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Radionuclide GRPR imaging in malignant pathology of the mammary and prostate glands: clinical experience

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ABSTRACT

In this lecture, we presented current clinical studies on targeted radionuclide imaging of breast and prostate tumors with overexpression of the gastrin-releasing peptide receptor (GRPR). GRPR is a transmembrane receptor, the activation of which promotes the growth and proliferation of tumor cells. The highest level of GRPR expression is observed in malignant pathologies of breast and prostate, which is of particular interest for radionuclide diagnostics.

The conducted clinical studies assessed the safety, pharmacological properties, and effectiveness of imaging using radiopharmaceuticals based on peptide agonists and antagonists of GRPR labeled with technetium-99m and gallium-68 radionuclides. The results clearly demonstrate the advantage of GRPR antagonists over GRPR agonists, since they have optimal pharmacological properties, good tolerability, rapid elimination by organs with a physiological level of receptor expression, and high imaging efficiency of mammary and prostate tumors with overexpression of GRPR.

Keywords: GRPR, targeted radionuclide diagnosis, breast cancer, prostate cancer

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Радионуклидная визуализация GRPR при злокачественной патологии молочной и предстательной желез: опыт клинического применения

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РЕЗЮМЕ

В лекции представлены актуальные клинические исследования относительно таргетной радионуклидной визуализации опухолей молочной и предстательной желез с гиперэкспрессией рецептора гастрин-высвобождающего пептида (GRPR). Рецептор GRPR представляет собой трансмембранный рецептор, активация которого способствует росту и пролиферации опухолевых клеток. Наиболее высокий уровень экспрессии GRPR наблюдается при таких злокачественных патологиях, как рак молочной и предстательной желез, что представляет особый интерес для радионуклидной диагностики.

В проведенных клинических исследованиях оценивались безопасность, фармакологические свойства, эффективность визуализации радиофармпрепаратов на основе пептидов-агонистов и антагонистов GRPR, меченных радионуклидами технецием-99m и галлием-68. Результаты испытаний наглядно демонстрируют преимущество антагонистов GRPR перед агонистами GRPR, поскольку обладают оптимальными фармакологическими свойствами, хорошей переносимостью, быстрым выведением органами с физиологическим уровнем экспрессии рецептора, высокой эффективностью визуализации опухолей молочной и предстательной желез с гиперэкспрессией GRPR.

Ключевые слова: GRPR, таргетная радионуклидная диагностика, рак молочной железы, рак предстательной железы

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

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INTRODUCTION

Breast cancer (BC) and prostate cancer (PC) are the most common malignancies among the female and male populations, respectively [1]. The rapidly developing fields of molecular biology and oncology continue to seek new promising targets to optimize the diagnosis and treatment of oncological diseases, including gastrin-releasing peptide receptors (GRPR, BB2, Gastrin Releasing Peptide Receptor) [2].

GRPR belongs to the bombesin receptor family (BB1, BB2, BB3) and is a 7-transmembrane receptor coupled to a G protein. Its endogenous ligand is gastrin-releasing peptide (GRP), a regulatory molecule involved in stimulating gastrin release from gastric G cells and a number of other processes by binding to GRPR and activating the phospholipase C signaling pathway. In the human body, GRPR is expressed in neuroendocrine cells of the gastrointestinal tract (GI tract), brain, lungs, prostate, exocrine cells of the pancreas and mammary glands providing exocrine and endocrine functions, contraction of smooth muscles of the GI tract and genitourinary system, effects on immune cells, thermoregulation, circadian rhythm, and the growth and proliferation of both normal and pathological cells [3].

