УДК 618.19-006.6-033.2:616.428:577.218]-073.916
https://doi.org/10.20538/1682-0363-2025-1-14-21

Radionuclide imaging of HER2/neu expression in metastatic axillary lymph nodes in breast cancer patients: comparing the efficacy of [99mTc]Tc-ADAPT6 and [^{99m}Tc]Tc-(HE)$_3$-G3

Bragina O.D.[1, 2], Tashireva L.A.[1], Garbukov E.Yu.[1], Vostrikova M.A.[1], Romanova A.A.[1], Deyev S.M.[2, 3, 5], Borodina M.E.[4], Chernov V.I.[1, 2, 5]

[1] *Cancer Research Institute, Tomsk National Research Medical Center (NRMC)*
5, Kooperativny Str., Tomsk, 634009, Russian Federation

[2] *National Research Tomsk Polytechnic University (NR TPU)*
30, Lenina Av., Tomsk, 634050, Russian Federation

[3] *Shemyakin – Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, 16/10, Miklukho – Maklaya Str., Moscow, 117997, Russian Federation*

[4] *P. Hertsen Moscow Oncology Research Institute*
3, 2nd Botkinsky Proyezd Str., Moscow, 125284, Russian Federation

[5] *National Research Center «Kurchatov Institute»*
1, Akademika Kurchatova Str., Moscow, 123098, Russian Federation

ABSTRACT

Aim. To conduct a direct comparative analysis of single-photon emission computed tomography (SPECT-CT) with [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-(HE)$_3$-G3 in patients with HER2-positive breast cancer (BC) with axillary lymph node metastases.

Materials and methods. The analysis included 8 patients with HER2-positive BC with axillary lymph node metastases before the systemic treatment. All patients were injected with [^{99m}Tc]Tc-ADAPT6 (500 μg) and [^{99m}Tc]Tc-(HE)$_3$-G3 (3,000 μg) with an interval of 3–4 days. The SPECT-CT scans of the chest and upper abdomen were performed after 2 hours for [^{99m}Tc]Tc-ADAPT6 and after 4 hours for [^{99m}Tc]Tc-(HE)$_3$-G3. The accumulation of radiopharmaceuticals was assessed by measuring the *maximum standardized uptake* values (SUV$_{max}$) in metastatic axillary lymph nodes, projections of the contralateral axillary lymph nodes, liver, latissimus dorsi muscle, and spleen. Additionally, mALN-to-background and mALN-to-reference organs ratios were calculated for each patient.

Results. Comparison of the mALN-to-background ratio revealed the advantage of [99mTc]Tc-ADAPT6 (38.93 (16.56–56.02)) over [^{99m}Tc]Tc-(HE)$_3$-G3 (19.39 (8.43–34.52)), p = 0.0391. The comparative analysis of the accumulation of the studied radiopharmaceuticals in the reference organs demonstrated higher SUV$_{max}$ for [^{99m}Tc]Tc-(HE)$_3$-G3 in the liver and spleen (4.44 (2.85–9.08) and 2.47 (1.28–4.41), respectively) than for [99mTc]Tc-ADAPT6 (2.98 (1.96–3.65) and 0.43 (0.14–0.62), respectively), p = 0.01 and p = 0.04. Comparison of the SUV$_{max}$ ratios in mALN and reference organs showed higher values of mALN / spleen for [99mTc]Tc-ADAPT6 (5.93 (1.04–11.85)) compared to [^{99m}Tc]Tc-(HE)$_3$-G3 (1.83 (0.46–4.54)), p = 0.02.

Conclusion. According to the results of the performed analysis, the diagnostic advantage of [99mTc]Tc-ADEPT6 for the detection of HER2/neu expression in metastatic lymph nodes in breast cancer patients was revealed.

Keywords: breast cancer, ADAPT6, DARPinG3, radionuclide diagnosis

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

✉ *Bragina Olga D.,* bragina_od@mail.ru

Source of financing. The work was performed at the expense of the grant from the Russian Ministry of Science and Higher Education No. 075-15-2024-536.

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study.

For citation: Bragina O.D., Tashireva L.A., Garbukov E.Yu., Vostrikova M.A., Romanova A.A., Deyev S.M. , Borodina M.E., Chernov V.I. Radionuclide imaging of HER2/neu expression in metastatic axillary lymph nodes in breast cancer patients: comparing the efficacy of [99mTc]Tc-ADAPT6 and [^{99m}Tc]Tc-(HE)3-G$_3$. *Bulletin of Siberian Medicine.* 2025;24(1):14–21. https://doi.org/10.20538/1682-0363-2025-1-14-21.

