm power relative to pre-ova-

Table 2. Indicators of the standardized ESAS questionnaire in patients with hormone-dependent breast cancer under conditions of total ovarian suppression

Indicator	3rd day after ovariectomy, *n* = 36		XOT group 9th day after ovariectomy, *n* = 19		No XOT group 9th day after ovariectomy, *n* = 17	
	%	score	%	score	%	score
Poor wellness	78.4	5.8 ± 2.4	26.3	1.1 ± 0.1	86.0	5.6 ± 0.2* *p* = 0.02
Pain	67.2	5.2 ± 2.6	13.2	1.1 ± 0.3	34.2	4.8 ± 0.2* *p* = 0.8
Dyspnea	5.6	1.7 ± 0.1	5.2	1.4 ± 0.2	5.6	1.7 ± 0.1 *p* = 0.01
Nausea	25.2	2.2 ± 0.5	5.2	1.1 ± 0.2	11.8	2.6 ± 0.8 *p* = 0.8
Weakness	25.2	3.9 ± 1.1	13.2	1.2 ± 0.1	75.4	6.8 ± 0.2* *p* = 0.03
Weakness	78.4	5.9 ± 2.5	13.2	1.9 ± 0.2	34.2	2.2 ± 1.2* *p* = 0.01
Sleep disturbance	100	6.2 ± 2.9	36.8	3.7 ± 0.2	87.0	4.9 ± 2.8* *p* = 0.04
Appetite disturbance	25.2	2.7 ± 1.9	36.8	3.6 ± 1.2	34.8	3.8 ± 1.2 *p* = 0.8
Anxiety	95.2	5.9 ± 2.7	26.3	1.9 ± 0.1	58.8	6.5 ± 0.2* *p* = 0.01

Note: * – statistically significant difference between indicators in the XOT and no-XOT groups ($p < 0.05$); XOT – xenon-oxygen therapy

riectomy values (Table 3). Changes included an increase in the spectral power of the alpha rhythm in the high-frequency subband (10.3–11.3 Hz) and a decrease in the low-frequency and mid-frequency subbands of the alpha rhythm. These findings indicated poor stress tolerance and increased functional load in the early postoperative period.

The data from our study correlate with established findings (Rodriguez-Larios J, et al., 2019) and characterize the changes in our patients as reflecting an anxious state with pronounced psychoemotional stress, which was confirmed by subjective survey data [11].

At the end of treatment, rANOVA analysis showed statistically significant differences in the bioelectric activity of the brain in patients with PMES and POES ($F(25) = 5.7$, $p = 0.001$) under conditions of restorative XOT and without it. In the XOT group, EEG spectral power was significantly higher in the theta rhythm frequency range of 5.6–7.8 Hz (df = 94; $p < 0.001$), the delta rhythm frequency range of 2.5–2.9 Hz (df = 94; $p < 0.001$), and the alpha rhythm frequency range of 8.1–9.8 Hz (df = 94; $p < 0.001$), and lower in the alpha rhythm frequency range of 11.0–11.5 Hz (df = 94; $p < 0.001$).

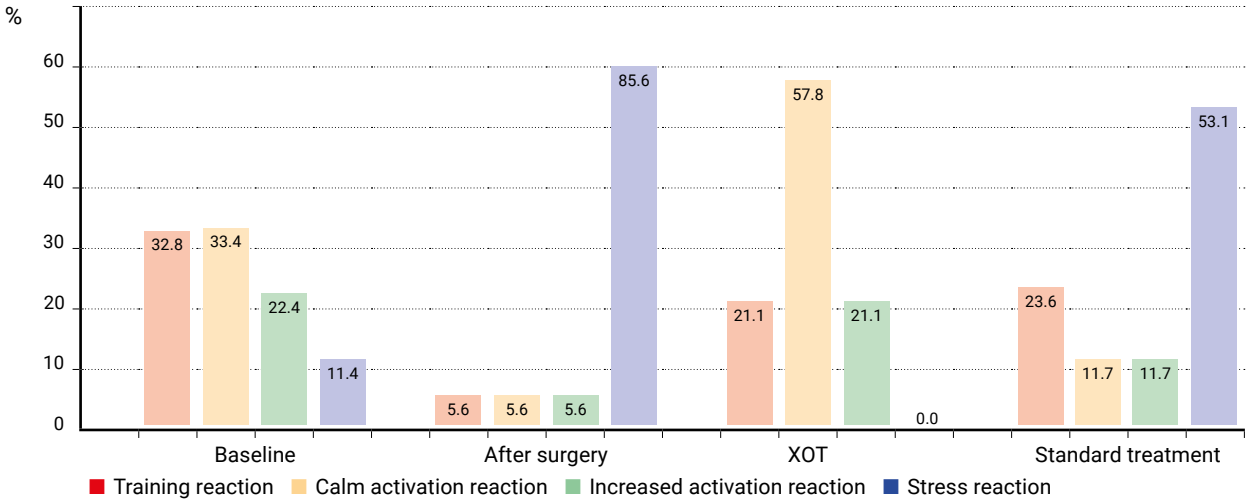

Fig. 1. Dynamics of the ratio of stress and antistress reactions in patients with hormone-dependent breast cancer under conditions of simultaneous PMES and POES

Table 3. Indicators of average EEG spectral power values in patients diagnosed with hormone-dependent breast cancer under conditions of total ovarian suppression

Indicators	XOT group, $n = 19$			Non-XOT group, $n = 17$		
	Baseline	3rd day after surgery	9th day after surgery	Baseline	3rd day after surgery	9th day after surgery
Alpha	348.5 ± 2.7	187.5 ± 17.2* $p = 0.02$	327.6 ± 34.1* $p = 0.02$	273.5 ± 17.4	180.4 ± 16.1* $p = 0.02$	156.1 ± 23.4 $p = 0.4$
Beta	27.8 ± 1.6	43.4 ± 2.1* $p = 0.03$	22.1 ± 1.8* $p = 0.05$	27.1 ± 2.7	46.3 ± 2.4* $p = 0.05$	21.3 ± 1.7* $p = 0.05$
Delta	56.3 ± 5.1	33.6 ± 4.7* $p = 0.03$	85.1 ± 8.5* $p = 0.02$	53.6 ± 5.7	36.7 ± 4.7* $p = 0.05$	41.5 ± 4.2 $p = 0.08$
Theta	45.7 ± 6.2	26.7 ± 4.1* $p = 0.05$	65.4 ± 4.1* $p = 0.03$	46.4 ± 3.1	28.2 ± 3.1* $p = 0.05$	33.8 ± 3.6 $p = 0.2$

In the group of patients without XOT, at the end of treatment, compared with EEG data after ovariectomy, a statistically significant decrease in spectral power was observed in the delta rhythm at 2.2 Hz, the theta rhythm at 6.9 and 7.8 Hz, and the alpha rhythm at 8.1–12.5 Hz.

The effect of XOT was most clearly demonstrated by a significant increase in the spectral power of the functionally important midrange alpha rhythm at 9.6 Hz and a decrease in the power of the beta rhythm at frequencies of 12.3 and 12.5 Hz. Slowing of beta rhythm activity was clinically manifested by marked psychoemotional relaxation in patients with PMES and POES.

DISCUSSION

This study analyzes the treatment results of a complex clinical group of reproductive-age patients diagnosed with hormone-dependent breast cancer (BC) under conditions of total ovarian suppression, with manifestations of post-mastectomy syndrome (PMES) and early signs of post-ovariectomy syndrome (POES).

It has previously been established that the negative psychological state in BC patients is often due to the anticipation of adverse aesthetic outcomes of surgery and the side effects of antitumor therapy. These are manifested by increased fatigue, memory impairment, irritability, marked emotional lability, and a prolonged course of psychological dysfunction requiring extended correction [12]. At the same time, in conditions of total ovarian suppression, artificially induced hypoestrogenism triggers complex metabolic changes in a woman's body long before the natural onset of menopause. This is accompanied by profound neurovegetative and psychoemotional changes mediated by the GABAergic, acetylcholine, dopamine, serotonin, norepinephrine, and opioid systems [3, 4].

It is known that the main mechanisms limiting or suppressing the development of acute stress reactions are directly activated in the higher regulatory centers of the central nervous system (CNS), forming systemic immune-hormonal relationships, regulating metabolic processes, and influencing proliferation and apoptosis [6].

Xenon, as a biologically active agent, has been shown to trigger complex functional changes in self-organization processes at both regulatory and executive levels. Its properties such as modulation of apoptosis, effects on various parts of the immune system, reduction of oxidative stress, and cytoprotective effects in ischemia of the heart, brain, liver, and kidneys are actively studied and applied in clinical practice. The exceptional qualities of xenon make it possible to fully utilize its therapeutic potential. Incorporating xenon into treatment regimens for adaptive disorders, including states of chronic psychoemotional stress, is based on its influence on both stress-realizing and stress-limiting systems of the body [5].

The above facts determined the concept of a safe and effective rehabilitation therapy for patients with PMES and POES presenting with depression and an imbalance in adaptive status. The results of our study demonstrated convincing clinical efficacy of XOT. Data from the cancer patient quality of life questionnaire and the menopausal index clearly showed regression of depressive and vegetative symptoms in the group receiving restorative XOT. XOT also contributed to the formation of new, stable antistress reactions. In the XOT group, 50 % of patients exhibited calm activation reactions a cluster characterized by moderate activation of immune and neuroendocrine systems, along with balanced regulation of energy, hormonal, plastic, and biochemical processes at all hierarchical levels. The antistress/stress coefficient in the XOT group reached its highest possible value, with no cases of stress reactions recorded.

Analysis of EEG bioelectric activity in BC patients after two hormone-reducing surgeries revealed significant changes in spectral power. XOT led to a slowing of rhythmic brain activity, with increased power in the slow-frequency theta, delta, and alpha rhythms, and decreased power in the fast-frequency alpha and beta rhythms. These changes reflected a balanced state between excitation and inhibition processes in the brain.

CONCLUSION

It follows from the above that xenon, as a biologically active factor, triggers a cascade of complex functional transformations at the level of the body's regulatory systems. The pool of antistress reactions formed after therapy clearly demonstrates the significant biotropic effect of xenon in normalizing the adaptive status of the female body.

Furthermore, the use of XOT for hormone-dependent subtypes of breast cancer in women of reproductive age under conditions of total ovarian suppression produced a pronounced clinical effect, expressed as positive dynamics in the psychoemotional state. Under these conditions, it becomes possible to mitigate the manifestations of surgical menopause, thereby improving the quality of life and promoting the social rehabilitation of young patients undergoing hormone-reducing surgery.

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Marykov E. A. – clinical support of the study.

South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 26-34
https://doi.org/10.37748/2686-9039-2025-6-3-3
https://elibrary.ru/gtrqsl
ORIGINAL ARTICLE

Features of the cell cycle in patients with colorectal cancer

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ABSTRACT

Purpose of the study. The objective of this study was to evaluate cell cycle indices in tumor cells and conditionally intact intestinal tissue (resection line) in male and female patients with colorectal cancer (CRC).
Patients and methods. Cell cycle phases were analyzed in 36 male and 36 female patients with CRC involving the rectum, and with right-sided or left-sided tumor localization. The mean age was 66 years. The degree of tumor differentiation in all cases corresponded to G2. None of the patients had received neoadjuvant treatment before surgery. In 10 % of tumor homogenates and resection line samples, cell cycle phases were determined using an ADAMII LS fluorescent cell analyzer (Korea). For cell cycle analysis, propidium iodide (PI), specially prepared for the ADAMII LS, was used. This reagent mixture contained PI and RNaseA, and cells were stained directly without an additional fixation step. The instrument's high sensitivity enabled precise discrimination of cells in the G0/G1 phase (resting cells [G0] and early G1), S phase, and G2/M phase. Statistical analysis was performed using Statistica 10.0 software.
Results. The proportions of viable and dead cells in the samples were generally comparable. In men, viable cells ranged from 56.6 % to 73.6 %, and dead cells from 26.4 % to 43.4 %. In women, viable cells ranged from 60.8 % to 77.3 %, and dead cells from 22.7 % to 39.2 %. In men, tumor samples from left-sided CRC contained predominantly S and G2 phase cells, whereas in right-sided CRC and rectal tumors, the majority of cells were in the G1 phase. In women with left-sided CRC, tumor samples showed the highest proportion of cells in the G1 phase, while samples from right-sided CRC and rectal tumors contained predominantly S phase cells.
Conclusion. The identified cell cycle characteristics and tumor cell death patterns in CRC patients, depending on sex and tumor localization, reflect the proliferative status of the tissue. These findings may provide a basis for personalized recommendations on the use of antitumor agents targeting cells in specific cell cycle phases.

Keywords: colorectal cancer, cell cycle, mitosis, G1 phase, S phase, tumor

For citation: Kit O. I., Frantsiyants E. M., Bandovkina V. A., Neskubina I. V., Ilchenko S. A., Petrova Yu. A., Snezhko A. V., Averkin M. A., Gabrichidze P. N. Features of the cell cycle in patients with colorectal cancer. South Russian Journal of Cancer. 2025; 6(3): 26-34. https://doi.org/10.37748/2686-9039-2025-6-3-3, https://elibrary.ru/gtrqsl

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Compliance with ethical standards: the work followed the ethical principles set forth in the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, ed. 2013). The study was approved by the Ethics Committee of the National Medical Research Center of Oncology (Protocol No. 1 dated 01/30/2023). Signed informed consent was received from all patients to take and transfer biological material for scientific research, government assignments for socially and socially useful purposes

Funding: this work was not funded

Conflict of interest: Kit O. I. has been the member of the editorial board of the South Russian Journal of Cancer since 2019; however, he has no relation to the decision regarding the publication of this article. The article underwent the standard peer-review process adopted by the journal. The authors declare no other conflicts of interest

The article was submitted 05.02.2025; approved after reviewing 10.04.2025; accepted for publication 12.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 26-34
https://doi.org/10.37748/2686-9039-2025-6-3-3
https://elibrary.ru/gtrqsl
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Особенности клеточного цикла у больных колоректальным раком

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РЕЗЮМЕ

Цель исследования. Оценка показателей клеточного цикла в клетках опухоли и условно интактной кишки (линии резекции) у больных колоректальным раком (КРР) обоих полов.
Пациенты и методы. Исследование фаз клеточного цикла проводили у 36 мужчин и 36 женщин больных КРР – прямой кишки, с правосторонней и левосторонней локализацией. Средний возраст пациентов составил 66 лет. Степень дифференцировки опухоли у всех больных соответствовала G2. Никто из больных до операции не получал неоадъювантного лечения. В 10 % гомогенатах опухоли и линии резекции определяли фазы клеточного цикла на флуоресцентном анализаторе клеток Adamii LS (Корея). Для определения клеточного цикла использовали пропидий йодид (PI), специально подготовленный для ADAMII LS, содержащий PI и RNase A, который используется путем прямого окрашивания клеток без прохождения дополнительного этапа фиксации. Точный анализ интенсивности реагента позволял прибору различать клетки в фазах G0/G1 (покоящиеся клетки (G0) и клетки в ранней фазе G1), S и G2/M. Статистический анализ результатов проводили с помощью пакета программ Statistica 10.0.
Результаты исследования. Количество живых и мертвых клеток в исследуемых образцах, в большинстве случаев, было однотипным: у мужчин живых клеток от 56,6 до 73,6 %; мертвых клеток от 26,4 до 43,4 %, у женщин живых клеток от 60,8 до 77,3 %; мертвых клеток от 22,7 до 39,2 %. У мужчин в образцах опухолей левостороннего КРР максимальных процент клеток находился в фазах S и G2, а в опухолях правосторонней локализации и прямой кишки в фазе G1. У женщин при левостороннем КРР максимальный процент клеток в образцах опухоли приходился на фазу G1, а образцы опухоли при правостороннем КРР и раке прямой кишки в S-фазе.
Заключение. Выявленные особенности клеточного цикла и гибели клеток опухолей у больных КРР, в зависимости от пола и локализации опухоли, описывают пролиферативный статус ткани и могут служить основой для персонализированных рекомендаций по применению противоопухолевых препаратов, действующих на клетки в определенной фазе.

Ключевые слова: колоректальный рак, клеточный цикл, митоз, фаза G1, фаза S, опухоль

Для цитирования: Кит О. И., Франциянц Е. М., Бандовкина В. А., Нескубина И. В., Ильченко С. А., Петрова Ю. А., Снежко А. В., Аверкин М. А., Габричидзе П. Н. Особенности клеточного цикла у больных колоректальным раком. Южно-Российский онкологический журнал. 2025; 6(3): 26-34. https://doi.org/10.37748/2686-9039-2025-6-3-3, https://elibrary.ru/gtrqsl

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено этическим комитетом ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (протокол № 1 от 30.01.2023 г.). Получено от всех пациентов подписанное информированное согласие на взятие и передачу биологического материала для проведения научных исследований, государственных заданий в общественно и социально-полезных целях

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: Кит О. И. является членом редакционной коллегии журнала «Южно-Российский онкологический журнал» с 2019 г., но не имеет никакого отношения к решению опубликовать эту статью. Статья прошла принятую в журнале процедуру рецензирования. Об иных конфликтах интересов авторы не заявляли

Статья поступила в редакцию 05.02.2025; одобрена после рецензирования 10.04.2025; принята к публикации 12.08.2025

BACKGROUND

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide and ranks second in cancer-related mortality [1]. The intestinal epithelium, consisting of a layer of epithelial cells grouped into the crypts of Lieberkühn, is a rapidly renewing tissue. The large intestine contains millions of crypts, each with more than 2,000 cells, which are replaced every 2–7 days. Renewal is carried out by colonic stem cells located at the base of the crypts [2]. There is a hypothesis that malignant cells of the large intestine originate from these stem cells. This hypothesis is supported by the fact that intestinal adenomas arise from stem cells [3].

The sequence of events occurring in a cell that leads to its division and duplication is known as the cell cycle [4]. The cell cycle consists of the G1 phase (presynthesis), S phase (DNA synthesis), G2 phase (late synthesis), and M phase (mitosis) [5]. During the G1 phase, the cell grows and prepares for DNA synthesis. In the S phase, DNA synthesis occurs, leading to the replication of genetic material [6]. In the G2 phase, the cell continues to grow and prepares for mitosis the stage of the cell cycle during which replicated DNA is distributed into two identical nuclei [7]. The cell cycle is strictly regulated by a complex network of proteins and signaling pathways. A failure in cell cycle control mechanisms can lead to various diseases, including cancer [8].

It is believed that any disruption of the stages of the cell cycle whether under the influence of genetic, carcinogenic, or infectious factors can result in uncontrolled cell proliferation and, ultimately, tumor formation [9]. Cancer is a disease characterized by uncontrolled cell growth and proliferation, which is the result of impaired regulation of normal cell cycle control mechanisms [10]. The development of cancer is often the result of mutations or changes in genes controlling the cell cycle, which disrupt the normal regulation of cell growth and division [11].