Literature data show that GRP and other peptides analogs of bombesin act as a growth factor contributing to proliferation of various cell types [4]. The binding of GRP to GRPR stimulates the phosphorylation of tyrosine kinase receptors, causing cross-talk of G-protein-coupled receptors (GPCR) [5]. Similarly, faster activation of the epidermal growth factor receptor (EGFR) is provided, through which subsequent signaling occurs via the mitogen-activated protein kinase (MAPK) signaling pathway in cells of head and neck carcinoma and non-small cell lung cancer [6]. In addition, GRPR is capable

of increasing the expression of cyclins, such as D1 and E, while simultaneously reducing p27 (cyclin-dependent kinase inhibitor) and hyperphosphorylating retinoblastoma protein (pRb), resulting in the cell transition from the G1 phase of the cell cycle to the S phase. Another effect may be the effect of GRP on cell survival and the involvement of PI3K-Akt signaling pathways after GRPR activation. This assumption has not been fully studied yet and requires further research (Figure) [7].

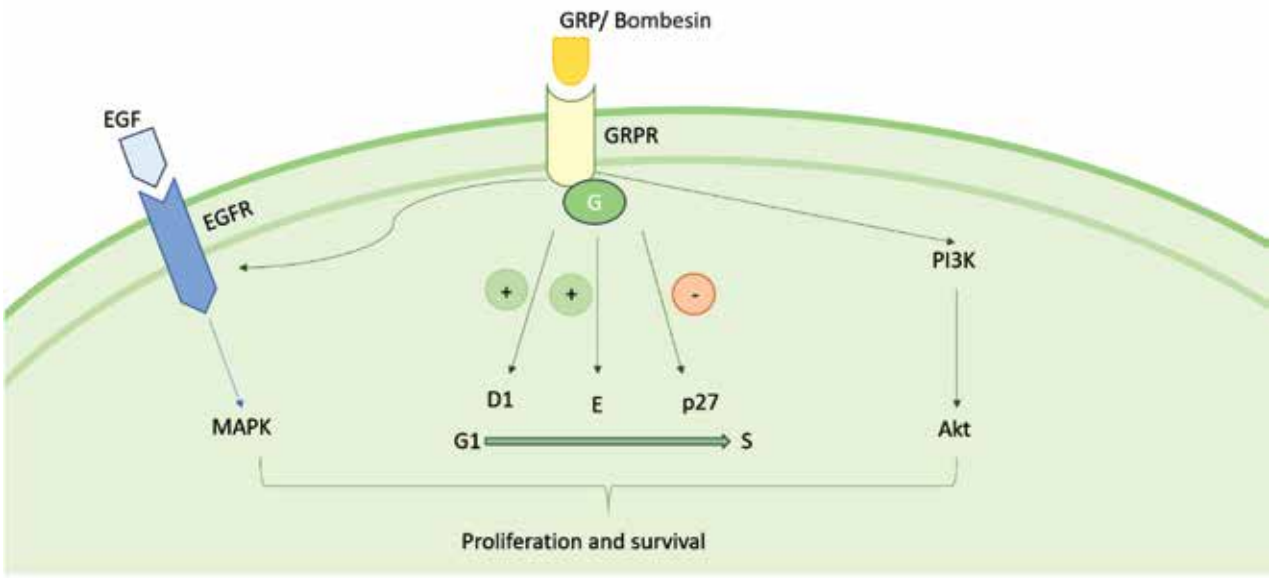

Figure. The role of GRPR in cell proliferation

Overexpression of GRPR has been found in a variety of malignant neoplasms, such as non-small cell lung cancer, kidney cancer, gastrinomas, gastrointestinal stromal tumors, head and neck cancers, and neuroblastomas. However, the highest expression of the GRPR is most often observed in prostate and breast cancers [4]. According to literature data, GRPR expression is found in 75.8% of malignant breast tumors and is largely associated with the expression of estrogen receptors (ER) [8, 9]. A greater number of GRPR expression cases are observed in luminal A – 86.2%, 70.5% – in luminal HER2-negative, 82.8% – in luminal HER2-positive, 21.3% – in HER2–positive (non-luminal), and 7.8% – in triple-negative (TNBC) subtypes of breast cancer [4]. According to the literature , the GRPR expression in prostate cancer is 63–100% [10].