Радионуклидная визуализация экспрессии HER2/NEU в метастатических аксиллярных лимфатических узлах у больных раком молочной железы: сравнение эффективности препаратов [^{99M}TC]TC-ADAPT6 и [^{99M}TC]TC-(HE)$_3$-G3

Брагина О.Д.[1, 2], Таширева Л.А.[1], Гарбуков Е.Ю.[1], Вострикова М.А.[1], Романова А.А.[1], Деев С.М.[2, 3, 5], Бородина М.Е.[4], Чернов В.И.[1, 2, 5]

Научно-исследовательский институт (НИИ) онкологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634009, г. Томск, пер. Кооперативный, 5

[2] *Национальный исследовательский Томский политехнический университет (НИ ТПУ)*
Россия, 634050, г. Томск, пр. Ленина, 30

[3] *Институт биоорганической химии (ИБХ) им. акад. М.М. Шемякина и Ю.А. Овчинникова Российской академии наук (РАН)*
Россия, 117997, г. Москва, ГСП-7, ул. Миклухо-Маклая, 16/10

[4] *Московский научно-исследовательский онкологический институт (МНИИОИ) им. П.А. Герцена – филиал НМИЦ радиологии*
Россия, 125284, г. Москва, 2-й Боткинский пр-д, 3

[5] *Национальный исследовательский центр (НИЦ) «Курчатовский институт»*
Россия, 123098, г. Москва, пл. Академика Курчатова, 1

РЕЗЮМЕ

Цель**.** Провести прямой сравнительный анализ данных однофотонной эмиссионной компьютерной томографии с препаратами [^{99m}Tc]Tc-ADAPT6 и [^{99m}Tc]Tc-(HE)$_3$-G3 у больных раком молочной железы (РМЖ) с HER2-позитивными метастазами в аксиллярные лимфатические узлы.

Материалы и методы. В анализ включены восемь больных РМЖ с HER2-позитивными метастазами в аксиллярные лимфатические узлы (мАЛУ) до начала системного лечения. Всем больным последовательно проводилось введение препаратов [^{99m}Tc]Tc-ADAPT6 (500 мкг) и [^{99m}Tc]Tc-(HE)$_3$-G3 (3 000 мкг) с интервалом 3–4 дня. Однофотонная эмиссионная компьютерная томография органов грудной клетки и верхнего этажа брюшной полости проводилась через 2 ч для [^{99m}Tc]Tc-ADAPT6 и через 4 ч для [^{99m}Tc]Tc-(HE)$_3$-G3. Оценка накопления соединений выполнялась путем измерения максимального стандартного захвата (SUV_{max}) в метастатических аксиллярных лимфоузлах, проекции контралатеральной аксиллярной области, проекций печени, широчайшей мышцы спины и селезенки. Дополнительно у каждой больной рассчитывались такие параметры, как мАЛУ/фон и мАЛУ/референсные органы.

Результаты. Сравнение соотношения мАЛУ/фон выявило преимущество препарата [^{99m}Tc]Tc-ADAPT6 (38,93 (16,56–56,02)) над [^{99m}Tc]Tc-(HE)$_3$-G3 (19,39 (8,43–34,52)), p = 0,0391. Сравнительный анализ аккумуляции изучаемых радиофармпрепаратов в референсных органах продемонстрировал более высокий SUV_{max} в печени и селезенке для [^{99m}Tc]Tc-(HE)$_3$-G3 (4,44 (2,85–9,08) и 2,47 (1,28–4,41) соответственно), чем при использовании [^{99m}Tc]Tc-ADAPT6 (2,98 (1,96–3,65) и 0,43 (0,14–0,62) соответственно), p = 0,01 и p = 0,04. Сравнение соотношений SUVmax в мАЛУ и референсных органах показало более высокие

значения параметра мАЛУ/селезенка для препарата [^{99m}Tc]Tc-ADAPT6 (5,93 (1,04–11,85)) по сравнению с [^{99m}Tc]Tc-(HE)$_3$-G3 (1,83 (0,46–4,54)), p = 0,02.

Заключение. По результатам выполненного анализа выявлено диагностическое преимущество препарата [^{99m}Tc]Tc-ADAPT6 для детекции HER2 статуса в метастатических лимфатических узлах у больных РМЖ.

Ключевые слова: рак молочной железы, ADAPT6, DARPinG3, радионуклидная диагностика

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работы поддержаны грантом Министерства науки и высшего образования РФ № 075-15-2024-536.