Dysregulation of the cell cycle is a common feature of cancer cells and plays a crucial role in their uncontrolled growth and proliferation. Understanding the mechanisms underlying cell cycle dysregulation in cancer cells is essential for the development of targeted therapies that can selectively suppress the growth of cancer cells while preserving normal cells [12].

Purpose of the study: to evaluate cell cycle indices in tumor cells and conditionally intact intestine (resection line) in patients with colorectal cancer of both sexes.

PATIENTS AND METHODS

The study included results obtained from 72 patients with colon cancer T2-3N0M0, comprising 36 women and 36 men, who underwent treatment at the Department of Abdominal Oncology, National Medical Research Centre for Oncology, during 2023–2024. The mean age of the patients was 66 (58–73) years. Groups were formed with 12 male and 12 female patients each diagnosed with left-sided CRC (sigmoid colon cancer), rectal cancer, and right-sided CRC (ascending colon cancer). The degree of tumor differentiation in all patients corresponded to G2. None of the patients received neoadjuvant therapy prior to surgery. A good performance status (ECOG 0 or 1) was observed in 98.5 % of the patients. All patients underwent surgical intervention.

During surgery, specimens of tumor tissue (1 cm from the visible tumor margin towards the center) and fragments of intestinal tissue at the resection line (proximal margin) were collected. On ice, 10 % homogenates were prepared in 0.1 M potassium phosphate buffer (pH 7.4), which were subsequently used for cell cycle analysis with the ADAMII LS fluorescent cell analyzer with image analysis capability (Korea). Cell viability was determined using a reagent designed for total cell count and viability assessment, consisting of a combination of acridine orange (AO), a cell-permeable DNA stain, and DAPI, a non-permeable DNA stain.

To determine the cell cycle, propidium iodide (PI), specially prepared for ADAMII LS and containing PI and RNaswA, was used for direct staining of cells without an additional fixation step. The instrument's precise reagent intensity analysis enabled the identification of cells in the G0/G1 phase (resting cells (G0) and cells in the early G1 phase), S phase, and G2/M phase.

Statistical analysis

Statistical analysis of the results was performed using the Statistica 10.0 software package. The Shapiro-Wilk test was used to assess the normality of distribution. The significance of statistical

differences between the studied parameters was determined using the Mann-Whitney U test. A value $p < 0.05$ was considered the threshold for statistical significance. Data in the tables are presented as the median and the 25th and 75th percentiles (Me (C25–C75)).

STUDY RESULTS

It was found that the number of living and dead cells in the studied samples was, in most cases, similar: in men, living cells ranged from 56.6 % to 73.6 %, and dead cells from 26.4 % to 43.4 %; in women, living cells ranged from 60.8 % to 77.3 %, and dead cells from 22.7 % to 39.2 %. The highest percentage of living cells was observed in the resection line of the rectum in men and in the resection line in left-sided CRC in women (73.6 % and 73.6 %, respectively). The highest percentage of dead cells was found in men in tumor samples of left-sided and right-sided CRC (41.1 % and 43.4 %, respectively) and in women in tumor samples of left-sided cancer and in the resection line of right-sided CRC (37.7 % and 39.2 %, respectively).

The study revealed differences in the percentage of cells in different phases of the cycle, depending on the sex of the patients and tumor location – rectum, left-sided, and right-sided colon tumors.

In men with rectal cancer, tumor samples were dominated by cells in the resting/synthetic phase (G0/G1), exceeding the levels in the S and G2/M phases by 1.8-fold and 1.9-fold, respectively (Table 1).

In the resection line of rectal cancer, the distribution across cell cycle phases was uniform; the percentage of cells in each phase showed no significant differences from each other. In rectal tumor samples, the proportion of cells in the G0/G1 phase was 1.4 times higher compared to intestinal tissue at the resection line, whereas the S and G2/M phases had on average, 1.5 times fewer cells.

In women with rectal cancer, tumor samples contained, on average, twice as many cells in the G0/G1 and S phases compared to the G2/M phase. In the resection line of the rectum, the percentage of cells in the G2/M phase was, on average, 3.4 times lower than in the G0/G1 and S phases. At the same time, in women, tumor samples had 1.4 times more cells in the mitotic phase, whereas in the resection line the percentage of cells in the resting phase (G0/G1) was significantly 1.4 times higher.

In men with left-sided CRC, the percentage of cells in the G0/G1 phase in the tumor was, on average, two times lower than in the S and G2/M phases. In the resection line for left-sided CRC in men, the lowest percentage of cells was found in the G2/M phase – 1.8 times lower than in G0/G1 and 3.5 times lower than in the S phase. In addition, in resection line samples of left-sided CRC, the percentage of cells in the S phase exceeded that in the G0/G1 phase by 1.9 times. In tumor samples of left-sided CRC in men, compared to the resection line, the percentage of cells in the G2/M phase was twice as high, but in the G0/G1 and S phases it was, on average, 1.5 times lower.

In women with left-sided CRC, the percentage of cells in the resting phase (G0/G1) in tumor samples was, on average, twice as high as in the mitotic phase and the S phase. In the resection line for left-sided CRC, cells predominated in the G0/G1 and S phases, with the percentage in the mitotic phase being, on average, 2.6 times lower. Tumor samples of left-sided CRC in women differed significantly only in having a twofold lower percentage of cells in the S phase compared to the resection line.

In men with right-sided CRC, tumor samples had a percentage of cells in the G2/M phase that was, on average, 1.6 times lower than in other phases. Similarly, in the resection line, the G2/M phase had 2.6 times fewer cells than the G0/G1 phase and 3 times fewer than the S phase. At the same time, there was a 1.4-fold higher percentage of G2/M-phase cells in tumor samples compared to the resection line, while other phases showed no significant differences between tumor and resection line.

In women with right-sided CRC, tumor samples showed no statistically significant differences in the percentage of cells in different phases. However, in the resection line, the lowest percentage of cells was in the resting phase, being 4.4 times lower than in the S phase and 2.2 times lower than in the mitotic phase. The maximum percentage of cells in the resection line for right-sided CRC was in the S phase, which was twice as high as in the G2/M phase. In tumor samples of right-sided CRC in women, the percentage of cells in the G0/G1 phase was 2.4 times higher than in the resection line, while in the S phase it was 1.4 times lower; only the mitotic phase showed no significant differences between tumor and resection line samples.

As a result, in men, tumor samples of right-sided CRC differed from left-sided tumors by having a 1.7-fold higher percentage of cells in the resting phase and a 1.6-fold lower percentage in the G2/M phase. The resection line in right-sided CRC in men also contained 1.4 times more cells in the G0/G1 phase.

In women, tumor samples of right-sided CRC, on the contrary, differed from left-sided tumors by having a 1.6-fold lower percentage of cells in the G0/G1 phase, but a 1.4-fold higher percentage in the G2/M phase and a 1.5-fold higher percentage in the S phase. Similarly, in resection line samples from women with right-sided CRC, the percentage of cells in the resting phase was four times lower, and the percentage in the G2/M phase was 1.5 times higher.

DISCUSSION

The location of malignant tumors of the colon and rectum can have a significant impact on clinical outcomes and response to drug therapy [13]. This is attributed to the fact that the colon and rectum are distinct anatomical tissues of the gastrointestinal tract [14]. Tumors located in the right colon (ascending colon and cecum) are more often diagnosed at later stages, exhibit high microsatellite instability, and tend to metastasize more frequently compared to tumors of the left colon (descending colon, sigmoid colon) [15]. This difference can be explained by their distinct embryological origins (midgut and hindgut, respectively), different genetic and epigen-

Table 1. Cell cycle in tumor and resection line in patients with colorectal cancer (% of living cells) (Me (Q25–Q75))

	Cell cycle phases		
	G0/G1	S	G2/M
Males			
Rectal cancer	32.56 (28.6; 35.9)[2,4]	18.63 (13.97; 20.14)[1,4]	16.8 (14.9; 18.8)[1,4]
Resection line, rectum	22.63 (19; 26.06)	27.06 (18.18; 28.71)	22.48 (19.45; 26.8)
Left-sided CRC tumor	12.43 (9.27; 12.75)[2,3,4]	27.84 (20.11; 31.56)[1]	21.37 (18.85; 23.54)[3,4]
Resection line, left-sided CRC	18.81 (15.05; 22.15)[2]	37.35 (35.38; 44.07)[1]	9.84 (7.79; 11.34)[1,2]
Right-sided CRC tumor	22.34 (16.44; 26.6)	21.64 (21.26; 22.9)	12.74 (11.12; 15.71)[1,2,4]
Resection line, right-sided CRC	25.57 (21.2; 29.7)	31.7 (22.07; 37.36)	8.45 (7.03; 12.58)[1,2]
Females			
Rectal cancer	25.44 (23.55; 27.42)[4]	27.56 (24.04; 29.5)	12.0 (10.24; 14)[1,2,4]
Resection line, rectum	36.12 (26.37; 38.35)	27.9 (25.33; 30.44)	7.94 (6.46; 9.53)[1,2]
Left-sided CRC tumor	31.2 (29.1; 34.2)[2,3]	15.07 (12.97; 20.2)[1,3,4]	14.6 (12.2; 16.9)[1,3]
Resection line, left-sided CRC	33.89 (23.36; 37.86)	33.99 (25.52; 40.55)	11.56 (9.9; 13.9)[1,2]
Right-sided CRC tumor	19.64 (18.9; 20.5)[4]	24.65 (20.58; 29.55)[4]	19.05 (18.1; 23.1)
Resection line, right-sided CRC	8.09 (7.35; 8.54)[2]	36.9 (27.27; 42.84)[1]	17.34 (16.5; 18.5)[1,2]

Note: Statistically significant differences compared with: [1] – G0/G1 phase; [2] – S phase; [3] – differences between the corresponding samples of right-sided CRC; [4] – differences compared with the corresponding resection line ($p < 0.05$)

etic profiles, as well as differences in microbiome composition and the immune environment of the mucosa [16].

It is known that the duration of the mitotic phase constitutes only a small fraction of the entire cell cycle, while the total time of the S, G2, and M phases is relatively constant. Therefore, the duration of the cell cycle depends mainly on the G0/G1 phase. The resting phase G0 is thought to predominate in most highly differentiated cells performing their specific functions [17]. In our study, colorectal cancer (CRC) patients' resection line samples did not demonstrate a predominance of cells in the resting phase, which may indicate impaired functional activity of colon cells in CRC patients.

We hypothesize that the predominance of a particular cell cycle phase in tumor samples of right-sided CRC, left-sided CRC, and rectal cancer may be associated with the aforementioned differences and may determine the biological aggressiveness of the neoplasm.

In men, the highest percentage of cells in the G0/G1 phase was observed in rectal cancer and right-sided CRC, and the lowest in left-sided tumors. In women, conversely, the highest percentage of cells in the G0/G1 phase was found in left-sided CRC and rectal cancer, and the lowest in right-sided tumors. It is known that the cell cycle is tightly regulated by a number of regulatory proteins and checkpoints [18]. The G1 checkpoint is a critical stage in the cell cycle, regulated by a complex network of proteins and signaling pathways, including CDKs and tumor suppressor proteins, ensuring that the cell possesses the necessary resources such as nutrients and growth factors to proceed through the cycle and that no DNA damage is present that could be passed on to daughter cells [19]. Blockade of the p53-dependent G1 checkpoint can persist for long periods until it is stimulated by external signals (growth factors) to re-enter the cell cycle [20]. One of the clear effects of prolonged G0/G1 arrest is cell enlargement, as total cellular protein and RNA content continues to increase. Oncogenic signals, in turn, cause excessive cell growth, which soon becomes toxic [21].

If oncogenes make tumor cells more vulnerable to G1 arrest, effective blockade of all G1 cells for certain periods of time may lead to cancer-specific overgrowth, DNA damage, and senescence [21]. Therefore, a high proportion of cells in the resting phase (G0/G1) in tumor samples may be a cause of low sensitivity to anticancer therapy.

Several researchers have demonstrated gender differences in markers of proliferation and neoangiogenesis in both tumor samples and resection line tissues in CRC patients, particularly in rectal cancer. Furthermore, identification of different molecular-biological subtypes of CRC may also influence the predominance of specific cell cycle phases in both tumor and resection line tissues [22].

In our study, the percentage of G0/G1-phase cells in resection line samples from men was approximately the same, regardless of tumor location, whereas in women, right-sided CRC resection lines stood out, with an extremely low proportion of resting-phase cells. In women with right-sided CRC, resection line samples were dominated by cells in the synthetic (S) phase, which may be one of the reasons for the unfavorable course of right-sided CRC. It is known that progression through the G1 checkpoint is determined by the balance of G1 activators and inhibitors, and this balance shifts toward activators as cells grow. This ability to "break through" G1 arrest is thought to underlie the cell-size checkpoint, ensuring that cells reach an optimal size before entering the S phase [21, 23–26]. Overall, in CRC patients, cells in the S phase were either predominant or comparable in percentage to those in G0/G1, with the only exceptions being male rectal tumor samples and female left-sided CRC tumor samples.

Progression through the S phase is believed to be modulated mainly by cellular levels of certain proteins. Excessive expression of cyclin A promotes cancer progression, while suppression of cyclin A blocks cell cycle progression and induces arrest in the S phase [27]. From a therapeutic perspective, cells in the S phase are generally more radioresistant than those in other phases [20]. However, pharmaceutical companies are developing drugs, such as DNA topoisomerase I inhibitors, targeting the DNA synthesis elongation stage to arrest tumor cells in the S phase and subsequently induce apoptosis [28]. Thus, determining the predominant cell cycle phase in a tumor may help guide an appropriate personalized anticancer therapy strategy.

In male patients with left-sided CRC, the proportion of cells in the G2/M phase was significantly higher than in rectal cancer and right-sided CRC.

In contrast, in women, the proportion of G2/M-phase cells in right-sided CRC was significantly higher than in left-sided CRC and rectal cancer. In the resection line, the situation was somewhat different: the percentage of cells in the G2/M phase was significantly higher in rectal cancer in men and in right-sided CRC in women compared to other locations.

A high proportion of cells in the G2/M phase may indicate high proliferative activity of tumors at this location in men. There is evidence that mutations in tumor suppressor genes, such as p53, may prevent cells from halting the cell cycle upon detecting DNA damage or other abnormalities, allowing damaged cells to continue dividing and accumulate further mutations [29]. In addition, various enzymes, including the protein kinases Chk1 and Chk2, are activated in the G2 phase [30].

It should be noted that all studies were conducted in patients of both sexes without metastases, and the obtained results demonstrate sex- and location-specific differences, highlighting the substantial heterogeneity of colorectal cancer. Further studies of the cell cycle in metastatic CRC patients are warranted.

CONCLUSION

Therefore, in CRC patients, cell cycle characteristics were found to vary depending on sex and tumor location. In male patients, tumor samples from left-sided CRC showed the highest percentage of cells in the S-G2 phases, whereas in right-sided CRC and rectal cancer the majority of cells were in the G1 phase. In female patients, left-sided CRC tumors had the highest proportion of cells in the G1 phase, while in right-sided CRC and rectal cancer the predominant proportion of cells was in the S phase. These findings may serve as a basis for personalized recommendations regarding the use of anticancer drugs targeting cells in specific phases of the cell cycle.

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South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 35-44
https://doi.org/10.37748/2686-9039-2025-6-3-4
https://elibrary.ru/ilqrhx
ORIGINAL ARTICLE

Preliminary Results of Two-Stage Radiosurgery for Brain Metastases

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ABSTRACT

Purpose of the study. To perform a preliminary assessment of local control after two-stage staged radiosurgery in patients with metastatic brain lesions.

Patients and methods. For staged radiosurgery, large lesions measuring ≥ 3 cm in the largest dimension were selected. The regimen consisted of delivering 12 Gy in a single fraction at the first stage and 14 Gy in a single fraction at the second stage, with a 14-day interval between the stages. If additional smaller lesions were present, they were irradiated simultaneously using the standard SRS technique in a single fraction with a dose per fraction (DPF) of 18–24 Gy. The prospective analysis included 32 patients of both sexes aged 34 to 76 years (mean age 57 ± 3.3 years) with brain metastatic lesions ≥ 3 cm in the largest dimension, or located in close proximity to critical brain structures, who underwent a two-stage course of staged radiosurgery at the National Medical Research Centre for Oncology.

Results. The evaluation of target lesion volumes was based on brain MRI performed before treatment, prior to the second stage, and one month after completion of treatment. At the one-month follow-up after the treatment course, local control was achieved in the vast majority of clinical cases. Sixteen lesions demonstrated a volume reduction of more than 70 % from baseline, eleven showed a reduction of more than 50 %, eight lesions exhibited a decrease of less than 50 %, and one lesion demonstrated a negative response.

Conclusion. Two-stage staged radiosurgery for brain metastases demonstrated satisfactory local control in patients with various primary tumor sites. The positive dynamics observed at this stage suggest the potential for favorable long-term outcomes.

Keywords: metastatic brain lesion, radiation therapy, stereotactic radiosurgery, staged radiosurgery

For citation: Lesnoy M. N., Sakun P. G., Voshedskiy V. I., Rozenko L. Ya., Vlasov S. G., Kazmenkova E. M., Babasinov A. A. Preliminary Results of Two-Stage Radiosurgery for Brain Metastases. South Russian Journal of Cancer. 2025; 6(3): 35-44. https://doi.org/10.37748/2686-9039-2025-6-3-4, https://elibrary.ru/ilqrhx

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set forth in the World Medical Association Declaration of Helsinki (1964, revised in 2013). The study protocol was approved by the Ethics Committee of the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation (extract from meeting protocol No. 31 dated 09/14/2023). Informed consent was obtained from all study participants

Funding: this work was not funded

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 11.02.2025; approved after reviewing 18.07.2025; accepted for publication 12.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 35-44
https://doi.org/10.37748/2686-9039-2025-6-3-4
https://elibrary.ru/ilqrhx
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Предварительные результаты радиотерапии метастазов головного мозга методикой двухэтапной стажированной радиохирургии

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РЕЗЮМЕ

Цель исследования. Предварительная оценка локального контроля после двухэтапной стажированной радиохирургии пациентов с метастатическими поражениями головного мозга.
Пациенты и методы. Для облучения методикой стажированной радиохирургии выбирались крупные очаги размером ≥ 3 см в наибольшем измерении. Методика представляла из себя подведение дозы 12 Гр за 1 фракцию на первом этапе и 14 Гр за 1 фракцию на втором этапе. Перерыв между этапами составлял 14 дней. При наличии других очагов меньшего размера, их облучение производилось одновременно по стандартной методике SRS за 1 фракцию с РОД 18–24 Гр. В проспективный анализ были включены 32 пациента обоих полов в возрасте от 34 до 76 лет, средний возраст 57 ± 3,3 года, с метастатическими очагами в головном мозге размером ≥ 3 см в наибольшем измерении, либо их близком расположении к критическим структурам головного мозга, получившие курс лечения двухэтапной стажированной радиохирургией на базе ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации.
Результаты. Оценка объема целевых очагов производилась на основании магнитно-резонансной томографии (МРТ) исследования головного мозга, проводимого пациенту до начала лечения, перед вторым этапом и через месяц после проведенного лечения. При оценке через месяц после пройденного курса лечения в подавляющем большинстве клинических ситуаций был достигнут локальный контроль. В 16 очагах было достигнуто уменьшение объема более чем на 70 % от изначального, в 11 – более чем на 50 %, 8 показали уменьшение менее чем на 50 % и в одном очаге мы зафиксировали отрицательный ответ.
Заключение. Двухэтапная стажированная радиохирургия метастазов головного мозга показала удовлетворительные результаты локального контроля пациентов с различными первичными локализациями злокачественных заболеваний. Положительная динамика, которую мы зафиксировали на данный момент, позволяет рассчитывать на благоприятные результаты в дальнейшей перспективе.