Соответствие принципам этики. Все лица подписали информированное согласие на участие в исследовании. Исследование одобрено комитетом по биомедицинской этике НИИ онкологии Томского НИМЦ (протокол № 26 от 15.02.2022, протокол № 4 от 04.03.2022).

Для цитирования: Брагина О.Д., Таширева Л.А., Гарбуков Е.Ю., Вострикова М.А., Романова А.А., Деев С.М., Бородина М.Е., Чернов В.И. Радионуклидная визуализация экспрессии HER2/NEU в метастатических аксиллярных лимфатических узлах у больных раком молочной железы: сравнение эффективности препаратов [^{99M}TC]TC-ADAPT6 и [^{99M}TC]TC-(HE)$_3$-G3. *Бюллетень сибирской медицины.* 2025;24(1):14–21. https://doi.org/10.20538/1682-0363-2025-1-14-21.

INTRODUCTION

Determining the status of regional lymph nodes is a mandatory step in the pre-hospital diagnosis of patients with breast cancer (BC). This information is primarily needed for planning the optimal scope of local and systemic treatment to achieve better overall and relapse-free survival rates [1]. Unfortunately, existing diagnostic methods, such as ultrasound (US), mammography, and computed tomography (CT), are not optimal and have a relatively high probability of false-positive and false-negative results [2–4].

For example, it has been proven that the sensitivity and specificity of US directly depend on the biological subtype of the tumor. According to R. Helfgott et al., the minimum sensitivity level of US in assessing the lymph node status was observed in patients with luminal HER2-negative BC (less than 40%), while the maximum sensitivity was noted for triple-negative and HER2-positive subtypes (68.8 and 71.4%, respectively) [3]. Moreover, rapidly evolving technologies and demands in clinical medicine create the necessity not only for anatomical detection, but also for the assessment of the molecular profile of the tumor to personalize systemic therapy in BC patients [1, 2].

Studying the molecular profile of identified metastatic changes is particularly relevant not only due to the need for additional invasive (sometimes difficult) diagnostic procedures, but also in light of existing intertumoral heterogeneity, which causes differences in the molecular characteristics of the primary tumor and metastatic foci [5]. According to the literature, the discrepancy in the receptor status between the primary tumor and regional lymph nodes can reach 30% for estrogen receptors, 20% for progesterone receptors, and 15% for HER2/neu [6].

One of the potential solutions to this clinical problem is exploring the capabilities of targeted radionuclide imaging for a specific molecular target [7]. Among “targeting” modules, alternative scaffold proteins have demonstrated the highest efficacy. These proteins are characterized by high specificity and affinity for the target antigen, low toxicity, and rapid clearance from the patient’s body after administration, thereby significantly reducing the time from the injection to the start of the diagnostic procedure [8]. One of the options for this targeted interaction could be human epidermal growth factor receptor 2 (HER2/neu), whose overexpression occurs in 20–30% of BC patients and requires the use of targeted therapy [9].

Phase II clinical trials with [^{99m}Tc]Tc-ADAPT6 (ClinicalTrials.gov Identifier: NCT05412446) and [^{99m}Tc]Tc-(HE)$_3$-G3 (ClinicalTrials.gov Identifier: NCT15122022) were conducted at the Department of Radionuclide Therapy and Diagnostics of Cancer Research Institute of Tomsk NRMC and assessed HER2/neu expression in metastatic axillary lymph nodes (mALNs) in patients with BC. The results indicated the efficacy of both agents ($p < 0.05$, Mann – Whitney test) [10, 11].

The aim of this study was to conduct a direct comparative analysis of SPECT-CT data using [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-$(HE)_3$-G3 in patients with HER2-positive BC and mALNs.

MATERIALS AND METHODS

The analysis included 8 patients with HER2-positive BC and metastases in the axillary lymph nodes prior to the initiation of systemic treatment. All patients were injected with [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-$(HE)_3$-G3 with an interval of 3–4 days.

Morphological and immunohistochemical studies of biopsy material obtained from the axillary lymph node tissue were performed in all patients. HER2/neu expression was considered positive if the immunohistochemistry (IHC) showed a score of 3+ or a score of 2+ with positive fluorescence *in situ* hybridization (FISH). Cases with receptor expression of 0 and 1+ by IHC were classified as negative, in accordance with the ASCO/CAP (American Society of Clinical Oncology and the College of American Pathologists) criteria from 2018 [12]. The size of the lymph nodes was measured using US before the initiation of systemic treatment and biopsy collection.

[^{99m}Tc]Tc-$(HE)_3$-G3 and [^{99m}Tc]Tc-ADAPT6 were prepared using the previously described tricarbonyl radiolabeling method under sterile conditions at the Department of Radionuclide Therapy and Diagnostics of Cancer Research Institute of Tomsk NRMC, immediately before intravenous administration. The dosage was 3,000 μg for [^{99m}Tc]Tc-$(HE)_3$-G3 and 500 μg for [^{99m}Tc]Tc-ADAPT6.

SPECT-CT of the chest and upper abdomen was performed in all patients 2 hours after the [^{99m}Tc]Tc-ADAPT6 injection and 4 hours after the [^{99m}Tc]Tc-$(HE)_3$-G3 injection. The accumulation of the radiopharmaceuticals was assessed by measuring the *maximum standardized uptake* values (SUV_{max}) in metastatic axillary lymph nodes and projections of the contralateral axillary lymph nodes and reference organs, such as liver, latissimus dorsi muscle, and spleen. Additionally, mALN-to-background and mALN-to-reference organs ratios were calculated for each patient. SUV_{max} was determined in the largest mALN, corresponding in anatomical location to the US description and biopsy material collection (Table).

Data analysis and visualization were performed using Prism 10 software (GraphPad, USA). The accumulation values of the agents were presented as the median and the interquartile range (Me (Q_1–Q_3)). The non-parametric Wilcoxon signed-rank test was used to determine the significance of differences between the accumulation values of the two agents. The differences were considered significant at $p < 0.05$.

Table

Accumulation of [^{99m}Tc]Tc-$(HE)_3$-G3 and [^{99m}Tc]Tc-ADAPT6 in metastatic HER2-positive axillary lymph nodes (SUV_{max}) and reference organs and mALN / reference organ ratios in patients with breast cancer

No.	SUV_{max} (mALN)	SUV_{max} (contralateral ALN)	mALNs/background	SUV_{max} (liver)	SUV_{max} (LDM)	SUV_{max} (spleen)	mALN/ liver	mALN/ LDM	mALN/ spleen
[^{99m}Tc]Tc-$(HE)_3$-G3									
1	1.8	0.3	6.7	9.1	0.3	4.0	0.2	6.2	0.5
2	2.6	0.2	15.2	5.2	0.3	2.5	0.5	8.6	1.0
3	2.2	0.2	13.5	3.0	0.3	1.3	0.7	6.2	1.7
4	10.7	0.3	33.3	4.7	0.4	2.5	2.3	26.0	4.3
5	8.7	0.3	34.9	5.7	0.4	2.1	1.5	21.3	4.2
6	2.4	0.4	5.9	4.1	0.2	1.7	0.6	10.9	1.5
7	14.0	0.3	41.2	2.9	0.5	3.1	4.9	25.9	4.5
8	8.7	0.4	23.5	3.4	0.3	4.4	2.6	27.2	1.9
[^{99m}Tc]^{99m}Tc-ADAPT6									
1	14.6	0.4	39.6	3.7	0.1	2.5	4.0	104.6	5.9
2	4.7	0.2	21.4	1.9	0.3	0.8	2.4	16.2	5.9
3	4.3	0.3	14.9	2.7	0.6	1.9	1.6	7	2.2
4	6.5	0.1	59.3	3.2	0.4	0.6	2.1	14.8	11.9
5	2.9	0.2	13.7	2.9	0.5	1.7	6	1.7	1.0
6	14.6	0.4	38.3	3.1	0.6	1.4	4.7	25.1	10.5
7	8.6	0.1	107.8	2.7	0.4	1.1	3.2	20.5	8.1
8	16.7	0.4	46.3	3.5	0.4	2.9	4.9	40.6	5.7

Note. mALN – metastatic axillary lymph node; LDM – latissimus dorsi muscle.

RESULTS

The results of the immunohistochemical analysis showed a HER2-positive status in the metastatic axillary lymph nodes of all patients included in the study. The obtained data were consistent with the results of the radionuclide studies with both agents. The average size of the lymph nodes was 20.5 ± 4.2 mm.

Comparing the accumulation of the agents showed comparable SUV_{max} levels in the metastatic axillary lymph nodes for [^{99m}Tc]Tc-ADAPT6 at 7.57 (4.43–14.62) and for [^{99m}Tc]Tc-$(HE)_3$-G3 at 5.65 (2.22–10.18) (p = 0.4609). The comparison of the mALNs / background ratio revealed an advantage of [^{99m}Tc]Tc-ADAPT6 (38.93 (16.56–56.02)) over [^{99m}Tc]Tc-$(HE)_3$-G3 (19.39 (8.43–34.52), p = 0.0391) (Fig. 1).