Ключевые слова: метастатическое поражение головного мозга, лучевая терапия, стереотаксическая радиохирургия, стажированная радиохирургия

Для цитирования: Лесной М. Н., Сакун П. Г., Вошедский В. И., Розенко Л. Я., Власов С. Г., Казьменкова Э. М., Бабасинов А. А. Предварительные результаты радиотерапии метастазов головного мозга методикой двухэтапной стажированной радиохирургии. Южно-Российский онкологический журнал. 2025; 6(3): 35-44. https://doi.org/10.37748/2686-9039-2025-6-3-4, https://elibrary.ru/ilqrhx

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по этике при ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 31 от 14.09.2023 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы проводилось в рамках диссертационного исследования

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 11.02.2025; одобрена после рецензирования 18.07.2025; принята к публикации 12.08.2025

BACKGROUND

Brain metastases are the most common intracranial neoplasms in adults. Secondary brain lesions most frequently occur in lung cancer (40 % of cases), breast cancer (20–30 %), and melanoma (5–15 %). Other malignant tumors metastasize to the brain less often. The problem is becoming increasingly relevant, as lung and breast cancers occupy leading positions in the structure of oncological morbidity [1].

Without specialized treatment, the median survival of patients with established brain metastases (BM) is 2–3 months, while adequate therapy can increase it to 8–12 months [2–3]. Therefore, the search for new approaches to the treatment of BM remains an important task in modern oncology and neurosurgery.

Due to the characteristics of the blood-brain barrier, systemic drug therapy is of limited effectiveness; thus, local treatment modalities play a leading role in the management of brain metastases. Surgical intervention is often impractical in cases with certain metastatic sites, multiple lesions, or tumors located in functionally critical areas of the brain [4].

With advances in technology, it has become possible to deliver high doses of ionizing radiation to the pathological focus while minimizing exposure to surrounding tissues. The technique of delivering the maximum permissible total focal dose (TFD) to the target in a single fraction is known as stereotactic radiosurgery (SRS). The term was first introduced by Lars Leksell in the mid-20th century, and for a long time, the method was limited to intracranial pathologies and considered an alternative to surgery for vascular malformations and brain tumors [5].

SRS demonstrates high efficacy however, delivering large doses in a single fraction can be associated with certain risks. Special challenges arise when irradiating large brain lesions (> 3 cm in maximum dimension), lesions with extensive peritumoral edema, or those located near critical structures. Therefore, modern clinical guidelines recommend the use of various hypofractionated stereotactic radiotherapy regimens. This approach involves delivering a comparable total focal dose over 3–5 fractions, which allows for a gentler impact on surrounding structures. However, it is known that increasing the number of fractions may reduce treatment efficacy, making this issue highly relevant in current radiation oncology [6].

To address this problem, stereotactic radiosurgery techniques are being refined. In particular, it has been proposed to deliver high single doses of radiation at specific intervals. Typically, the breaks between treatment stages range from 2 to 4 weeks, depending on the number of stages and the dose delivered at each. Literature reports describe the use of two- or three-stage approaches, with variations in the single focal dose (SFD) from 10 to 15 Gy and intervals between sessions from 14 to 30 days [7].

Given the novelty of this technique and the variable nature of brain metastases, the optimal algorithm for staged radiosurgery remains undefined; therefore, research in this field remains relevant and in demand in clinical practice.

Purpose of the study: to conduct a preliminary assessment of the primary treatment effect after two-stage staged radiosurgery in patients with metastatic brain lesions.

PATIENTS AND METHODS

An analysis was performed on the treatment outcomes of 56 patients with brain metastases selected for the study. Eligible lesions were either ≥ 3 cm in maximum diameter or smaller but located in close proximity to critical brain structures (optic chiasm, optic pathways, brainstem, etc.). Patients were divided into two groups. The main group was prospectively recruited and consisted of 32 patients who underwent two-stage staged radiosurgery of the target metastatic lesions. The control group included 24 patients whose treatment efficacy was retrospectively evaluated; in accordance with clinical guidelines, they had received radiotherapy using the standard stereotactic radiotherapy technique in a hypofractionated regimen with a total focal dose of 24 Gy in 3 fractions (8 Gy per fraction for 3 consecutive days) [10]. Treatment and follow-up were carried out from July 2023 to December 2024 at the Radiotherapy Department No. 2, National Medical Research Centre for Oncology.

The mean age of patients at treatment initiation was 57 ± 3.3 years (range 34–76 years, 95 % CI = 6.7). According to the localization of the primary tumor, the groups were divided into three subgroups. In the main group: brain metastases from breast cancer – 18 patients (56.25 %), from lung cancer – 8 patients (26.8 %), from melanoma – 6 patients (18.75 %). In the control group: brain metastases from breast cancer – 13 patients (54.17 %), from lung cancer – 7 patients (29.17 %), from melanoma – 4 patients (16.67 %). In the main group, 13 patients had solitary brain lesions, 6 patients had oligometastatic disease, and 10 patients had multiple brain metastases. Similarly, in the control group: 10 patients had solitary lesions, 8 patients had oligometastatic disease, and 9 patients had multiple brain metastases.

At the time of hospitalization, all patients showed no extracranial progression of the primary disease, had a Karnofsky Performance Status score above 70 %, and had no acute or decompensated chronic or infectious diseases, as confirmed diagnostically.

All patients included in the study underwent brain MRI prior to each treatment stage and one month after treatment completion. Before each radiotherapy stage, preliminary topometric preparation was carried out, including fabrication of an individual three-layer thermoplastic immobilization mask for stereotactic radiotherapy, placement of radiopaque markers, and determination of the isocenter using an LAP Laser navigation system. Topometric computed tomography (CT) was performed using a Siemens Somatom scanner, with an effective dose per examination of 3.7 mSv. Preliminary topometric data were processed on a Singo Via virtual simulation workstation.

Treatment plans were created and calculated using the Elements and Aria systems (Varian, USA). Three-dimensional reconstructions of the target lesions were generated, and their volumes were measured on each follow-up MRI. Patient-specific quality assurance of the treatment plan was performed using the SRS MapCheck array, SunNuclear (USA). The detector positioning and resolution of this array are designed specifically for verification of SRS/SBRT plans, ensuring high-dose measurement accuracy under conditions involving small fields and non-coplanar arcs.

Irradiation was delivered using a Novalis Tx linear accelerator (Varian, USA). Dose delivery was performed with conformal arcs. Patient positioning was verified using the ExacTrac stereotactic positioning system (BrainLab, Germany).

Staged Radiosurgery Technique

For staged radiosurgery, large lesions measuring ≥ 3 cm in their greatest dimension were selected for treatment. The gross tumor volume (GTV) and clinical target volume (CTV) were defined as the volume of the target lesion visualized on brain MRI as pathological tissue with contrast enhancement. During topometric preparation, a three-layer thermoplastic immobilization mask was used. The planning target volume (PTV) was created by adding a 1 mm margin to the GTV.

The treatment protocol consisted of delivering 12 Gy in a single fraction during the first stage and 14 Gy in a single fraction during the second stage, with a 14-day interval between stages. In the presence of other, smaller lesions, these were irradiated simultaneously according to the standard SRS protocol in a single fraction with a dose of 18–24 Gy [10].

The volume of target lesions was assessed based on brain MRI performed before treatment initiation, before the second stage, and one month after completion of treatment.

Statistical Analysis

Statistical analysis was performed using the Statistica 12.0 software package on a personal computer. Student's t-test was used, with differences considered statistically significant at a probability of error-free prediction of at least 95 % ($p < 0.05$). As part of the follow-up, the current volume of metastatic lesions and the patient's clinical status were evaluated.

STUDY RESULTS

Brain MRI follow-up was successfully performed for all patients in the study group. Monitoring data on changes in the local volume of lesions at all stages of follow-up are presented in Table 1.

The mean lesion volume at baseline was 10.8 ± 1.8 cm³ in the main group and 11.6 ± 2.0 cm³ in the control group. Lesion volumes were also as-

sessed according to the primary tumor site. In the main group, the mean volume of brain metastases was 14.2 ± 2.6 cm³ for lung cancer, 11.1 ± 2.5 cm³ for breast cancer, and 10.2 ± 2.6 cm³ for melanoma. In the control group, the corresponding mean volumes were 11.6 ± 2.0 cm³, 9.5 ± 2.7 cm³, and 8.1 ± 2.4 cm³, respectively. Thus, prior to treatment, the sizes of metastatic lesions in both groups were comparable.

In the main group, evaluation was performed 14 days after the first stage of treatment using follow-up brain MRI. The mean volumes of the lesions included in the study were 9.1 ± 2.0 cm³ for lung cancer metastases, 5.4 ± 1.9 cm³ for breast cancer metastases, and 9.1 ± 2.6 cm³ for melanoma metastases. Despite the fact that only a partial radiation dose had been delivered by this stage, a statistically significant reduction in metastatic lesion size was already observed compared with baseline. The mean lesion volume at the time of assessment before the second stage was 6.7 ± 1.4 cm³ (p = 0.05), corresponding to a 38 % reduction.

The third MRI assessment was performed one month after completion of treatment for both patient groups. The mean lesion volume in the main group was 4.3 ± 0.6 cm³ (p = 0.05), compared with 6.27 ± 1.4 cm³ in the control group. Relative to baseline, this represented a 60.1 % and 35.4 % reduction, respectively. Notably, the best response to radiotherapy was observed in metastatic lesions from disseminated breast cancer. In the main group, the mean baseline volume was 11.1 ± 2.5 cm³, and one month after completion of the two-stage treatment it had decreased significantly to 2.1 ± 0.6 cm³ (p < 0.05), representing a more than fivefold reduction (77.5 %). In the control group, the mean baseline volume was 9.5 ± 2.7 cm³, and one month after radiotherapy it decreased to 5.2 ± 0.7 cm³ (a 45.3 % reduction), which was not statistically significant.

An example of lesion volume reduction in a patient who underwent staged radiosurgery is presented in Figure 1.

In the subgroup of patients with metastatic lung cancer, one month after treatment we recorded a statistically significant decrease in lesion volume to 4 ± 1.1 cm³ (p < 0.05) in the main group (a 77 % reduction from baseline) and to 7.3 ± 0.9 cm³ in the control group (a 37.7 % reduc-

Table 1. Mean volume of metastatic lesions in patients at three stages of treatment, taking into account morphological type

Primary tumor site	Number of patients		Lesion volume before treatment (cm³)		Lesion volume before the second stage (cm³)	Lesion volume one month after treatment (cm³)	
	Main group	Control group	Main group	Control group	Main group	Main group	Control group
Lung cancer	8	7	14.2 ± 2.6	11.6 ± 2.0	9.1 ± 2.0	4 ± 1.1*	7.3 ± 0.9
Breast cancer	18	13	11.1 ± 2.5*	9.5 ± 2.7	5.4 ± 1.9*	2.1 ± 0.6*	5.2 ± 0.7
Melanoma	6	4	10.2 ± 2.6	8.1 ± 2.4	9.1 ± 2.6	7.0 ± 1.1	6.3 ± 1.2
Total	32	24	10.8 ± 1.8*	9.7 ± 2.1	6.7 ± 1.4*	4.3 ± 0.6*	6.27 ± 1.4

Note: * – Statistically significant reduction compared with baseline volume (p = 0.05). The "± n" value indicates the standard error of the mean (SEM)

tion from baseline). Hypofractionated irradiation in the control group did not result in a statistically significant difference.

The smallest reduction in mean lesion volume was observed in the subgroup of patients with melanoma metastases: from 10.2 ± 2.6 cm³ at baseline to 6.3 ± 1.2 cm³ on MRI one month after treatment.

In addition to the evident clinical changes in lesion volume, we were also able to assess the reduction of peritumoral edema observed in some patients. Pronounced peritumoral edema was noted in 12 cases in the main group and 9 cases in the control group. Edema volume was assessed separately from the volume of the target lesion. The mean peritumoral edema volume before treatment was 7.53 ± 1.2 cm³ in the main group and 5.6 ± 0.7 cm³ in the control group. At the assessment before the second treatment stage, the mean peritumoral edema volume in the main group was 5.3 ± 0.6 cm³, representing a 30 % reduction from baseline. One month after treatment, peritumoral edema was no longer detectable on imaging in 3 patients from the main group. In the remaining 9 patients, the mean edema volume was 3.47 ± 0.5 cm³ (p = 0.05). In the control group, peritumoral edema was not detectable in 1 patient at the one-month follow-up. In the remaining 8 patients, the mean edema volume was 3.55 ± 0.7 cm³, corresponding to a 33 % reduction. Given the relatively small patient sample, we cannot draw definitive conclusions regarding the statistically significant impact of staged radiosurgery on peritumoral edema reduction. However, the fact that measurable edema reduction was observed as early as 14 days after the first treatment stage comparable to the results in the control group at one month suggests that this approach may represent a promising direction for further, larger-scale research.

DISCUSSION

It is well known that in the treatment of brain metastases (BM), a particular challenge is posed by large metastatic brain lesions (> 3 cm in their greatest dimension) or even smaller lesions located in close proximity to functionally critical areas of the brain (eyes, lenses, optic nerves, chiasm, optic tracts, brainstem, hippocampus) [11]. It has been established that the maximum radical dose for lesions up to 2 cm in diameter, located away from critical structures, is approximately 24 Gy. As the lesion volume increases, the volume of uninvolved brain tissue affected by the irradiation grows proportionally. Accordingly, the maximum permissible dose decreases. For lesions larger than 3 cm, the highest safe dose is around 15 Gy.

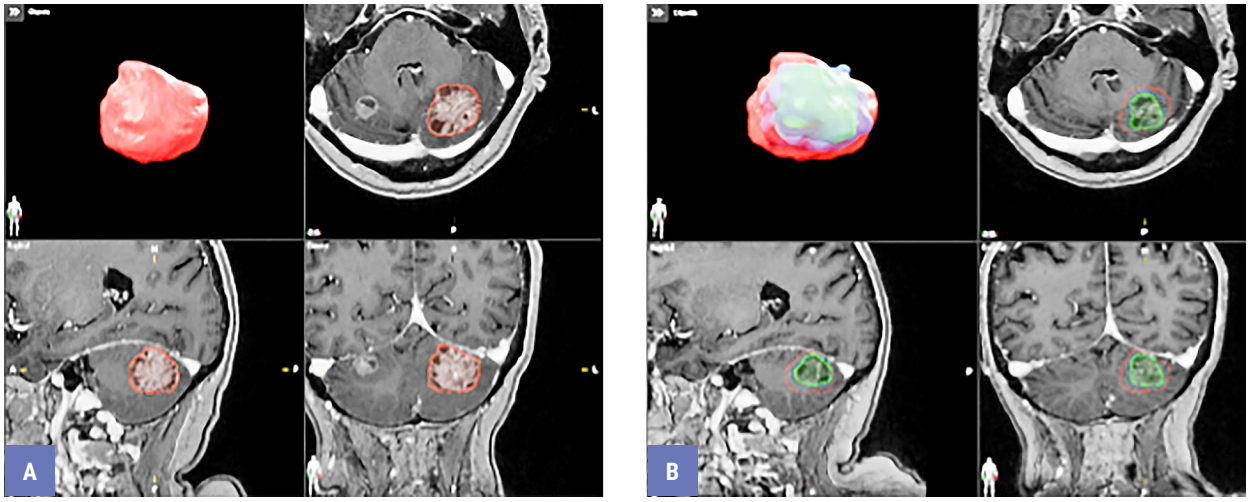

Fig. 1. Volumetric contours of a metastatic lesion in a patient with disseminated breast cancer: A) before the initiation of radiotherapy; B) one month after completion of radiotherapy

A radical reduction in the total lesion dose inevitably leads to reduced treatment efficacy and an increased risk of intracranial progression [12].

For such large lesions, hypofractionated radiotherapy can be employed. Clinical guidelines describe a regimen of 8 Gy per fraction over three fractions, thereby delivering a total dose of 24 Gy [10]. Although the final total dose remains the same as in classical radiosurgery, some evidence suggests that fractionation reduces tumoricidal efficacy. Nevertheless, this regimen remains sufficiently intensive, delivering a high total dose over a relatively short period, and therefore retains the risk of complications associated with peritumoral edema and involvement of nearby critical structures [13].

In search of a solution to this problem, ongoing work has been devoted to the development of staged stereotactic radiosurgery (stSRS), in which an equivalent radical dose for large brain metastases is delivered in multiple stages with intervals of 2–4 weeks.

Higuchi Y, et al. (2009) conducted a prospective study including 43 patients with large BM volumes (> 10 cm³, range 10–35.5 cm³). The treatment scheme consisted of 10 Gy per fraction in a radiosurgical mode, followed by a 14-day break, repeated twice for a total of three sessions. Thus, the total dose after three stages was 30 Gy. The mean tumor volume reduction was 18.8 % and 39.8 % at the time of the second and third sessions, respectively. Intracranial progression-free survival at 12 months was 80.7 %. Local control was not achieved in three cases due to recurrence, in five cases due to symptomatic peritumoral edema, and in one case due to hemorrhage. New lesions were detected in 24.8 % of patients at 6 months and in 34.2 % at 12 months [8].

Medvedeva KE, et al. (2022) analyzed the treatment of 31 BM patients who underwent two-stage stSRS using the Gamma Knife platform. The median total dose after two stages was 30 Gy (range 22–49 Gy), with an interval of up to 33 days between sessions. The median tumor volume before therapy was 10.4 cm³. MRI follow-up was performed at four time points: before the second stage, and at 3, 6, and 12 months after treatment. Follow-up data were available for 21, 14, 11, and 4 patients at each respective time point, the reduction being due to extracranial disease progression. Mean lesion volume reductions at each stage were 41.4 %, 43 %, 56.4 %, and 56.7 %. Intracranial progression was observed in two patients at the first, second, and third follow-ups. Radionecrosis was detected in two cases, at 4 and 15 months after treatment [9].

In the present study, a two-stage regimen was used: 12 Gy in a single fraction at the first stage and 14 Gy in a single fraction at the second stage, with a 14-day interval between them [8].

The choice of the dosing regimen at the stages of radiosurgery was based on the calculation of the biologically effective dose (BED) using the formula BED = D × (1 + d/(a/b)) [14]. The reference point was the standard radiosurgery regimen for metastatic lesions from breast cancer measuring less than 3 cm at the largest dimension. Delivering 24 Gy to the lesion with a radiosensitivity coefficient a/b = 4.6 (for breast cancer histology) resulted in a biologically effective dose of 149.22 isoGy.