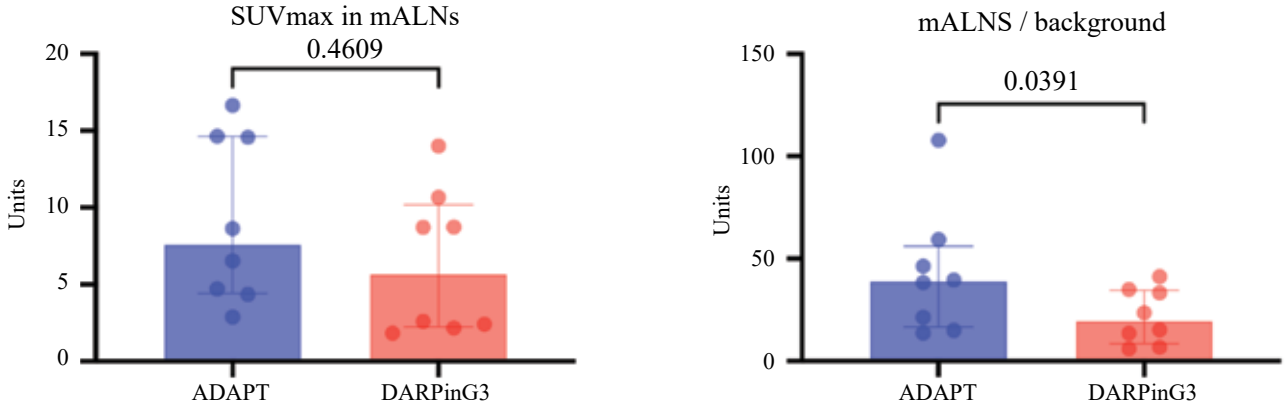

Fig. 1. SUV_{max} in mALNs and the mALNs / background ratio using [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-$(HE)_3$-G3 in patients with HER2-positive breast cancer

The comparative analysis of the accumulation of the studied radiopharmaceuticals (RPs) in the reference organs demonstrated higher SUV_{max} in the liver and spleen for [^{99m}Tc]Tc-$(HE)_3$-G3 (4.44 (2.85–9.08) and 2.47 (1.28–4.41), respectively) than for [^{99m}Tc]Tc-ADAPT6 (2.98 (1.96–3.65) and 0.43 (0.14–0.62), respectively) (p = 0.01 and p = 0.04). The analysis of [^{99m}Tc]Tc-ADAPT6 (0.43 (0.14–0.6)) and [^{99m}Tc]Tc-$(HE)_3$-G3 (0.33 (0.22–0.54)) accumulation in the projection of the spleen did not reveal any significant differences (p = 0.5) (Fig. 2).

Comparison of the SUV_{max} ratios in the mALNs and reference organs showed higher values for mALNs / spleen for [^{99m}Tc]Tc-ADAPT6 (5.93 (1.04–11.85)) compared to [^{99m}Tc]Tc-$(HE)_3$-G3 (1.83 (0.46–4.54), p = 0.02). The comparison of the mALNs / liver (3.58 (1.58–6.00) and 1.12 (0.20–4.91), respectively) and mALNs / latissimus dorsi muscle ratios (18.37 (1.70–104.6) and 16.12 (6.17–27.22), respectively) did not show significant differences between the studied agents (p = 0.06 and p = 0.55, respectively) (Fig. 3).

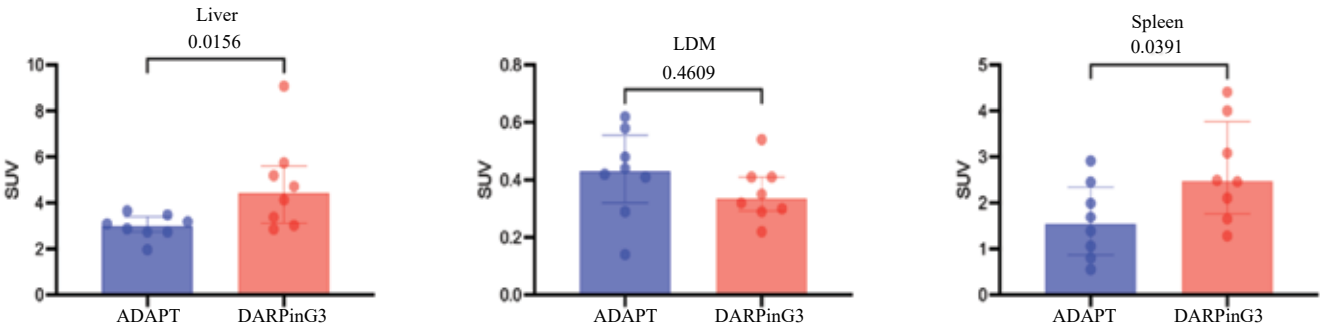

Fig. 2. SUV_{max} in the liver, latissimus dorsi muscle, and spleen using [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-$(HE)_3$-G3 in patients with HER2-positive breast cancer

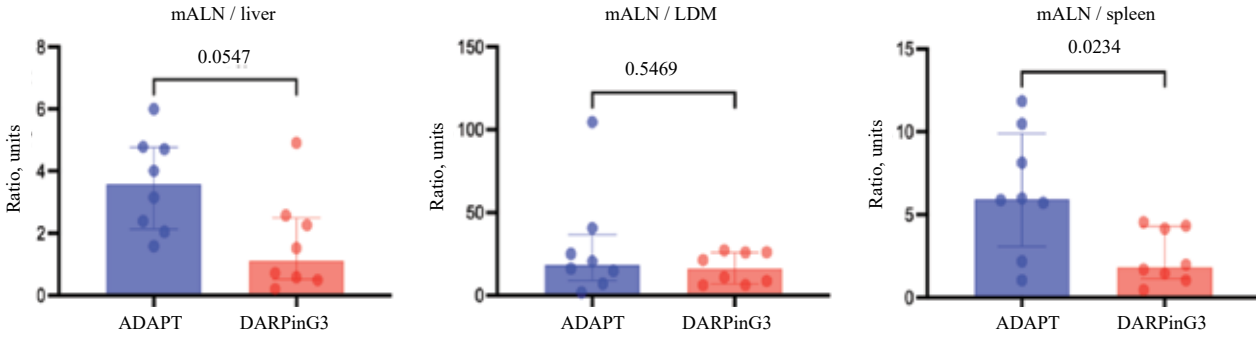

Fig. 3. Ratios of mALNs / liver, mALNs / latissimus dorsi muscle (LDM), and mALNs / spleen using [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-(HE)$_3$-G3 in patients with HER2-positive breast cancer

DISCUSSION

Despite advancements in imaging technology, the challenge of assessing the status of regional lymph nodes in BC patients remains unresolved. This issue is particularly critical at the pre-hospital diagnostic stage, where obtaining the most accurate information is essential for determining appropriate local and systemic treatment strategies. One approach to anatomical detection and molecular typing of detected lesions (both primary tumors and metastatic sites) is to expand the use of radioisotope methods and focus on targeted molecular imaging. This approach, based on the use of RPs that are tropic to specific molecular targets, has gained significant popularity over the past 10 years. It was during this period that the active use of alternative scaffold proteins as "targeting" modules began, along with their clinical testing for the theranostics of cancers.

The Department of Radionuclide Therapy and Diagnostics at Cancer Research Institute of Tomsk NRMC has extensive experience in conducting clinical trials on the diagnosis of malignant tumors using labeled scaffold proteins [13]. Studies involving RPs targeting the human epidermal growth factor receptor 2 (HER2) have been particularly widespread. Phase I clinical trials of [^{99m}Tc]Tc-ADAPT6 (ClinicalTrials.gov Identifier: NCT03991260 and NCT05412446), [^{99m}Tc]Tc-(HE)$_3$-G3 (ClinicalTrials.gov Identifier: NCT05695859), and [^{99m}Tc]Tc -ZHER2:41071 (ClinicalTrials.gov Identifier: NCT05203497) were conducted in patients with BC in collaboration with Tomsk Polytechnic University (Tomsk), Shemyakin – Ovchinnikov Institute of Bioorganic Chemistry (Moscow), and Uppsala University (Sweden) and demonstrated the feasibility of determining the HER2/neu status in the primary tumor [14, 15].

The results obtained and the accumulated experience have allowed for the expansion of the scope of clinical characteristics studied with [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-(HE)$_3$-G3. This expansion aims at defining diagnostic algorithms in the anatomical staging of metastatic axillary lymph nodes and assessing their molecular characteristics [10, 11].

The results obtained in this study almost completely replicate the direct comparison of [^{99m}Tc]Tc-ADAPT6 and [^{99m}Tc]Tc-(HE)$_3$-G3 performed within phase II clinical trials on the effectiveness of detecting the HER2/neu status in primary breast tumors [16, 17]. At the same time, it is obvious that the compound [^{99m}Tc]Tc-ADAPT6 has greater diagnostic accuracy in typing the HER2/neu status in primary tumors and metastases to regional lymph nodes, which can be widely used in clinical practice. In the meantime, the agent [^{99m}Tc]Tc-(HE)$_3$-G3 could be used for the dynamic assessment of the malignant process during neoadjuvant treatment, as it does not have competing characteristics with targeted agents, such as trastuzumab and pertuzumab.