When recalculating the biologically effective dose for hypofractionated irradiation with a single dose of 8 Gy for three fractions and a total focal dose (TFD) of 24 Gy, we obtain 65.74 isoGy, which clearly demonstrates how the effectiveness of radiotherapy decreases when the dose is reduced and a hypofractionated approach is used.

Therefore, aiming to increase the iso-effectiveness of the delivered dose, a two-stage irradiation regimen with doses of 12 Gy and 14 Gy was chosen, resulting in a cumulative iso-effectiveness of 99.9 isoGy with an arithmetic cumulative TFD of 26 Gy. A lower dose is delivered at the first stage because initially we are dealing with a large lesion, which may also be surrounded by peritumoral edema and therefore requires a more sparing irradiation regimen to avoid neurocognitive impairment. By the second stage, due to the dose already delivered and the use of anti-edema therapy, the volume of the lesion and the peritumoral edema area usually decreases, making it possible to deliver a higher dose while maintaining patient safety.

Attention in this study may also be drawn to the varying responses of lesions to treatment depending on the location of the identified primary tumor and histological type. In our cohort, the best results were observed in metastatic lesions from

generalized breast cancer, where the mean volume reduction exceeded 70 % and was clinically significant. In contrast, metastatic melanoma lesions demonstrated greater radioresistance, which is characteristic of the histological structure of the tumor. We cannot draw definitive conclusions on this matter because a larger sample size would be needed for statistically reliable research. However, the preliminary results of this study suggest that in an attempt to improve the clinical effect of the proposed treatment, radiomodification could be considered.

Of note in our data is the variability in treatment response depending on the primary tumor site and histology. The best results were seen in breast cancer BM, with mean volume reductions exceeding 70 %, a clinically significant effect. By contrast, melanoma BM demonstrated greater radioresistance, consistent with known histological characteristics. Definitive conclusions are limited by the sample size, but these preliminary findings suggest that radiomodification might improve outcomes.

We also note the potential impact of stSRS on reducing peritumoral edema, which is clinically important in intracranial symptomatology and limits radiotherapy planning [13]. Our findings suggest that a lower first-stage dose may reduce pronounced peritumoral edema, creating more favorable conditions for delivering a radical dose at the second stage, thereby increasing both efficacy and safety in BM treatment.

There are also grounds to hypothesize that staging may positively affect radioresistant tumor characteristics. In melanoma BM, increased resistance to DNA double-strand breaks from radiation is well-documented [15]. With hypofractionated regimens, the marginal dose is delivered to an essentially unchanged tumor because the period for radiation effect manifestation is short, potentially explaining the lower volume reductions observed in melanoma BM in our study. In contrast, stSRS yielded better outcomes, possibly because the interstage interval allowed partial tumor pathomorphosis, reducing radioresistance.

CONCLUSION

Two-stage staged stereotactic radiosurgery for brain metastases has demonstrated satisfactory local control in patients with various primary tumor sites. Follow-up is ongoing, but the positive dynamics observed thus far support the expectation of favorable long-term results. Investigating correlations between histology and treatment response, comparing this technique to other staged radiosurgery protocols, and exploring possible clinical effects associated with stSRS remain promising areas for further research. At this stage, the achieved degree of local control with the proposed dosing and interstage interval offers a viable treatment option for large brain metastases.

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South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 45-52
https://doi.org/10.37748/2686-9039-2025-6-3-5
https://elibrary.ru/kuzycl
ORIGINAL ARTICLE

A method for determining resection margins in basal cell carcinoma of the skin

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ABSTRACT

Purpose of the study. To investigate the feasibility of applying a method of visual diagnosis of basal cell carcinoma (BCC) under ultraviolet (UV) light using Photoditazine for determining tumor margins in clinical practice.
Patients and Methods. The study was conducted at the Department of Reconstructive and Plastic Surgery and Oncology, National Medical Research Center for Oncology. Sixty patients (men and women) with cytologically verified stage I–II BCC were included. Among them, 30 patients (15 men and 15 women) presented with a superficial growth pattern, and 30 patients (15 men and 15 women) with a solid growth pattern. In all cases, Photoditazine gel-penetrant was applied topically to the tumor surface and the surrounding area (1.5–2 cm) for 30 minutes. The gel was then removed with a gauze swab moistened with distilled water. Under UV light in a dark room, a characteristic fuchsia fluorescence of the tumor and a pale or dark-red halo around the lesion were observed. This enabled assessment of the tumor spread into adjacent tissues that initially appeared visually unaffected.
Results. The study yielded the following findings: in 33 patients, the peritumoral area showed no fluorescence, whereas in 27 patients, zones of enhanced fluorescence ("hot spots") were detected around the tumor. These areas exhibited a round or irregular shape and were characterized by an intense dark-red fluorescence surrounding the tumor focus. Extensive "hot spots" indicated active adsorption of the photosensitizer in the area, which may result from altered hormonal and metabolic properties of the peritumoral skin. In cases where extensive peritumoral fluorescence was identified, the area should be included within the resection field as a potentially high-risk zone for subsequent recurrence.
Conclusion. The proposed method is simple to use, does not require expensive equipment or systemic administration of the photosensitizer, and therefore avoids patient inconvenience and precautionary restrictions. Detection of peritumoral fluorescence enables accurate determination of true tumor margins and facilitates subsequent surgical excision with an optimal margin from the visible edge of the lesion. These advantages support the recommendation of this method for broad implementation in routine practice of specialized medical institutions.

Keywords: basal cell carcinoma of the skin, photoditazine, recurrence, resection line, ultraviolet light

For citation: Larina N. I., Shatova Yu. S., Frantsiyants E. M., Bandovkina V. A., Pozdnyakova V. V., Legostaev V. M., Khokhlova O. V., Zakharova N. A. A method for determining resection margins in basal cell carcinoma of the skin. South Russian Journal of Cancer. 2025; 6(3): 45-52. https://doi.org/10.37748/2686-9039-2025-6-3-5, https://elibrary.ru/kuzycl

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles outlined in the World Medical Association Declaration of Helsinki (1964, revised 2013). Ethical approval was obtained from the Ethics Council of the National Medical Research Center of Oncology (Protocol No. 29, dated 09/09/2022). Informed consent was obtained from all participants in the study

Funding: this work was not funded

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 18.02.2025; approved after reviewing 03.08.2025; accepted for publication 13.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 45-52
https://doi.org/10.37748/2686-9039-2025-6-3-5
https://elibrary.ru/kuzycl
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Метод определения границ резекции базальноклеточного рака кожи

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РЕЗЮМЕ

Цель исследования. Изучение возможности применения в клинической практике метода визуальной диагностики базальноклеточного рака кожи в ультрафиолетовом свете с использованием фотодитазина для определения границ распространения опухоли.

Пациенты и методы. Данное исследование проводилось на базе отделения реконструктивно-пластической хирургии и онкологии ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации. В исследование были включены 60 мужчин и женщин с цитологически верифицированным базальноклеточным раком кожи I–II стадии, из них: 30 человек (15 мужчин и 15 женщин) с поверхностным типом роста опухоли, 30 человек (15 мужчин и 15 женщин) с солидным типом роста опухоли. Всем пациентам на поверхность опухоли и зону вокруг нее (1,5–2 см) наносился гель-пенетратор фотодитазин в виде аппликации на 30 мин., затем удалялся марлевой салфеткой, смоченной дистиллированной водой. Далее в темном помещении при помощи ультрафиолетового источника света отмечалось характерное свечение опухоли цвета фуксии и бледный или темно-красный ореол вокруг опухоли. Таким образом определялось распространение опухолевого процесса на окружающие, изначально визуально не измененные ткани.

Результаты. В ходе исследования были получены следующие результаты: у 33 пациентов зона вокруг опухоли не демонстрировала никакого свечения, тогда как у 27 – наблюдались участки повышенной флуоресценции вокруг опухоли – так называемые «засветы». Эти области имели округлую или неправильную форму и характеризовались интенсивным темно-красным свечением, окружающем опухолевый очаг. Обширные «засветы» свидетельствуют об активной адсорбции фотосенсибилизатора в данной области, которая возникает вследствие изменения гормонально-метаболических свойств кожи вокруг опухоли. При выявлении обширного перитуморального «засвета» данную область следует включать в резецируемое поле как потенциально опасную зону в отношении последующего рецидивирования.

Заключение. Предлагаемый метод прост в использовании, не требует дорогостоящего оборудования и системного пути введения фотосенсибилизатора, что позволяет избежать ряда неудобств и соблюдения мер предосторожности пациентами. Перитуморальная флуоресценция позволяет определить истинные границы распространения опухолевого процесса и выполнить дальнейшее хирургическое иссечение с оптимальным отступом от видимого края опухолевого поражения. Все вышеперечисленные достоинства позволяют рекомендовать данный метод для широкого внедрения в рутинную практику специализированных лечебных учреждений.

Ключевые слова: базальноклеточный рак кожи, фотодитазин, рецидив, линия резекции, ультрафиолетовый свет

Для цитирования: Ларина Н. И., Шатова Ю. С., Франциянц Е. М., Бандовкина В. А., Позднякова В. В., Легостаев В. М., Хохлова О. В., Захарова Н. А. Метод определения границ резекции базальноклеточного рака кожи. Южно-Российский онкологический журнал. 2025; 6(3): 45-52. https://doi.org/10.37748/2686-9039-2025-6-3-5, https://elibrary.ru/kuzycl

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено на заседании совета по этике при ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 29 от 09.09.2022 г.).
Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 18.02.2025; одобрена после рецензирования 03.08.2025; принята к публикации 13.08.2025

BACKGROUND

Due to its high prevalence and increasing incidence, the timely and accurate diagnosis and treatment of basal cell carcinoma (BCC) of the skin remain a relevant focus of numerous studies and innovative developments. The tumor microenvironment plays a pivotal role in BCC carcinogenesis. It is becoming increasingly evident that the stromal microenvironment, in which neoplastic cells develop, exerts a profound influence on many stages of cancer progression [1]. Detection of tumor cells in the perifocal zone is possible only through histological examination of surgical specimens following excision. It is well established that the visually unchanged skin surrounding a neoplasm undergoes structural and biochemical alterations, thereby creating a so-called "tumor bed". In cases of incomplete excision, this area may become a source of continued tumor growth or recurrence.

One of the non-invasive treatment modalities for BCC is photodynamic therapy (PDT). Prior to the procedure, a photosensitizer (PS) is administered intravenously, which becomes selectively adsorbed in tumor cells (exposure time ~3 hours). Currently, second-generation photosensitizers are widely used; unlike those of the first generation, they are activated by light in the long-wavelength red region of the spectrum (λ = 650–680 nm). They penetrate deeper into tissues, accumulate more selectively in tumor cells, and are eliminated more rapidly from the body [2–4].

Several second-generation photosensitizers derived from chlorin e6 (such as Photoditazine) were developed between 1996 and 1998 by Prof. G. V. Ponomarev at the Institute of Biomedical Chemistry, Russian Academy of Sciences (RF Patent No. 2144538). Clinical trials of Photoditazine commenced in 1998 at the State Research Center of Laser Medicine. Among second-generation PSs, chlorin derivatives such as Radachlorin (Radapharma, Russia), Photoditazine (Veta-Grand LLC, Russia), Photolon (Belmedpreparaty, Belarus), and Foscan (Biolitec AG, Germany) are the most widely applied in clinical practice [4].

Photoditazine accumulates rapidly in tumor tissues, reaching maximum concentration within 1.5–2.5 hours [5]. It demonstrates high photodynamic activity and has several advantages compared to other chlorin e6 derivatives:

– a high selectivity index for tumor accumulation versus surrounding intact tissues (10, compared with 6 for Radachlorin and 4 for Photolon) [5–7];

– high quantum yield owing to its monomeric, hydrophilic, and homogeneous properties, ensuring strong phototoxicity [5];

– the ability to bind to tumor cell membranes [8];

– a lower therapeutic dose (0.3–1.5 mg/kg body weight) compared to Radachlorin (0.5–2.4 mg/kg) and Photolon (2.5–3.0 mg/kg).

The clinical efficacy of PDT using Photoditazine has been reported in several studies [9– 12]. Two methods of administration have been described: intravenous (RF Patent No. 2347567, RF Patent No. 2482893) and topical (RF Patent No. 2286780). Photoditazine (N-dimethylglucamine salt of chlorin e6) accumulates most intensively in proliferating areas. Its structural formula is provided in [13]. In the electronic absorption spectrum, Photoditazine exhibits five characteristic absorption bands with maxima at 400 ± 2 nm, 504 ± 2 nm, 534 ± 2 nm, 608 ± 2 nm, and 662 ± 2 nm (RF Patent No. 2448745, publ. 27.04.2012, A61B 5/06). The main absorption peak occurs at 402 nm, where energy requirements for excitation are threefold lower than in the 660-nm spectrum.

The intravenous route of administration poses certain limitations for patients: for two days post-infusion, they must observe precautionary measures avoid direct sunlight, preferably remain indoors until sunset, and wear UV-protective sunglasses.

The pharmaceutical company Veta-Grand manufactures Photoditazine as a 0.5 % topical gel-penetrant [4]. Registration certificate: No. FSR 2012/13043, dated 06/08/2017. Chemical name: N-dimethylglucamine salt of chlorin e6. Description: greenish polymer gel for topical use. Dosage form: 0.5 ml, 1.0 ml, or 2.0 ml of gel supplied in a 2.0 ml disposable injection syringe with a plastic cap in sterile packaging. Composition: 1 ml of gel contains 5 mg of the active substance (Photoditazine) and excipients (methylhydroxyethylcellulose ethers).

An alternative technique contact fluorescent biomicroscopy using acridine orange (concentration 1:5000) is described in RF Patent No. 23887376. This method requires specialized contact lenses (LK 25 × 0.75) and costly equipment (LUMAM–IZ), configured for detection in a broad spectral range (480–700 nm), which significantly limits its use in routine clinical practice. This technique identifies BCC tumor complexes by detecting clusters of intensely fluorescent cells against the background of green fluorescence of the intercellular matrix and collagen fibers, thereby enabling diagnosis of BCC.

Purpose of the study. To evaluate the feasibility of applying a method of visual diagnosis of basal cell carcinoma under ultraviolet light using Photoditazine for determining tumor margins in clinical practice.

PATIENTS AND METHODS

The study included 60 patients of both sexes: 30 men and 30 women with stage I–II basal cell carcinoma (BCC) of the skin. The diagnosis of BCC had been cytologically verified at the pre-hospital stage. The cohort comprised 15 patients with the nodular growth pattern and 15 with the superficial growth pattern, none of whom had received prior treatment. In all cases, Photoditazine gel-penetrant was applied topically as an occlusive dressing to the tumor surface and the visually unchanged skin surrounding the lesion, extending 1.5–2 cm from the tumor margin. The dosage was calculated as 1 ml of gel per 3–5 cm² of treated surface, with an exposure time of 30 minutes. Following application, the gel was removed from the tumor and adjacent skin with a gauze swab moistened with distilled water. In a darkened room, under directed ultraviolet (UV) light, characteristic fuchsia fluorescence of the carcinoma and a pale or dark-red halo surrounding the lesion were observed and documented by photographic registration.

The following results were obtained: in 33 patients (55 %), the peritumoral zone exhibited no fluorescence (Fig. 1), whereas in 27 patients (45 %), areas of increased peritumoral fluorescence so-called "hot spots" were detected (Fig. 2).

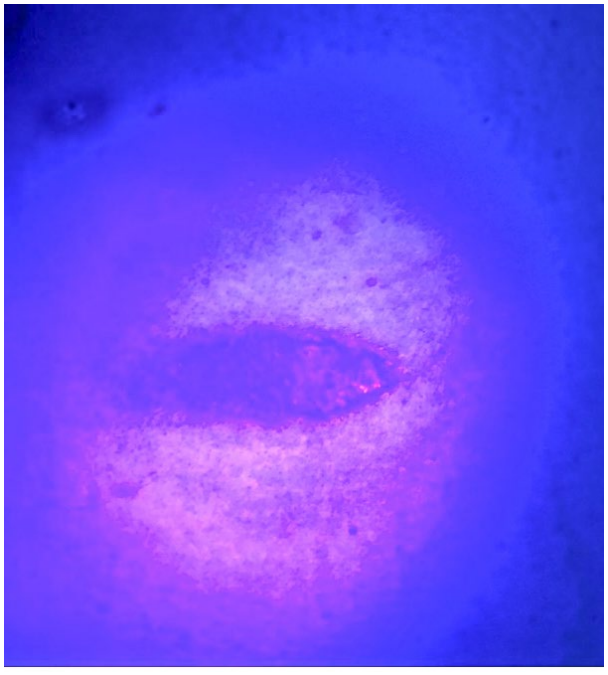

Fig. 1. Under directed ultraviolet light: skin of the lumbar region with a tumor lesion (basal cell carcinoma of the back, T1N0M0, stage I, clinical group 2). Photoditazine gel-penetrant was applied to the tumor surface and the peritumoral zone. No fluorescence of the perifocal area is observed

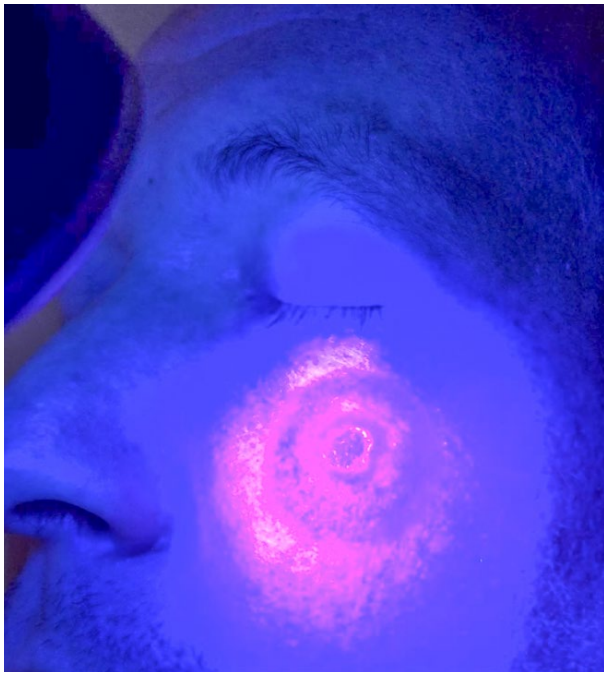

Fig. 2. Under directed ultraviolet light: skin of the left cheek with a tumor lesion (basal cell carcinoma of the left cheek, T1N0M0, stage I, clinical group 2). Photoditazine gel-penetrant was applied to the tumor surface and the peritumoral zone. An extensive round-shaped peritumoral "hot spots" is observed around the tumor

These regions displayed either round or irregular contours and were characterized by intense dark-red fluorescence encircling the tumor focus. In our view, such areas should be unconditionally included in the resection field, as they represent potentially hazardous zones with respect to local recurrence. Active adsorption of the photosensitizer in these regions indicates alterations in the hormonal and metabolic properties of the peritumoral skin, thereby signifying the formation of a tumor field.Additionally, growth factor content, receptor expression, and fibrinolytic system activity were analyzed in the surgical material obtained after tumor excision. Our previously published findings demonstrated that, despite the absence of tumor cells at the resection margin, elevated levels of VEGF-A, VEGF-C, TGF-β, and EGF [14], along with activation of the fibrinolytic system [15], contributed to continued malignant growth. This was confirmed by recurrence diagnosed 12–15 months postoperatively in three male patients with solid-type BCC who had exhibited the most extensive peritumoral "hot spots".