CONCLUSION

Therefore, [^{99m}Tc]Tc-ADAPT6 has greater efficacy in determining the HER2/neu status in primary tumors and regional lymph node metastases. The clinical use of [^{99m}Tc]Tc-(HE)$_3$-G3, upon further study, may be possible for assessing tumor dynamics during preoperative treatment.

REFERENCES

1. Tyulyandin S.A., Artamonova E.V., Zhigulev A.N., Zhukova L.G., Koroleva I.A., Parokonnaya A.A. et al. Practical recommendations for drug treatment of breast cancer. Practical

Recommendations of RUSSCO, part 1. *Malignant Tumors.* 2023;3:157–165 (in Russ.). DOI: 10.18027/2224-5057-2023-13-3s2-1-157-200.
2. Apanasevich V.I., Artamonova E.V., Ashrafyan L.A., Besova N.S., Biryukova A.M., Bozhok A.A. et al. *Gold standard for prevention, diagnosis, treatment, and rehabilitation of patients with breast cancer.* 2024:17–30 (in Russ.).
3. Helfgott R., Mittlböck M., Miesbauer M. The influence of breast cancer subtypes on axillary ultrasound accuracy: A retrospective single center analysis of 583 women. *Eur. J. Surg. Oncol.* 2019;45(4):538–543. DOI: 10.1016/j.ejso.2018.10.001.
4. Gordeeva O.O., Zhukova L.G., Koliadina I.V., Gan'shina I.P. Assessment of the receptor status of the primary breast tumor and synchronous regional metastases: their clinical and prognostic role. *Siberian Journal of Oncology*. 2019;18(2):78–82 (in Russ.). DOI: 10.21294/1814-4861-2019-18-2-78-82.
5. Lower E.E., Khan S., Kennedy D., Baughman R.P. Discordance of the estrogen receptor and HER-2/neu in breast cancer from primary lesion to first and second metastatic site. *Breast Cancer – Targets and Therapy*. 2017;9:515–520. DOI: 10.2147/BCTT.S137709.
6. Han L., Li L., Wang N., Xiong Y., Li Y., Gu Y. Relationship of epidermal growth factor receptor expression with clinical symptoms and metastasis of invasive breast cancer. *Interferon Cytokine Res*. 2018;38(12):578–582. DOI: 10.1089/jir.2018.0085.
7. Bragina O.D., Deev S.M., Chernov V.I., Tolmachev V.M. Evolution of targeted radionuclide diagnostics of HER2-positive breast cancer. *Acta Naturae.* 2022;14(2):4–15 (in Russ.). DOI: 10.32607/actanaturae.11611.
8. Tolmachev V., Orlova A., Sorensen J. The emerging role of radionuclide molecular imaging of HER2 expression in breast cancer. *Semin. Cancer Biol*. 2021;72:185–197. DOI: 10.1016/j.semcancer.2020.10.005.
9. Pernas S., Tolaney S.M. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. *Ther. Adv. Med. Oncol.* 2019;11:1758835919833519. DOI: 10.1177/1758835919833519.
10. Bragina O.D., Tashireva L.A., Loos D.M., Chernov V.I., Hober S., Tolmachev V.M. Evaluation of approaches for the assessment of HER2 expression in breast cancer by radionuclide imaging using the scaffold protein [^{99m}Tc]Tc-ADAPT6. *Pharmaceutics.* 2024;16(4):445. DOI: 10.3390/pharmaceutics16040445.
11. Bragina O.D., Tashireva L.A., Loos D.M., Vtorushin S.V., Shulga A.A., Konovalova E.N. et al. Assessment of the expression of the HER 2/ neu receptor in the tissue of metastatic lymph nodes in patients with breast cancer using [^{99m}Tc]Tc-$(HE)_3$-G3. *Acta Naturae*. 2024;16(2):64–71 (in Russ.). DOI: 10.32607/actanaturae.27448.
12. Wolff A.C., Hammond M.E.H., Allison K.H., Harvey B.E., Mangu P.B., Bartlett J.M. et al. Human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology / College of American pathologist clinical practice guideline focused update. *Pathol. Lab. Med*. 2018;142(11):1364–1382. DOI: 10.5858/arpa.2018-0902-SA.
13. Chernov V., Rybina A., Zelchan R., Medvedeva A., Bragina O., Lushnikova N. et al. Phase I trial of [^{99m}Tc]Tc-maSSS-PEG2-RM26, a bombesin analogue antagonistic to gastrin-releasing peptide receptors (GRPRs), for SPECT imaging of GRPR expression in malignant tumors. *Cancers.* 2023;15(6):1631. DOI: 10.3390/cancers15061631.
14. Bragina O.D., Chernov V.I., Garbukov E.Yu., Doroshenko A.V., Vorobyeva A.G., Orlova A.M. et al. Possibilities of radionuclide diagnostics of HER2-positive breast cancer using technetium-99m-labeled target molecules: the first experience of clinical use. *Bulletin of Siberian Medicine.* 2021;20(1):23–30 (in Russ.). DOI: 10.20538/1682-0363-2021-1-23-30.
15. Bragina O., Chernov V., Larkina M., Rybina A., Zelchan R., Garbukov E. et al. Phase I clinical evaluation of ^{99m}Tc-labeled affibody molecule for imaging of HER2 expression in breast cancer. *Theranostics*. 2023;13(14):4858–4871. DOI: 10.7150/thno.86770.
16. Tolmachev V., Bodenko V., Oroujeni M., Deyev S., Konovalova E., Shulga A. et al. Direct in vivo comparison of ^{99m}Tc-labeled scaffold proteins, DARPin G3 and ADAPT6, for visualization of HER2 expression and monitoring of early response for trastuzumab therapy. *Int. J. Mol. Sci*. 2022;23(23):15181. DOI: 10.3390/ijms232315181.
17. Bragina O., Chernov V., Schulga A., Konovalova E., Hober S., Deyev S. et al. Direct intra-patient comparison of scaffold protein-based tracers, [^{99m}Tc]Tc-ADAPT6 and [99mTc]Tc-(HE)3-G3, for imaging of HER2-positive breast cancer. *Cancers.* 2023;15(12):3149. DOI: 10.3390/cancers15123149.