The total time required for the diagnostic procedure prior to surgery did not exceed 70 minutes. Indication for use of the proposed method: cytologically verified BCC.

STUDY RESULTS AND DISCUSSION

Among 60 patients, peritumoral "hot spots" were detected in 27 cases (45.0 %): in 24 patients (40.0 %) with solid-type tumor growth and in 3 patients (5.0 %) with superficial-type growth. For these patients, surgical excision was performed with a margin greater than 4 mm from the fluorescent zone. In cases with a pale peritumoral halo or without fluorescence, standard excision with a 4-mm margin from the visible tumor border was carried out. In all cases, histological analysis confirmed the radicality of surgery: the tumors were completely excised within healthy tissues, with no evidence of malignant growth at the resection margins.

Example of clinical use of the proposed method can be illustrated by the following case records.

Example No. 1. Patient I., female, 71 years old. History: a flat pink spot appeared 3 years ago, periodically covered with a crust, slowly increased in size, treated with Akriderm – without improvement. Local status: on the skin of the left lumbar region – a flat pink lesion measuring 0.6 × 1.3 cm in diameter, without ulceration. Dermatoscopy with HEINE DELTA 20 revealed arborizing vessels (presumably basal cell carcinoma). After cytological examination, the result was obtained – a few groups of basal cell carcinoma on the background of basal cell hyperplasia with proliferation, with polymorphism of some cells, hyperkeratosis. Photoditazine gel-penetrant was applied to the lesion and peritumoral zone, then examined under directed ultraviolet light. No peritumoral fluorescence was observed. The tumor was surgically excised according to clinical guidelines with a 4-mm margin from the visible edge. The skin-fat flap with the tumor, 1.4 × 2.1 cm, was sent for histological examination. Final histology: superficial basal cell carcinoma without ulceration, without vascular or perineural invasion, with focal lymphocytic peritumoral infiltration, maximum horizontal spread 9.5 mm, thickness 0.3 mm. No tumor cells detected at the resection margins, pT1. Result: the patient was followed for 1 year and 3 months without signs of recurrence.

Example No. 2. Patient M., male, 55 years old. History: according to the patient, a "pimple" appeared 1.5 years ago, self-treated with celandine, followed by ulcer formation and gradual growth. Local status: on the skin of the left cheek – a pink lesion measuring 0.8 cm in diameter, irregular in shape, with central ulceration and pearly rolled borders. Dermatoscopy with HEINE DELTA 20 revealed an ulcerated defect with elevated rolled edges and arborizing vessels (presumably basal cell carcinoma). Cytological examination confirmed basal cell carcinoma. Photoditazine gel-penetrant was applied to the lesion and peritumoral zone, then examined under directed ultraviolet light. An extensive round peritumoral “hot spot” was detected around the tumor. The lesion was surgically excised with a 7-mm margin from the visible edge, taking into account the fluorescence zone. The excised skin-fat flap, 1.5 cm in diameter, was sent for histological examination. Flap plasty was performed to close the defect. Final histology: basal cell carcinoma, nodular form, solid variant. Clark level IV invasion. Tumor thickness – 2 mm. The tumor was excised within healthy tissues,

pT1. Result: the patient was followed for 1 year and 2 months without signs of recurrence.

Among patients with solid-type tumor growth, three male patients developed recurrence within 12–15 months after treatment. All had shown extensive peritumoral "hot spots". In our previously published studies, metabolic changes in the peritumoral zone of these patients were described [14]. In particular, elevated concentrations of VEGF-A and VEGF-C were found both in tumor tissue and in the peritumoral zone, as well as in conditionally healthy skin, preceding the development of recurrence. Thus, these indicators are prognostically significant markers of recurrence risk (RF Patent No. 2823211 C1, 07/22/2024).

In addition, in patients with nodular BCC who subsequently developed recurrences, activation of the fibrinolytic system was observed both in the tumor and in the peritumoral zone [15]. This combination of changes reflected metabolic disturbances characteristic of an extended tumor field and created prerequisites for local recurrence. The obtained data emphasize the importance of a comprehensive assessment of not only morphological but also molecular and biological features of the tumor and surrounding tissues for predicting disease progression.

CONCLUSION

Thus, the results obtained indicate that determining the true boundaries of tumor cell spread by the method of photosensitization has significant advantages over known diagnostic approaches for BCC. Its application allows: 1. to determine the boundaries of tumor spread with maximum accuracy; 2. to perform the study without systemic administration of the drug; 3. to carry out subsequent surgical excision with an optimal margin.

It is recommended to implement the use of the photosensitization method into routine practice, as it does not require expensive specialized equipment, is effective, and is simple to perform.

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Pozdnyakova V. V. – data collection, final conclusions;
Legostaev V. M. – idea, research concept, data collection;
Khokhlova O. V. – data collection, final conclusions;
Zakharova N. A. – data collection, final conclusions.

South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 53-62
https://doi.org/10.37748/2686-9039-2025-6-3-6
https://elibrary.ru/llbjxl
ORIGINAL ARTICLE

Ki-67 expression in triple-negative breast cancer and its correlation with age

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ABSTRACT

Purpose of the study. To analyze the correlation between the proliferative activity of atypical cells in triple-negative breast cancer (BC) and patient age.

Patients and methods. The study included 80 women with a newly diagnosed BC, in whom a triple-negative surrogate molecular genetic subtype was identified based on histological and immunohistochemical examination with assessment of hormone receptor expression and Ki-67. Statistical analysis was performed using Statistica 13.5.0.17 software (TIBCO Software Inc.). The Shapiro-Wilk test was applied to assess the normality of the distribution. Correlation between variables was evaluated using the Kendall tau rank correlation coefficient.

Results. The median age of patients was 53.9 years (95 % confidence interval [CI]: 50.0–57.8) (Fig. 3). Among them, 65 % of patients were younger than 50 years and 35 % were older. The median proliferative activity, assessed by Ki-67 expression according to the St. Gallen Consensus (2009), was 76.4 % (95 % CI: 73.28–79.66). However, this indicator varied depending on patient age. The analysis revealed a correlation between Ki-67 expression level and patient age, with a Kendall tau coefficient of −0.449 ($p < 0.05$), corresponding to a weak-to-moderate negative association.

Conclusion. The analysis showed that the degree of Ki-67 expression correlates with the age at breast cancer onset. Thus, there is a tendency toward higher proliferative activity of cancer cells in younger patients.

Keywords: breast cancer, triple negative, Ki-67

For citation: Demyashkin G. A., Belokopytov D. V., Guzik A. A. Ki-67 expression in triple-negative breast cancer and its correlation with age. South Russian Journal of Cancer. 2025; 6(3): 53-62. https://doi.org/10.37748/2686-9039-2025-6-3-6, https://elibrary.ru/llbjxl

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set in the World Medical Association Declaration of Helsinki (1964, revised in 2013). The research was approved by the Joint Problem Commission of the P. A. Hertsen Moscow Oncology Research Institute – branch of the National Medical Research Radiological Center (extract from the meeting protocol No. 2 dated 03/15/2024). Informed consent was obtained from all study participants

Funding: this work was not funded

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 16.03.2025; approved after reviewing 26.07.2025; accepted for publication 14.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 53-62
https://doi.org/10.37748/2686-9039-2025-6-3-6
https://elibrary.ru/llbjxl
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Экспрессия Ki-67 при трижды негативном раке молочной железы, возрастные особенности

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РЕЗЮМЕ

Цель исследования. Проанализировать степень корреляции между уровнем пролиферативной активности атипичных клеток трижды негативного рака молочной железы (РМЖ) и возрастом пациента.
Пациенты и методы. В исследование было включено 80 женщин с впервые установленным диагнозом РМЖ, у которых по результатам гистологического и иммуногистохимического исследования с оценкой экспрессии гормональных рецепторов и Ki-67 был установлен трижды негативный суррогатный молекулярно-генетический подтип РМЖ. Статистический анализ выборки проводился с применением программного обеспечения Statistica 13.5.0.17 software (TIBCO Software inc.). Для оценки нормальности распределения признака, применялся критерий Шапиро-Уилка (Shapiro-Wilk). Степень корреляции между признаками оценивалась с применением коэффициента корреляции Кенделла (Kendall tau rank correlation coefficient).
Результаты. Медиана возраста у пациентов в полученной выборке составляла 53,9 лет (95 % доверительный интервал [ДИ] 50,0–57,8). Среди них 65 % пациентов были моложе, а 35 % – старше 50 лет. Медианный уровень пролиферативной активности, оцененный по уровню экспрессии Ki-67 по шкале St. Gallen Consensus (2009 г.) составил 76,4 % (95 % ДИ 73,28–79,66). Однако значение данного показателя варьировало в зависимости от возраста пациентов. При проведении анализа выявлено, что существует корреляция между уровнем экспрессии Ki-67 и возрастом пациента, коэффициент корреляции Кенделла составил –0,449 ($p < 0,05$), что соответствует слабой-умеренной отрицательной связи.
Заключение. В ходе проведенного анализа выявлено, что степень экспрессии Ki-67 коррелирует с возрастом дебюта РМЖ у пациента. Таким образом, имеется тенденция к более высокой пролиферативной активности раковых клеток у молодых пациентов.

Ключевые слова: рак молочной железы, трижды-негативный рак, Ki-67

Для цитирования: Демяшкин Г. А., Белокопытов Д. В., Гузик А. А. Экспрессия Ki-67 при трижды негативном раке молочной железы, возрастные особенности. Южно-Российский онкологический журнал. 2025; 6(3): 53-62. https://doi.org/10.37748/2686-9039-2025-6-3-6, https://elibrary.ru/llbjxl

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Объединенной проблемной комиссией при Московский научно-исследовательский онкологический институт им. П. А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 15.03.2024 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 16.03.2025; одобрена после рецензирования 26.07.2025; принята к публикации 14.08.2025

BACKGROUND

Breast cancer (BC) is a malignant tumor arising from the luminal epithelium of the terminal ductal lobular units and represents one of the most common oncological diseases worldwide [1].

In Russia, in 2023, breast cancer accounted for 22.5 % of all newly diagnosed cancers in women, corresponding to 12.3 % of the total population or 84,299 cases in absolute numbers. Such a high incidence also explains the significant contribution of breast cancer to cancer-related mortality, which was 15.9 % or 18,580 deaths in 2023. Nevertheless, there are clear positive trends in the diagnosis and treatment of breast cancer: compared with 2013, the mortality growth rate decreased by 16.2 % [2].

One of the reasons for the decline in mortality is the early detection of malignancies, as well as the development and implementation of innovative therapeutic approaches, including those based on the genetic characteristics of tumors. A particularly effective advancement has been the introduction of surrogate molecular genetic subtyping of breast cancer into routine clinical practice. Indeed, "breast cancer" is an umbrella term that encompasses a heterogeneous group of tumors with distinct genetic and transcriptomic features [3–5]. Based on genetic research, four intrinsic subtypes of breast cancer have been identified: luminal A, luminal B, HER2-enriched, and basal-like. Each subtype is distinguished by its specific expression profile of estrogen receptors, progesterone receptors, and HER2/neu receptors.

However, from both technical and economic perspectives, genetic testing of every tumor remains difficult to implement in daily practice. Therefore, an immunohistochemical (IHC) approach was developed as a surrogate for genetic testing, based on the assessment of hormone receptor expression and proliferative activity (Ki-67 index). Using this method, five surrogate molecular subtypes are distinguished: luminal A, luminal B HER2-negative, luminal B HER2-positive, HER2-enriched, and triple-negative [1, 6, 7]. These subtypes allow clinicians to select the most appropriate treatment strategy [7].

Among all subtypes, triple-negative breast cancer (TNBC) is characterized by the most aggressive clinical course and the highest mutational burden [8–10]. Due to severe alterations in the genetic apparatus, TNBC cells lack expression of estrogen, progesterone, and HER2/neu receptors (Fig. 1), which greatly limits therapeutic options, as both hormone therapy and anti-HER2 targeted therapy (e. g., trastuzumab) are ineffective [8, 9, 11]. The overall prevalence of TNBC is about 10–15 %, but it varies by age. According to Anders, et al., 34.3 % of breast cancers in women younger than 40 years had a basal-like phenotype, compared with 17.9 % in women over 65 years [12]. It is also well established that early-onset breast cancer is a strong negative prognostic factor, being associated with larger tumor size, higher rates of lymph node involvement, more aggressive histological features, and increased recurrence rates, both after breast-conserving surgery and mastectomy [9, 13].

We hypothesize that the aggressive course of the disease in younger patients is related not only to the higher proportion of the triple-negative phenotype compared with older patients, but also to the fact that age at disease onset itself may be an independent prognostic factor influencing tumor biology.

Purpose of the study: To analyze the correlation between the proliferative activity of atypical cells in triple-negative breast cancer and patient age.

PATIENTS AND METHODS

In this retrospective study, we analyzed data from 80 patients (medical records and pathomorphological reports) who received treatment at the P. A. Herzen MNIOI – Branch of the National Medical Research Radiological Center. Inclusion criteria were: female sex, age over 18 years, a confirmed diagnosis of breast cancer with ≥ T1a stage, histological subtype – invasive carcinoma of no special type (ICD-O: 8500/3), and triple-negative surrogate molecular subtype. Exclusion criteria were: pregnancy, severe comorbid conditions, history of malignant tumors, and the presence of BRCA1/2 mutations, determined by RT-PCR (DTPrime4; DNA-Technology). According to the medical records, all patients underwent diagnostic biopsy followed by morphological and immunohistochemical examination using the following monoclonal antibodies: anti-Estrogen Receptor (ER, clone SP1, Ventana), anti-Progesterone Receptor (PgR, clone 1E2, Ventana), anti-HER2/NEU (clone 4B5, Ventana), and anti-Ki-67 (clone 30–9, Ventana) on the Ventana Benchmark XT universal staining system with the ultra-View Universal DAB Detection Kit (Ventana).

Tumor grade was assessed according to the Nottingham Histologic Score (Table 1).

The surrogate molecular genetic profile and the proliferative activity grade were determined in accordance with the recommendations of the WHO and the College of American Pathologists using the Allred scoring system (Table 2) [7, 14]. A triple-negative phenotype was defined as an Allred score of ≤ 2 for ER and PR, as well as the absence of HER2/neu expression (Table 3). For the assessment of proliferative activity, at least 1000 tumor cells were analyzed. Counting was performed across the entire tumor material, with special attention to "hot spots" (Figs. 2–5) [15].

Based on the results of the immunohistochemical study, the surrogate molecular genetic subtype was determined according to the hormonal receptor expression profile (Table 4).

Table 1. Nottingham Histologic Grading System

Показатель	Score		
	1	2	3
Tubule formation	< 10 %	10–75 %	> 75 %
Nuclear pleomorphism	Mind	Moderate	Marked
Mitotic count*	≤ 12	12–24	> 25
Total score	3–5	6–7	8–9
	Grade 1	Grade 2	Grade 3

Note: * – mitotic count is determined in hot spots across 10 high-power fields, adjusted for the field area (values are given for a field diameter of 0.65 mm)

Table 2. Evaluation of Estrogen and Progesterone Receptor Expression by the Allred Scoring System

Proportion of expression	Positive cells, %	Intensity/ Score
0	0	No staining / 0
1	< 1	Weak /1
2	1 – 10	Moderate /2
3	11 – 33	Strong / 3
4	34 – 66	
5	≥ 67	

Note: The final score = proportion score + intensity score. 0–2 – negative result, 3–8 – positive result

Table 3. Assessment of HER2/neu Expression

HER2/статус	Criteria
Negative	No staining, or incomplete and weak membrane staining observed in ≤ 10 % of tumor cells
Negative	Incomplete weak membrane staining observed in ≥ 10 % of tumor cells
Equivocal	Weak to moderate complete membrane staining in ≥ 10 % of tumor cells, or complete intense membrane staining in ≤ 10 % of tumor cells
Positive	Complete intense membrane staining in > 10 % of tumor cells

Statistical analysis

Statistical analysis was performed using Statistica software version 13.5.0.17 (TIBCO Software Inc.). The Shapiro-Wilk test was applied to assess the normality of distribution. The degree of correlation between variables was evaluated using the Kendall tau rank correlation coefficient.

STUDY RESULTS AND DISCUSSION

In all breast tissue samples of the patients (n = 80), a morphological pattern of invasive carcinoma of no special type (NST), grade G3 according to the Nottingham grading system (Bloom-Richardson modification), was identified. Breast microfragments with pathologically altered tissue (tissue and cellular atypia of the parenchyma) showed clusters of pleomorphic atypical cells (> 300), forming solid structures. The cytoplasm of these cells appeared as a thin rim; their nuclei, displaying polymorphism, were eccentrically located, round in shape, with irregular ("moth-eaten") nuclear membranes. The stromal component demonstrated a weak desmoplastic reaction (Fig. 1).

In the immunohistochemical analysis of samples from patients with breast cancer (n = 80), no Her2/neu membrane staining of atypical cells was detected. ERα and PR according to the Allred score: 0 (PS) + 0 (IS) = 0 (TS) (Immunoreactivity score – negative). The status (ER, PR, Her2/neu) was defined as triple-negative breast cancer (Fig. 2). At the same time, immunohistochemical reactions with antibodies to Ki-67 demonstrated pronounced nuclear immunostaining of tumor cells (Fig. 2). The median proliferative activity level, assessed by Ki-67 expression according to the St. Gallen Consensus scale (2009), was 76.4 % (95 % confidence interval [CI] 73.28–79.66) (Fig. 3). However, the value of this indicator varied depending on the patients' age.

The median age of patients in the studied cohort was 53.9 years (95 % confidence interval [CI] 50.0– 57.8) (Fig. 4). Among them, 65 % of patients were younger and 35 % were older than 50 years. In all patients, breast carcinoma corresponded to a high grade of malignancy (grade 3). The distribution by disease stage is presented in Table 5. Statistical analysis of the correlation between Ki-67 expression level and patient age showed a Kendall's tau coefficient of –0.449 (p < 0.05), indicating a weak-to-moderate negative correlation.