Authors' contribution

Bragina O.D., Deyev S.M., Chernov V.I. – conception and design, analysis and interpretation of the data, justification of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Garbukov E.Yu., Vostrikova M.A., Romanova A.A., Borodina M.E. – collection of the clinical material, clinical adaptation. Tashireva L.A.– statistical processing of the data.

Authors' information

B**ragina Olga D.** – Dr. Sci. (Med.), Principal Researcher, Department of Nuclear Therapy and Diagnostics, Cancer Research Institute; Senior Researcher, Oncotheranostics Research Center, NR TPU, Tomsk, bragina_od@mail.ru, http://orcid.org/0000-0001-5281-7758

Tashireva Lyubov A. – Dr. Sci. (Med.), Head of the Laboratory for Molecular Cancer Therapy, Cancer Research Institute, Tomsk, tashireva@oncology.tomsk.ru, http://orcid.org/0000-0003-2061-8417.

Garbukov Eugenii Yu. – Cand. Sci. (Med.), Senior Researcher, General Oncology Department, Cancer Research Institute, Tomsk NRMC, Tomsk, jrmaximum9@gmail.com, http://orcid.org/0000-0002-6016-7078

Vostrikova Maria A. – Junior Researcher, General Oncology Department, Cancer Research Institute, Tomsk NRMC, Tomsk, vostrikova.m@mail.ru, http://orcid.org/0000-0002-0256-5342

Romanova Anastasiya A. – Junior Researcher, General Oncology Department, Cancer Research Institute, Tomsk NRMC, Tomsk, rom9133207716@yandex.ru, http://orcid.org/0009-0009-6426-9416

Borodina Mariya E. – Researcher, P. Hertsen Moscow Oncology Research Institute, Moscow, 6571544@mail.ru, http://orcid.org/0009-0002-2779-0746

Deyev Sergei M. – Dr. Sci. (Biology), Professor, Academician of the RAS, Head of Molecular Immunology Department, Shemyakin – Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow, deev_sm@tpu.ru, http://orcid.org/0000-0002-3952-0631

Chernov Vladimir I. – Dr. Sci. (Med.), Professor, Corresponding Member of the RAS, Head of the Department of Nuclear Therapy and Diagnostics, Cancer Research Institute, Tomsk, chernov@tnimc.ru, http://orcid.org/0000-0002-5524-9546

(✉) **Bragina Olga D.,** bragina_od@mail.ru

Received 01.07.2024;
approved after peer review 16.07.2024;
accepted 12.09.2024