According to the results of our study, it was found that the degree of proliferative activity of triple-negative breast cancer has a negative correlation with patient age, i. e., in younger women, tumor cells exhibit higher proliferative activity. Taking into account the charac-

Table 4. Surrogate molecular genetic subtypes of breast cancer

Surrogate molecular genetic subtype	Characteristics	Prevalence
Luminal A	ER-positive PR-positive HER2-negative Ki-67 ≤ 20 %*	55 %
Luminal B, HER2-negative	ER-positive HER2-negative and at least one of the following: Ki-67 ≥ 30 % PR < 20 % (percentage of expressing cells)	15 %
Luminal B, HER2-positive	ER-positive HER2-positive Ki-67 any PR any	
HER2-enriched	ER-negative PR-negative HER2-positive	15–20 %
Triple-negative	ER-negative PR-negative HER2-negative	10–15 %

Note: * – the threshold values of Ki-67 may vary depending on the institutional guidelines [1, 15]. ER – estrogen receptor; PR – progesterone receptor

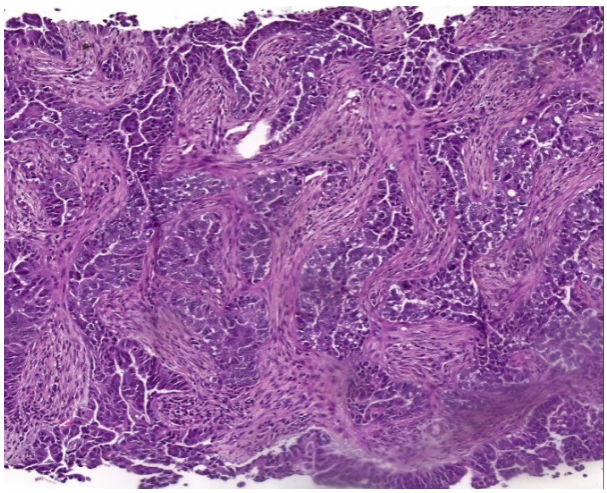

Fig. 1. Patient T., 58 years old. Invasive breast carcinoma of no special type, G3 according to the Nottingham grading system (Bloom-Richardson modification). Staining: hematoxylin and eosin, magnification ×200

teristics of our cohort namely, the absence of estrogen and progesterone receptor expression in tumor cells we can exclude the influence of these hormones on proliferative activity. However, in our opinion, thyroid hormones may play an important role, since one of their functions is the regulation of cellular proliferative activity at different sites [16]. It is known that triiodothyronine levels decrease linearly with age, and there are studies indicating that the use of tyrosine kinase inhibitors, i. e., drug-induced hypothyroidism, is associated with improved survival in patients with non-thyroid solid malignant tumors [17, 18]. This hypothesis is supported by the study of Tawfik, et al., which demonstrated that breast carcinoma cells are capable of capturing T3, which in turn stimulates their proliferative activity [19].

The result obtained in our study can be explained not only by the influence of the macroorganism on tumor biology [20], but also by the genetic characteristics of triple-negative breast cancer. For example, when analyzing data from The Cancer Genome At-

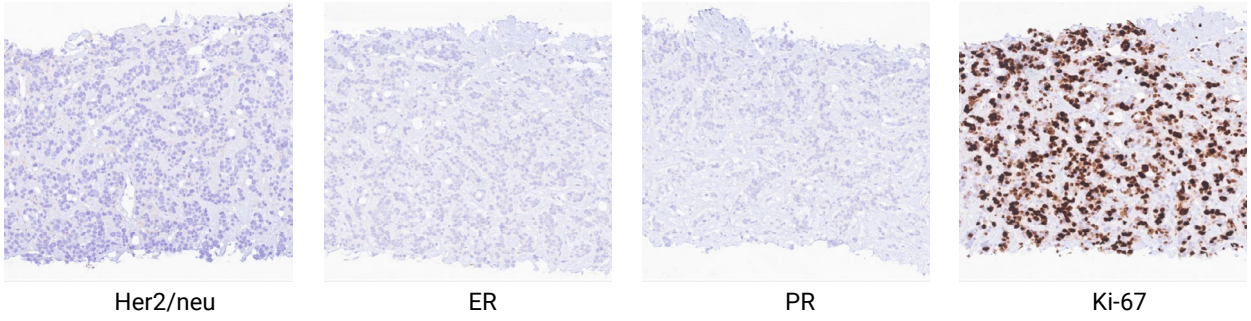

Fig. 2. Patient T., 58 years old. Invasive breast carcinoma of no special type, G3 according to the Nottingham grading system (Bloom-Richardson modification); immunophenotype – triple-negative. Immunohistochemical staining with antibodies, counterstaining with hematoxylin and eosin, magnification ×200

Table 5. Distribution of patients by disease stage according to TNM classification (UICC, 8th edition, 2018)

Disease stage	Number of patients (%)
Stage IA	4 (5 %)
Stage IB	0
Stage IIA	44 (55 %)
Stage IIB	8 (10 %)
Stage IIIA	4 (5 %)
Stage IIIB	8 (10 %)
Stage IIIC	12 (15 %)
Stage IV	0

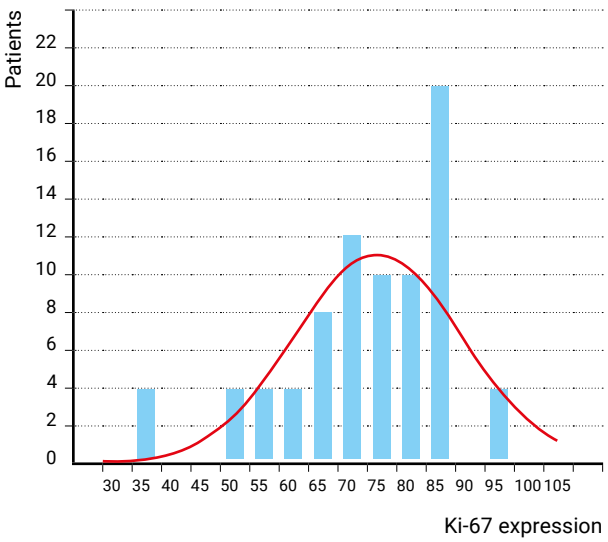

Fig. 3. Level of Ki-67 expression in triple-negative breast cancer

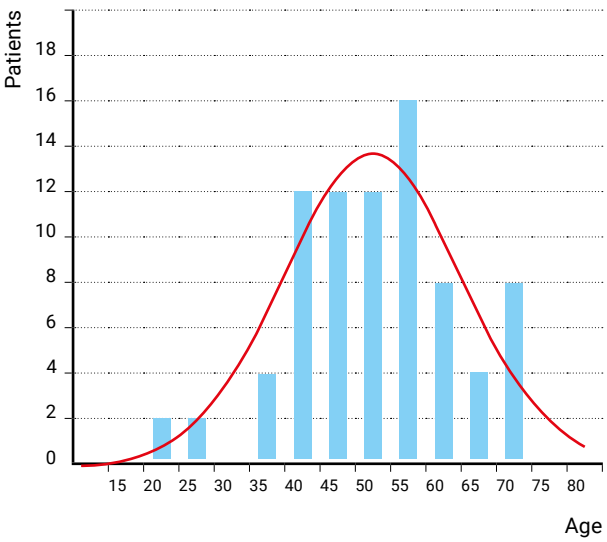

Fig. 4. Age characteristics of the cohort

las in the TCGA-BRCA (Breast invasive carcinoma) cohort using the Oncomatrix tool, a higher frequency of *TP53* mutations can be observed in patients younger than 45 years 42.6 % compared to 37.7 % in women older than 45 years (Figs. 6, 7) [21]. It is well established that TP53 mutations are associated with increased tumor proliferative activity [22]. Thus, according to published data, when comparing p53-mutant and p53-wt breast carcinomas, the Ki-67 index was on average 16 % higher in p53-mutant tumors (51.77 ± 24.53 vs. 35.81 ± 19.54) [23]. We hypothesize that the higher frequency of *TP53* mutations in younger women is one of the key factors determining both the greater proliferative activity of the tumor and the higher incidence of triple-negative breast cancer. From a clinical standpoint, higher proliferative activity represents a factor negatively affecting patient prognosis and relapse-free survival.

Main outcome of the study. In the course of the analysis of triple-negative breast cancer, a statistically significant negative correlation was revealed between the level of proliferative activity of tumor cells and patient age. The Kendall-tau coefficient was −0.449 ($p < 0.05$), which corresponds to a weak-to-moderate negative association.

CONCLUSION

In patients with triple-negative breast cancer, a weak-to-moderate negative correlation was identified between the proliferative activity index, assessed by the percentage of Ki-67-positive tumor cells, and the age at onset. A high mitotic potential was observed in younger women, which suggests that age may serve as an independent prognostic factor. The phenomenon is most likely associated with a higher frequency of *TP53* mutations, as well as age-related and physiological features of the tumor microenvironment. However, this hypothesis requires further confirmation through large-scale prospective studies employing molecular biological and molecular genetic methods.

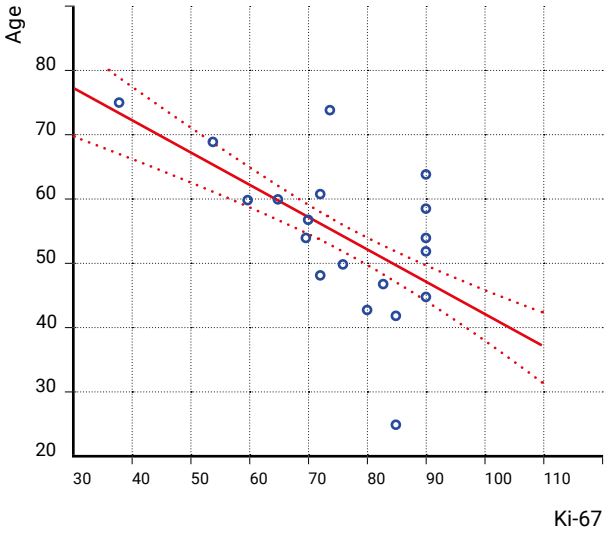

Fig. 5. Scatter plot of Ki-67 expression by age in patients with triple-negative breast cancer

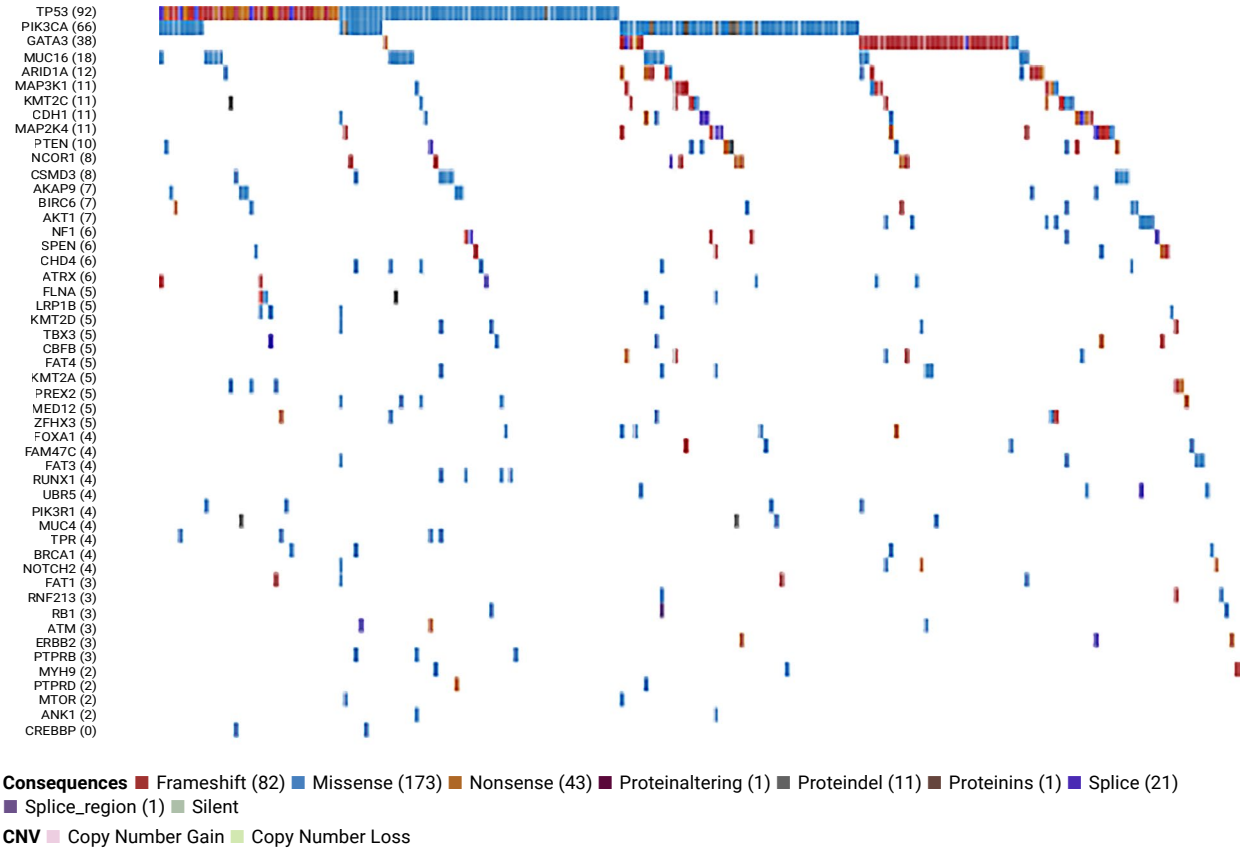

Fig. 6. Mutational profile of breast cancer patients. Age < 45 years

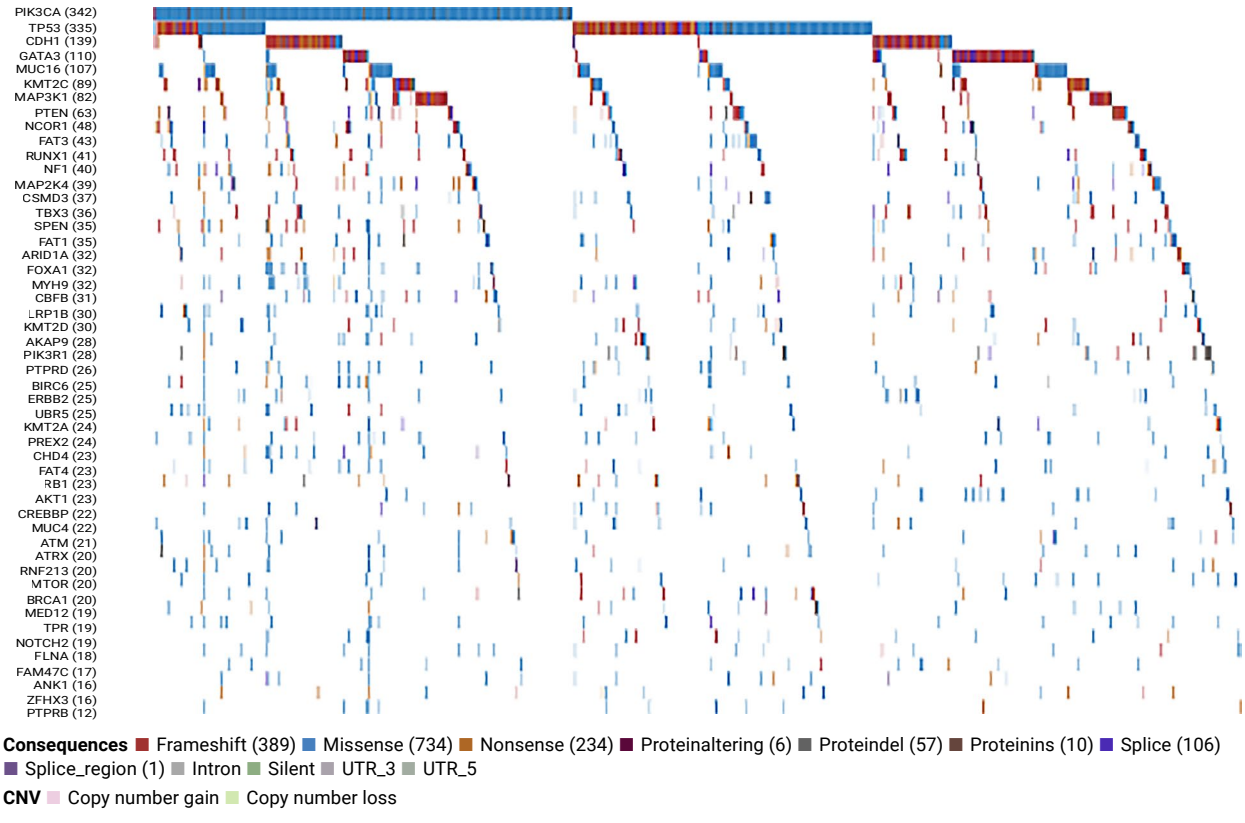

Fig. 7. Mutational profile of breast cancer patients. Age ≥ 45 years

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South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 63-76
https://doi.org/10.37748/2686-9039-2025-6-3-7
https://elibrary.ru/oxfxgi
REVIEW

Lymph nodes as a target for the use of dendritic cell vaccines: modern approaches and prospects

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ABSTRACT

This article provides an overview of current approaches to cancer immunotherapy, with an emphasis on the role of dendritic cells (DCs), lymph nodes (LNs), and innovative methods of vaccine delivery. Immunotherapy using DC-based vaccines represents a promising direction, capable of stimulating a specific immune response against tumor cells and forming long-term immune memory. Tumor-draining lymph nodes (TDLNs) play a key role in immune activation, as they are the sites where dendritic cells present tumor antigens and activate T-cells. In cancer, unlike viral infections, CD8+ T-cell activation occurs in two stages, and the effectiveness of this process depends on signals from the tumor microenvironment, which explains why the immune response to cancer is often weak.

The article also discusses modern strategies for delivering vaccines to lymph nodes, including the use of nanoparticles, bioorthogonal reactions, and photothermally induced materials. These approaches help overcome the "granularity paradox", associated with the need to balance vaccine size for LN penetration and uptake by immune cells. The prospects of adoptive cell therapy using T-cells from TDLNs, as well as the role of exosomes and whole-cell tumor antigens in the development of effective vaccines, are also considered. Combination strategies, such as the use of vaccines together with checkpoint inhibitors (e.g., anti-PD1), demonstrate potential for enhancing antitumor immunity.

The further advancement of cancer immunotherapy requires the integration of new knowledge about the biology of dendritic cells, modern methods of cell engineering, and nanotechnology to create personalized and effective antitumor vaccines.

Keywords: cancer, dendritic cells, lymph nodes, dendritic cell vaccine, nano vaccines, exosomes, neoantigens, personalized medicine

For citation: Frantsiyants E. M., Bandovkina V. A., Moiseenko T. I., Petrova Yu. A., Goroshinskaya I. A., Zhukova G. V., Trepitaki L. K., Surikova E. I. Lymph nodes as a target for the use of dendritic cell vaccines: modern approaches and prospects. South Russian Journal of Cancer. 2025; 6(3): 63-76. https://doi.org/10.37748/2686-9039-2025-6-3-7, https://elibrary.ru/oxfxgi

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Funding: this work was not funded

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 04.04.2025; approved after reviewing 31.07.2025; accepted for publication 14.08.2025

Южно-Российский онкологический журнал. 2025. Т. 6, № 3. С. 63-76
https://doi.org/10.37748/2686-9039-2025-6-3-7
https://elibrary.ru/oxfxgi
3.1.6. Онкология, лучевая терапия

ОБЗОР

Лимфатические узлы как точка приложения при использовании дендритноклеточных вакцин: современные стратегии усиления иммунного ответа

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РЕЗЮМЕ

Статья представляет собой обзор современных подходов к иммунотерапии рака, акцентируя внимание на роли дендритных клеток (ДК), лимфатических узлов (ЛУ) и инновационных методов доставки вакцин. Иммунотерапия с применением вакцин на основе ДК представляет собой перспективное направление, способное стимулировать специфический иммунный ответ против опухолевых клеток и формировать долговременную иммунную память. Дренирующие опухоль лимфатические узлы (TDLN) играют ключевую роль в активации иммунного ответа, так как именно в них происходит презентация опухолевых антигенов дендритными клетками и активация Т-клеток. При раке, в отличие от вирусных инфекций, активация CD8+ Т-клеток происходит в два этапа, и эффективность процесса зависит от сигналов, поступающих из опухолевого микроокружения, что объясняет, почему иммунный ответ на рак часто бывает слабым.
В статье также обсуждаются современные стратегии доставки вакцин в лимфатические узлы, включая использование наночастиц, биоортогональных реакций и фототермически индуцированных материалов. Эти подходы позволяют преодолеть «парадокс гранулярности», связанный с необходимостью баланса между размером вакцин для их проникновения в ЛУ и захвата иммунными клетками.
Рассматриваются перспективы адаптивной клеточной терапии с использованием Т-клеток из TDLN, а также роль экзосом и цельноклеточных опухолевых антигенов в создании эффективных вакцин. Комбинированные подходы, такие как сочетание вакцин с ингибиторами контрольных точек (например, анти-PD1), демонстрируют потенциал для усиления противоопухолевого иммунитета.
Дальнейшее развитие иммунотерапии рака требует интеграции новых знаний о биологии дендритных клеток, современных методов клеточной инженерии и нанотехнологий для создания персонализированных и эффективных противоопухолевых вакцин.

Ключевые слова: рак, дендритные клетки, лимфатические узлы, дендритноклеточная вакцина, нановакцины, экзосомы, неоантигены, персонализированная медицина

Для цитирования: Франциянц Е. М., Бандовкина В. А., Моисеенко Т. И., Петрова Ю. А., Горошинская И. А., Жукова Г. В, Трепитаки Л. К., Сурикова Е. И. Лимфатические узлы как точка приложения при использовании дендритноклеточных вакцин: современные стратегии усиления иммунного ответа. Южно-Российский онкологический журнал. 2025; 6(3): 63-76. https://doi.org/10.37748/2686-9039-2025-6-3-7, https://elibrary.ru/oxfxgi

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Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 04.04.2025; одобрена после рецензирования 31.07.2025; принята к публикации 14.08.2025

BACKGROUND

In recent years, cancer immunotherapy has revolutionized the traditional paradigm of cancer treatment [1]. Interest in tumor vaccines has been growing due to their ability to elicit specific immune responses and to establish durable immune memory [2]. This progress has opened new opportunities for the development of more effective cancer treatment strategies, including the use of dendritic cells (DCs) in immunotherapy.

Immunotherapy using DC-based vaccines represents a biologically rational approach that harnesses the patient's immune system to eliminate malignant cells. The development of DC-based technologies has become possible owing to the study of impaired differentiation and functional alterations of DCs in cancer [3]. DCs, which play a pivotal role in T-cell activation, constitute the foundation of modern immunotherapy strategies aimed at restoring the functional activity of exhausted T cells within the tumor microenvironment [4]. These advances have led to a significant increase in the number of clinical trials of DC-based vaccines over the past three decades. Most of these vaccines are autologous and derived from patient monocytes; however, in recent years, the spectrum of DC subtypes utilized has expanded.

As a rule, tumor antigens are introduced into patient-derived DCs *ex vivo* prior to adjuvant therapy. With the advent of personalized medicine, tumor neoantigens are increasingly being employed to develop individually tailored vaccines. Therapeutic cancer vaccines based on cells utilize different sources of antigens, including autologous tumor cells obtained from the patient, allogeneic cancer cell lines, and autologous antigen-presenting cells (APCs). These vaccines mimic natural immune processes by stimulating an adaptive immune response against tumor antigens [5]. However, for successful immune activation, it is critical to understand the role of lymph nodes (LNs) in this process, as they are strategically positioned immune organs where antigens drain from peripheral tissues.

Purpose of the study: to summarize current advances in the development of cancer immunotherapy strategies, with a particular focus on the role of dendritic cells and lymph nodes in shaping the antitumor immune response.

The Role of Lymph Nodes in the Formation of the Immune Response

LNs harbor various immune cells, including APCs, B lymphocytes, T lymphocytes, and natural killer cells. They are key organs for immune surveillance, regulation, and APC activation [6]. DCs, with their ability to cross-present antigens, play a particularly important role in this process. LNs contain a significant population of phagocytic DCs, well known for their cross-presentation capacity [7]. This refers to the presentation of exogenous antigens to CD8+ T cells via major histocompatibility complex class I (MHC I), which results in the production of cytotoxic T lymphocytes that specifically destroy tumor cells [8]. An increasing body of evidence supports that tumor vaccines targeted to LNs significantly enhance immune responses [9–12].

Tumor-draining lymph nodes (TDLNs) are the first LNs reached by tumor cells through lymphatic vessels. Within TDLNs, DCs capture and present tumor antigens, activating T cells in the paracortical zone of the LN. In other words, TDLNs serve as immune compartments where antitumor immune responses are generated and regulated [13]. This makes TDLNs a critical element in the development of new immunotherapy strategies.

The Two-Step Model of CD8+ T-Cell Activation in Malignancies

Studies by Prokhnevska N, et al. [14] demonstrated that CD8+ T cells, which typically combat infections and tumors, are activated and function differently in neoplasia compared with viral infections. In response to malignant tumors, CD8+ T-cell activation occurs in two stages:

Initial priming: In TDLNs, CD8+ T cells acquire a "stem-like phenotype". This means they remain in an immature state, retaining the capacity for long-term persistence and proliferation. Upon encountering tumor antigens, CD8+ T cells begin proliferating within the TDLN. However, unlike their response to viruses, they do not immediately differentiate into mature effector cells. Instead, they preserve their "stem-like phenotype", which allows them to remain immature for years in human LNs.

Co-stimulatory phase: These immature T cells gradually migrate from the LN into the tumor. Once there, they receive additional signals that trigger

changes in gene activity (transcriptional and epigenetic reprogramming), enabling them to become fully competent "killers" of tumor cells. A range of activating co-stimulatory receptors expressed on CD8+ T cells play a crucial role in shaping T-cell function, such as CD28, NKG2D, 4-1BB, and OX-40. These receptors transmit signals that enhance T-cell responses, ultimately supporting T-cell proliferation and survival, cytokine production, and the generation and maintenance of memory T cells, despite initial activation through distinct signaling pathways. Each receptor appears to induce these functions to varying degrees, and this differential signaling alters gene expression profiles and effector functions, creating a unique activation state [15].

The two-step model of T-cell activation helps explain why anti-PD1 checkpoint blockade therapy does not work for all patients. Tcf1+ CD8+ T cells, which expand in response to anti-PD1, require a CD28 co-stimulatory signal for successful activation [16–18].

CD8+ T cells play a central role in the adaptive immune response to neoplasia. Their abundance and activity within the tumor can serve as important prognostic factors: the higher the infiltration of such cells, the greater the likelihood of patient survival and favorable response to therapy, including checkpoint inhibitors [19, 20].

Table 1. Classification of Current Approaches in Cancer Immunotherapy

Category	Approach		Example	Advantages	Limitations
Antigen modification	Chemical conjugation	Conjugation of antigens with lipids/ polymers to improve delivery	DSPE-OVA-Gel (Zhou L, et al.)	Enhanced lymph node drainage, precise delivery	Standardization challenges
	Nanotechnology-based platforms	Use of nanoparticles for controlled delivery	Phase-transition vaccines (Wang J, et al.), DNA nanoparticles (Zha Y, et al.)	Dynamic size control, enhanced immune response	Potential toxicity, manufacturing complexity
	Alternative antigen sources	Use of whole-cell vaccines, exosomes, iPSCs	α-melittin-NP (Yu X, et al.), Hy-M-Exo (Xu J, et al.)	Broad antigen spectrum, personalization	Tumor heterogeneity, limited efficacy
Нагрузка ДК	*Ex vivo*	Loading dendritic cells with antigens prior to reinfusion	DCvax-IT (Sprooten J, et al.)	Personalized approach, T-cell activation	Labor-intensive, high cost
	In vivo	Targeting dendritic cells in situ (hydrogels, bioorthogonal chemistry)	DSPE-OVA-Gel (Zhou L, et al.), bioorthogonal modification (Qin H, et al.)	Simplified delivery, minimized side effects	Limited efficacy in certain tumor types
Combination therapy	ACT + vaccines	Use of T cells from TDLN or neoantigen-specific T cells	ACT (Okamura K, et al.), OCDC (Li Q, et al.)	Enhanced immune response, overcoming immunosuppression	Low frequency of neoantigen-specific T cells
	Checkpoint inhibitors	Combination with PD-L1/PD-1 blockers	DCvax-IT + anti-PD-L1 (Sprooten J, et al.)	Strengthened antitumor response, overcoming resistance	Side effects, high cost

The tumor microenvironment also plays a critical role in this process. In the absence of specific signals, T cells cannot become effective effectors, which explains why antitumor immune responses are often weak. Importantly, the signals necessary for T cells to become cytotoxic do not occur during the initial priming stage (as in viral infections) but are generated only after T cells migrate into the tumor [14]. This finding emphasizes that the tumor microenvironment is essential for T-cell activation and that its dysfunction renders antitumor immunity ineffective.

Thus, antitumor immune activity is primarily induced in TDLNs, which play a key role in shaping effective antitumor T-cell responses [13, 21, 22]. To date, a wide range of immunotherapeutic approaches for malignant tumors has been developed, summarized in Table 1.

Utilization of Lymph Nodes in Immunotherapy

Currently, the development of cancer immunotherapy with antitumor vaccines is progressing in two directions: the generation of cytotoxic T lymphocyte (CTL) populations *ex vivo* (adoptive cell therapy) and *in vivo* through natural immunological mechanisms occurring within lymph nodes (LNs).

During surgical procedures, tumor-draining lymph nodes (TDLNs) are usually removed together with the primary tumor(s) to eliminate potential residual tumor cells, and the excised LNs are examined for metastatic involvement [23]. It is now well established that extensive LN dissection has provided little clinical benefit in terms of long-term survival for patients with colorectal cancer (CRC) with high microsatellite instability/deficient mismatch repair [24]. It is assumed that preservation of LNs may be beneficial for host immune responses against tumor cells [25]. An interesting study by Okamura K, et al. [26] investigated the potential of non-metastatic LNs as a novel therapeutic option for CRC patients with poor prognosis. The authors questioned whether TDLN removal deprives the body of an important antitumor resource and explored the possibility of using these LNs to improve immunotherapy outcomes in CRC. Okamura K, et al. [26] proposed employing LNs for adoptive cell therapy a method in which T cells are isolated from patient LNs, expanded *ex vivo*, and subsequently reintroduced into the body to exert antitumor effects. Their results demonstrated that non-metastatic LNs could serve as a viable source of cells for this therapeutic strategy.

Adoptive cell therapy using neoantigen-specific T cells represents a promising immunotherapeutic approach. However, the naturally low frequency of these cells in patients makes their detection and screening a challenging task, limiting broad clinical application. To overcome these obstacles, Li Q, et al. [27] proposed a strategy for preparing neoantigen-specific T cells for adjuvant therapy following immunization with dendritic cell (DC) vaccines loaded with oxidized tumor cell lysates (OCDC). Theoretically, this strategy offers several advantages and clinical potential. First, preventive administration of the OCDC vaccine improves the condition of immunosuppressed patients, induces neoantigen-specific immune responses, and facilitates the preparation of neoantigen-reactive T cells by eliminating the need for labor-intensive screening. Second, OCDC vaccine preparation is simple and rapid, and pre-vaccination enables timely initiation of patient treatment, thereby increasing the likelihood of therapeutic success. Moreover, combining OCDC vaccination with neoantigen-reactive T cells enhances efficacy in patients with non-small cell lung cancer, CRC, and melanoma, and this approach could potentially be extended to other immunogenic tumors.

The development of the second direction *in vivo* generation of CTL populations requires novel vaccine delivery strategies aimed at enhancing the immune response.

Modern Strategies for Vaccine Delivery

Given their key role in antitumor immunity, lymph nodes (LNs) are considered a primary target for cancer immunotherapy. Targeted delivery of antigens and adjuvants to LNs enables modulation of their microenvironment, thereby enhancing immune responses, and represents a promising avenue in anticancer vaccine development. Many researchers believe that efficient and precise delivery of tumor vaccines to LNs where they are taken up by antigen-presenting cells (APCs) is a critical determinant for achieving effective antigen presentation and subsequent induction of potent antitumor vaccine effects [6, 10, 28].

A major challenge in this context is the design of vaccine particle size optimized for LN target-

ing. The so-called "granularity paradox" regarding LN delivery and subsequent APC uptake remains a critical issue in the development of effective cancer vaccines. On the one hand, a particle size of 10–100 nm is favorable for lymphatic drainage. Larger particles tend to be trapped in the interstitial matrix, whereas smaller ones are more likely to enter systemic circulation. On the other hand, particles ranging from 50–500 nm are most efficiently internalized by dendritic cells (DCs), with larger sizes stimulating more robust uptake and activation. Thus, an optimal balance is required vaccines must be designed with dimensions that ensure both enhanced lymphatic drainage and efficient DC uptake [6, 29].

To address this issue, Wang J, et al. [29] developed a phase-transition vaccine with dynamically modulated particle size, based on a thermosensitive polymer conjugated with a photothermally responsive molecule and an antigen. Initially small in size (~20 nm), the vaccine drained efficiently into LNs and then transformed *in situ* into larger particles (~480 nm) upon exposure to an external trigger (laser irradiation). This size modulation promoted efficient LN DC endocytosis, ultimately leading to a rapid and robust *in vivo* antitumor response [29].

A different approach was demonstrated by Zha Y, et al. [6], who designed a novel tumor vaccine based on manganese dioxide (MnO_2) nanoparticles for LN delivery. These nanoparticles exhibited an optimal size (~90 nm), facilitating LN penetration. To enhance immune cell uptake, the nanoparticles were coated with short DNA chains, which increased their size. This DNA base-pairing strategy for controlling nanoparticle size, thereby improving antigen presentation and vaccine efficacy, represents a new concept for anticancer vaccine development. Importantly, vaccines must not only reach LNs but also be rapidly internalized by APCs. Otherwise, they may pass through the subcapsular sinus into peripheral LN regions and exit via efferent lymphatic vessels [30]. Nanovaccines meeting both criteria efficient LN drainage and APC endocytosis hold significant promise.

In addition to particle size optimization, Qin H, et al. [31] proposed direct LN targeting via chemical modification of lymphatic endothelial cell surfaces (bioorthogonal reaction). Their results demonstrated improved delivery of encapsulated antigens and adjuvants into LNs, leading to a stronger *in vivo* CD8+ T-cell response. This strategy resulted in markedly enhanced therapeutic efficacy, including

Table 2. Comparison of vaccine delivery strategies to lymph nodes

Strategy	Particle Size	Mechanism of Action	Efficacy	Clinical Potential
Phase-transition vaccines	20–480 nm	Dynamic size alteration under external stimuli (laser)	High, enhanced dendritic cell endocytosis	Flexibility, controllable activation
DNA-functionalized nanoparticles	~90 nm	Size control through DNA base-pairing	High, optimal balance of drainage and uptake	ersonalization, low toxicity
Hybrid nanovesicles (Hy-M-Exo)	30–150 nm	Combination of tumor-derived exosomes and dendritic cell membranes	Very high, T-cell activation and Treg suppression	Multifunctionality
Bioorthogonal modificatio	–	Chemical alteration of lymphatic vessels to improve delivery	Moderate, tumor-type dependent	Broad spectrum of applications

prolonged survival in mice with metastatic melanoma [31].

A summary of the approaches discussed in this section is provided in Table 2.

Nanovaccines

Several recent studies have shown that the delivery of nanovaccines to lymph nodes (LNs) activates both humoral and cellular immune responses to combat neoplasia [32]. Somatic mutations generate specific neoantigens – unique tumor antigens that play a crucial role in antitumor immune responses [33, 34]. However, the number of available tumor-associated antigens (TAAs) necessary for vaccine development is limited for most tumor types [35], and the prediction and identification of individual tumor-associated neoantigens remain challenging due to the complexity of the required technologies [33, 36]. To overcome the lack of knowledge about specific tumor antigens and to ensure accurate delivery to LNs, various approaches have been explored.

Adaptive immune responses rely on the ability of mature dendritic cells (DCs) to migrate to LNs for further antigen presentation. Considering this, Zhou L, et al. [37] developed a DSPE-ovalbumin (DSPE-OVA) peptide using one-step chemical crosslinking of DSPE-PEG and the model antigen peptide OVA. This peptide accumulates in lymphoid organs through interaction with endogenously migrated DCs. To enhance antigen uptake, the authors created an injectable DSPE-OVA hydrogel (DSPE-OVA-Gel), which serves as a local environment for vaccine transport via DCs. The hydrogel is composed of pH-sensitive DSPE-OVA, granulocyte-macrophage colony-stimulating factor (GM-CSF) to recruit and activate DCs, and porous PLGA (polylactide-co-glycolide) microspheres that facilitate cell attachment. Upon recruitment, the DSPE-OVA hydrogel efficiently integrates into DC membranes due to the high affinity of the lipophilic DSPE tail for cell membranes, thereby enhancing antigen uptake. This process ensured a high concentration of OVA without damaging the membrane or disrupting DC signal transmission. Owing to the natural ability of mature DCs to migrate to LNs, OVA-loaded cells effectively reached their target. In the acidic LN microenvironment, OVA was released from the cell surface and delivered to local APCs. This study demonstrates that an injectable combined hydrogel vaccine significantly enhances antitumor immunity by ensuring precise antigen delivery to LNs and stimulating a robust adaptive immune response.

To address the weak immunoreactivity of LNs caused by inefficient stimulation of cytotoxic T lymphocytes, Liu M, et al. [38] developed a nanovaccine mimicking high-density lipoproteins (HDLs), loaded with the chemotherapeutic drug docetaxel. This platform represents a system for delivering chemotherapy into the tumor microenvironment (glioblastoma). The results showed that dying tumor cells released tumor antigens, which were subsequently captured *in situ* by DCs, initiating the activation of antigen-specific CD8+ T cells that directly induced tumor cell death. The authors examined the efficiency of LN delivery and DC uptake of the nanoparticles using fluorescence imaging and flow cytometry. The optimized nanovaccine facilitated simultaneous delivery of antigens and adjuvants to LNs and sustained antigen presentation by DCs, which resulted in a long-term immune response characterized by increased cytotoxic lymphocyte frequency in lymphoid organs and tumor tissue. Immunization with the nanovaccine significantly suppressed tumor formation and growth and enhanced the therapeutic efficacy of immune checkpoint inhibitors, particularly in highly malignant melanoma models in mice.

Compared with vaccines based on specific tumor antigens, whole-cell tumor vaccines contain a broad spectrum of antigens, thereby avoiding the costly and labor-intensive process of TAA (neoantigen) identification for a specific tumor type. Importantly, whole-cell tumor vaccines have the potential to elicit a stronger antitumor immune response, markedly reducing the likelihood of tumor development and recurrence. Based on this concept, Yu X, et al. [36] hypothesized that the ideal LN-targeted nanovaccine should employ the full spectrum of tumor antigens rather than individual neoantigens or model antigens. This approach would enable a sustained immune response against multiple tumor antigen epitopes by activating both CD4+ and CD8+ tumor-specific T cells. The authors discovered that α-melittin-NP, a peptide-phospholipid scaffold mimicking

high-density lipoproteins (HDLs), could serve as an effective nanovaccine even without specific tumor antigens or adjuvants. On the one hand, α-melittin-NP retained the cytotoxic effect of melittin, inducing tumor antigen release at the injection site. On the other hand, α-melittin-NP of optimal size could efficiently penetrate LNs and acti vate local APCs. In experiments using a bilateral B16F10 melanoma mouse model, administration of α-melittin-NPs as a whole-cell nanovaccine induced a systemic immune response, resulting in suppression of primary tumor growth and even complete regression of distant tumors [36].

Use of Tumor Cell Lysates as a Source of Antigens

In several studies, tumor cell lysates, which contain fragments of tumor cells released during chemotherapy and irradiation, have been used as TAAs [39, 40]. However, tumor cell lysates with low immunogenicity may induce immune tolerance and reduce the efficiency of antigen uptake [41]. Moreover, the types and quantities of antigens released as a result of chemotherapy and irradiation vary among patients, making standardization of this approach difficult. Therefore, there is a need for novel strategies for vaccine development that are not dependent on specific TAAs.

Exosomes as an Alternative Source of Antigens

In recent years, exosomes membrane vesicles measuring 30–150 nm secreted by cells into the extracellular environment and involved in intercellular communication have gained increasing importance in the development of antitumor vaccines.

Tumor-derived exosomes have been found to contain multiple TAAs and neoantigens and effectively deliver them to DCs, thereby stimulating tumor-specific immunity [42]. Importantly, tumor exosomes demonstrated superior antitumor efficacy compared with tumor lysates as a source of antigens [43]. In this study, exosome-pulsed DCs induced significant inhibition of hepatocellular carcinoma (HCC) growth and a stronger immune response characterized by higher T lymphocyte counts, increased interferon-γ levels, and reduced interleukin-10 and transforming growth factor-β levels within tumor tissues in both ectopic and orthotopic murine models of HCC, compared with DCs pulsed with tumor lysates. Furthermore, the use of tumor-derived exosomes not only mediated specific cytolysis of HCC cells but also elicited cross-protective effects against pancreatic cancer cells [43]. Thus, this combined approach leveraging a complex array of tumor antigens with efficient targeted delivery to LNs, where APCs (DCs) and effector T cells interact renders tumor-derived exosomes a highly promising tool for the development of effective antitumor vaccines.

Hybrid Nanovesicles (Hy-M-Exo)

Building upon this concept, Xu J, et al. [44] developed hybrid nanovesicles (Hy-M-Exo), created by fusing tumor-derived exosomes with DC-derived membrane vesicles and incorporating monophosphoryl lipid A. The resulting Hy-M-Exo contained proteins characteristic of DCs, such as CD86 (an activation marker) and CCR7 (a receptor responsible for LN homing), and showed significant effects within the paracortical LN region, where DCs and T cells are located. Hy-M-Exo induced robust DC activation and stimulated T-cell immune responses in LNs, leading to strong inhibition of head and neck squamous cell carcinoma growth in mice. Additionally, the authors found that Hy-M-Exo could suppress immunosuppressive regulatory T cells, further enhancing the immune response. These findings highlight the potential of hybrid nanovesicles to amplify immune responses and inhibit tumor growth. The authors also proposed that delivering antitumor agents into LNs via the CCR7-CCL21/19 pathway (a mechanism regulating LN homing) represents a promising strategy [44].

Dendritic Cell-Based Vaccines

In parallel, immune surveillance of poorly immunogenic tumors can be enhanced through dendritic cell (DC)-based vaccines designed to stimulate antigen-specific immune responses, for example, by using targeted therapies directed at myeloid cells. Myeloid cells (including monocytes, macrophages, and DCs) are key components of the tumor microenvironment (TME), performing diverse functions ranging from immunosuppressive to immunostimulatory. The myeloid cell pool is highly heterogeneous comprising monocytes, macrophages, DCs, and granulocytes and exhibits remarkable plasticity, with the capacity to differentiate into dif-

ferent phenotypes depending on TME signals [45]. Perez CR and De Palma M [46], investigating the role of DC subtypes in the TME, placed particular emphasis on conventional type 1 DCs. These cells are able to migrate between lymphoid and non-lymphoid tissues, thereby regulating cytokine and chemokine distribution, which influences both inflammation and lymphocyte trafficking. DCs are considered uniquely capable of cross-presentation, i. e., presenting exogenous antigens to CD8+ T cells in lymph nodes [47].

Despite their immunogenic potential, DC-based vaccines have not yet achieved widespread clinical application due to difficulties in standardization and limited efficacy in some patients. In this context, Sprooten J, et al. [48] found that the major limitation of human DC-based vaccines is the diversity of their functional states rather than the process of maturation. The authors identified the most immunogenic DC vaccine state, which correlated with effective antigen-specific immunity and favorable clinical responses in patients with various tumors. Surprisingly, their preclinical vaccine DCvax-IT performed suboptimally: instead of promoting effector T-cell formation, it increased the number of PD-L1$^+$ lymphoid-associated macrophages (LAMs) via activation of the type I interferon pathway and associated genes. Moreover, DCvax-IT stimulated pre-existing tumor-associated macrophages (TAMs) expressing PD-L1, thereby suppressing T-cell activity and creating an immunosuppressive environment. This mechanism was identified as a key factor underlying resistance to DCvax-IT. Importantly, combining DCvax-IT with PD-L1 inhibitors successfully controlled tumors in immunodeficient mice phenotypic analogues of human tumors with T-cell deficiency [48]. These findings demonstrate the potential to enhance the efficacy of immunological interventions in human tumors with impaired effector cell function.

Induced Pluripotent Stem Cells (iPSCs)

In addition to tumor lysates and tumor-derived exosomes, induced pluripotent stem cells (iPSCs) are also being explored as a promising source of tumor antigens. iPSCs express a broad spectrum of tumor-associated antigens and can induce immune responses that prevent the development of various tumor types. However, iPSCs face certain limitations, including potential oncogenicity, difficulties in delivery to lymph nodes and the spleen, and limited efficacy in suppressing tumor growth. Wang R, et al. [49] evaluated the antitumor effects of exosomes derived from iPSCs and incubated with DCs (DC+EXO) in murine melanoma models. The immune responses induced by the DC+EXO vaccine were assessed both *in vitro* and *in vivo* by analyzing T-cell activation and cytokine

Table 3. Alternative sources of tumor antigens

Source	Description	Advantages	Limitations
Tumor cell lysates	Cell fragments after chemotherapy/ irradiation	Broad spectrum of antigens	Low immunogenicity, variability among patients
Exosomes	Membrane vesicles (30–150 nm) carrying tumor antigens	Natural carriers, high biocompatibility	Isolation and standardization challenges
iPSCs	Induced pluripotent stem cells	Broad spectrum of antigens, potential for personalized therapy	Potential oncogenicity, difficulties in delivery
Hybrid nanovesicles (Hy-M-Exo)	Combination of tumor-derived exosomes and DC membranes	High immunogenicity, suppression of regulatory T cells (Treg)	Complex manufacturing process

levels. After DC+EXO vaccination, T cells isolated from the spleen exhibited high *in vitro* cytotoxicity against melanoma, lung cancer, breast cancer, and colorectal cancer cell lines. Moreover, DC+EXO vaccination induced long-term T-cell responses and prevented melanoma recurrence, while significantly suppressing primary melanoma growth and reducing lung metastases. Finally, biocompatibility studies confirmed that DC+EXO vaccination did not cause significant toxicity to normal cells or tissues in mice.

As shown above, multiple sources of tumor antigens are currently being investigated for the development of antitumor vaccines, each with specific advantages and limitations (Table 3).

Platforms for cell therapy

A promising avenue to increase the efficacy of tumor vaccines is the use of alternative mechanisms of antitumor cytotoxicity that do not rely exclusively on CD8+ T-cell activity. Ghasemi A, et al. [50] described a cell therapy platform based on mouse or human dendritic cell progenitors (DCPs), genetically engineered to express two immunostimulatory cytokines IL-12 and FLT3L. These modified DCPs differentiated into type 1 conventional DCs (cDC1s) and were able to suppress tumor growth, including melanoma and spontaneously arising liver tumors in mice, without prior antigen loading or myeloablative conditioning. The antitumor response resulted from synergy between IL-12 and FLT3L and was associated with infiltration and activation of natural killer (NK) cells and T cells, polarization of macrophages toward an M1 phenotype, and induction of ischemic necrosis in tumors. Importantly, the immunity induced was dependent on endogenous expansion of cDC1s and interferon-γ signaling, but not on CD8+ T-cell cytotoxicity. Moreover, cytokine-expressing DCPs interacted effectively with GD2-targeted CAR-T cells, enhancing their proliferation and cytotoxicity against intracranial gliomas in mice, highlighting the potential of combining DCPs with adoptive cell therapy.

CONCLUSION

It is now clear that lymph nodes (LNs) not only maintain immune homeostasis but also act as central hubs for dendritic cell-mediated antitumor immunity. Recognizing LNs as therapeutic targets has enabled modern immunotherapy to advance toward the development of innovative dendritic cell vaccines (DCVs). Current strategies aim to improve precision of vaccine delivery into LNs, either by modulating particle size or by modifying lymphatic vessels, and to diversify sources of tumor antigens for dendritic cell presentation. The integration of tumor cell lysates, exosomes, hybrid nanovesicles, dendritic cell-based vaccines, induced pluripotent stem cells, and cell therapy platforms provides new opportunities to strengthen immune responses, minimize side effects, and enhance personalization. Combination approaches, including checkpoint blockade, offer a way to control tumors with effector-cell deficiencies and to overcome resistance of poorly immunogenic cancers. Despite the progress, challenges remain potential toxicity, selection of the most effective tumor antigens, antigen delivery, standardization of personalized vaccines, and large-scale production. Nevertheless, the diversification of dendritic cell-based vaccine strategies is expected to enable effective immunotherapy across the wide heterogeneity of malignancies and clinical contexts.

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Zhukova G. V. – research concept, follow on revision of the text;
Trepitaki L. K. – research concept, follow on revision of the text;
Surikova E. I. – follow on revision of the text, final conclusion.

South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 77-78
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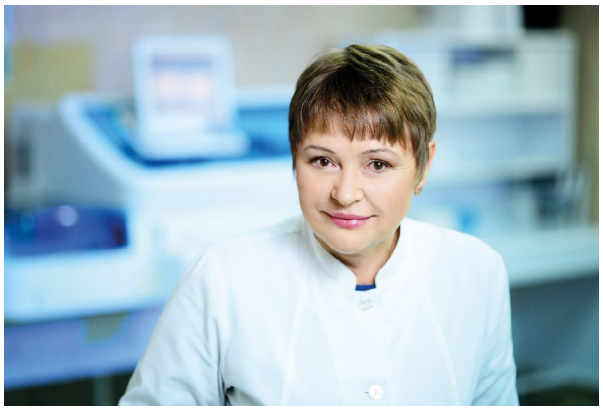
ANNIVERSARY

On the 70th Anniversary of Elena M. Frantsiyants



Elena M. Frantsiyants, Doctor of Biological Sciences, Professor, Deputy General Director for Scientific Work at the National Medical Research Center for Oncology, and Honored Healthcare Worker of the Russian Federation, celebrate her 70th birthday on September 23, 2025.

Dr. Frantsiyants is a distinguished scientist, pathophysiologist, and biochemist whose contributions to the understanding of the fundamental mechanisms of tumor development are invaluable. Born in Taganrog into a family of educators, she chose her path early, dedicating her life to science. After graduating from the Faculty of Biology and Soil Science at Rostov State University in 1978, Dr. Frantsiyants began her professional career at the Central Research Laboratory of Rostov State Medical University. In 1985, she joined the Rostov Scientific Research Oncological Institute, where she progressed from senior researcher to head of the Biochemical Laboratory (1990–2000), and later to head of the Laboratory for the Study of the Pathogenesis of Malignant Tumors (2014–2017). Since 2017, she has served as Deputy General Director for Science.

Her scientific interests center on the pathogenesis of tumors, particularly the role of antioxidant systems in carcinogenesis and tumor growth. Her pioneering research has uncovered novel aspects of metabolic restructuring that contribute to tumor initiation and progression. These findings laid the groundwork for the introduction of biochemical markers into clinical practice for predicting disease course and evaluating antitumor treatment efficacy. Moreover, she developed a set of biochemical techniques for the individualization of targeted cancer therapies. Dr. Frantsiyants has also made significant contributions to understanding hormonal imbalances and mediator dysfunctions in the development of malignancies.

Currently, she leads research at the National Medical Research Center for Oncology focusing on mitochondrial dysfunction in malignant tumor growth, and the experimental development of targeted therapies and dendritic cell vaccines.

Her extensive body of work includes over 1,000 scientific publications, 205 patents, and 8 monographs, such as Lipid Peroxidation in the Pathogenesis of Tumor Disease (1995), Complex Treatment of Primary Malignant Glial Tumors of the Cerebral Hemispheres (2014), Cytological, Morphological and Immunohistochemical Diagnostics of Central Nervous System Tumors (2015), Pathogenetic Aspects of Metastatic Liver Damage: An Experimental Study (2022), and Neuroendocrine and Metabolic Aspects of Melanoma Pathogenesis: An Experimental and Clinical Study (2023).

Over her more than 40-year tenure at the National Medical Research Center of Oncology, Dr. Frantsiyants has emerged as a leading expert in basic oncology research. She serves as a scientific consultant, supervises graduate and doctoral candidates (7 Ph.D. and 7 doctoral dissertations), and holds positions as Deputy Chair of the Academic Council and member of the Dissertation Council at the National Medical Research Center for Oncology.

Professor Frantsiyants is not only a brilliant and passionate scientist endowed with deep knowledge, intellectual rigor, and analytical prowess, but also a person of warmth, grace, and the rare ability to balance scientific achievement with a fulfilling family life.

The staff of the National Medical Research Center for Oncology and the editorial board of the South Russian Journal of Cancer extend their heartfelt congratulations to Dr. Frantsiyants on her anniversary! We wish you continued health, prosperity, new scientific accomplishments, and boundless energy in the pursuit of your goals. May your research continue to serve society and earn the recognition it so richly deserves. You have rightfully earned deep respect and admiration from your colleagues and students alike!

South Russian Journal of Cancer. 2025. Vol. 6, No. 3. P. 79-80
https://elibrary.ru/otenrc

ANNIVERSARY

On the 55th Anniversary of Oleg I. Kit

On August 31, 2025, the scientific community and colleagues sincerely congratulate Oleg Ivanovich Kit, Academician of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, and General Director of the National Medical Research Centre for Oncology, on his 55th anniversary!

Dr. Oleg I. Kit is an outstanding oncologist and a recognized leader in the field of healthcare organization and higher medical education. His 30-year scientific and practical activity at the National Medical Research Centre for Oncology is reflected in more than 1,000 publications, including 21 monographs, 15 study guides, and 236 patents of the Russian Federation.

Dr. Kit is the Editor-in-Chief of the scientific and practical journal South Russian Journal of Cancer, which is reviewed by the Higher Attestation Commission. He is also a member of the editorial boards of the journals Voprosy Onkologii, Russian Journal of Oncology, Oncology. P. A. Herzen Journal of Oncology, Problems of Hematology/Oncology and Immunopathology in Pediatrics, Biomedicine, Science in the South Russia, and Cardiometry.

Under the leadership of Dr. Kit, over a 15-year period, an authoritative scientific school in the field of oncology and oncosurgery was formed, oriented toward the development and implementation of innovative surgical approaches and treatment methods based on an in-depth study of the molecular-genetic, pathogenetic, and immunological mechanisms of malignant neoplasms. He is the initiator of the introduction of organ-preserving, reconstructive, and minimally invasive operations, as well as the improvement of surgical techniques aimed at the prevention of postoperative complications.

Dr. Kit made a significant contribution to the creation of modern infrastructure for oncological research, including the organization of a unified pathological and anatomical center and the establishment of a comprehensive depository of tumor samples and DNA and RNA isolated from them, which made it possible to conduct large-scale genetic research. Under his leadership, studies are being conducted on the molecular profiling of pancreatic neuroendocrine tumors, the identification of prognostic markers of cardiotoxicity, the determination of molecular-genetic predictors of the course of gliomas, as well as preclinical trials of new antitumor agents.

For the development and implementation of an interdisciplinary strategy in the treatment of colorectal cancer, in 2016 he was awarded the Prize of the Government of the Russian Federation in the field of science and technology and was given the title of "Laureate of the Prize of the Government of the Russian Federation in the field of science and technology".

As the Chief Freelance Oncologist of the Ministry of Health of the Russian Federation in the Southern Federal District, he devotes great attention to raising the professional level of physicians. For the development of oncological care and the improvement of cancer treatment in the Southern Federal District, in 2020 Dr. Kit was awarded the N. N. Trapeznikov Medal "For Contribution to the Development of Oncology Service".

Since 2015, Dr. Kit has been Head of the Department of Oncology of Rostov State Medical University.

Dr. Kit is the Chairman of the Academic Council and the Dissertation Council for the defense of doctoral and candidate dissertations at the National Medical Research Centre. Under his supervision, 21 doctoral and 23 candidate dissertations have been successfully defended.

The large-scale work of O. I. Kit in the field of education, science, practical medicine, organizational and public activity has been recognized by numerous state, ministerial, and public awards, including the badge of distinection "Excellence in Healthcare", the Medal of the Order “For Merit to the Fatherland" II degree, the Medal "For Merit to Russian Healthcare", the Medal of the Order "For Merit to the Rostov Region", and a Letter of Gratitude from the President of the Russian Federation.

His high professionalism, sense of duty, attentive and benevolent attitude toward people have earned him authority and respect among the scientific community, colleagues, students, and patients.

The staff of the National Medical Research Centre for Oncology and the editorial board of the South Russian Journal of Cancer sincerely congratulate Dr. Kit on his anniversary! We wish You good health, well-being, inexhaustible energy, new scientific achievements, and continued success in your responsible and multifaceted work! May your knowledge and experience continue to serve the advancement of Russian science and healthcare.

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South Russian Journal of Cancer

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Южно-Российский
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