Currently, several techniques are used to determine the level of GRPR expression in tumors, such as autoradiography of frozen sections, quantitative reverse transcription polymerase chain reaction (RT-qPCR); however, immunohistochemistry (IHC) of formalin-fixed and paraffin-embedded material, or matrix RNA (mRNA) are used more often [11]. As a rule, rabbit or mouse recombinant human polyclonal antibodies are used for IHC, as they form an antigen – antibody complex with the desired GRPR receptor. The expression of this receptor is evaluated in the form of an immunoreactivity index (II), which takes into account the intensity of staining (0 – no detectable staining, 1 – weak staining, 2 – moderate staining and 3 – strong staining) and the percentage of stained tumor cells (0 – no positive cells, 1 – ≤ 10% of positive cells, 2 – 11–50% positive cells, 3 – 51–80% positive cells and 4 – > 80% positive cells). Thus, the final assessment of II (staining intensity × percentage of positive cells) varies from 0 to 12: 0–1 – no GRPR expression, 2–3 – weak GRPR expression, 4–8 – moderate GRPR expression, 9–12 – strong GRPR expression [12].

Despite its accessibility, high sensitivity and specificity, IHC has a number of disadvantages. They include the necessity of an invasive procedure, the failure to obtain tumor samples due to tumor localizationn, violation of the methodology, for example, the molecular characteristics of the antigen may change during the fixation of histological material under the influence of fixing agents and different factors (such as long delivery of the material to the laboratory, the choice of a fixing agent,

failure to observe the fixation time), as a result of which the antigen – antibody reaction will be disrupted [13, 14].

Targeted radionuclide diagnosis. Currently, one of the areas in the diagnosis of malignant tumors is targeted radionuclide imaging, where synthetic proteins are increasingly used as a targeting module. Proteins are characterized by their small size, structure stability, affinity for antigen, optimal pharmacological and pharmacodynamic properties, and low cost of production due to expression in the bacterial system. Intravenous administration of this type of radiopharmaceuticals makes it possible to detect not only the primary tumor, but also the possible metastatic sites in in regional lymph nodes and distant organs and tissues. It also allows to detect the molecular biological characteristics of the identified tumor sites [15–18].

There are two main methods of radionuclide diagnostics – single-photon emission computed tomography (SPECT) and positron emission tomography (PET), which allow to detect areas of pathological hyperfixation of radiopharmaceuticals in metabolically active neoplasms *in vivo* [16]. Due to the high level of GRPR in mammary and prostate tumors compared with normal tissues (in particular in the pancreas and neuroendocrine cells of the GI tract), SPECT and PET are considered to be promising methods to detect GRPR expression [19, 20].

RADIONUCLIDE DIAGNOSIS OF PROSTATE CANCER WITH GRPR OVEREXPRESSION

Labeled peptides – bombesin analogues. Over the past two decades, studies with bombesin receptor agonists have been actively conducted as it was assumed that targeting GRPR using bombesin receptor agonists in radionuclide diagnosis of prostate cancer would allow for visualization of a primary tumor with high specificity due to its high affinity for this receptor. One of the first compounds which underwent clinical trials was the protein *RP527*, labeled with technetium-99m *([^{99m}Tc]Tc-RP527*). The study conducted in 2001 involved 10 patients: six patients had breast cancer, and four patients had prostate cancer. After the administration of *[^{99m}Tc]Tc-RP527*, its pathological accumulation in the tumor was observed in 4 out of 6 cases of breast carcinomas and in one out of four cases of prostate carcinomas [21]. This analysis was the starting point for further GRPR-targeted radionuclide imaging and allowed for further studies in that direction.

A clinical trial with the N-terminal modified BBN protein (1-14) labeled with ^{99m}Tc (*[^{99m}Tc]Tc-BN*) conducted in 2003 involved ten patients: eight patients had prostate cancer, two – benign prostate adenoma. According to the results of SPECT, there was high tumor uptake of radiopharmaceuticals in all 8 patients with prostate cancer after the administration of *[^{99m}Tc]Tc-BN* [22].

The *DB4* protein labeled with ^{99m}Tc (*[^{99m}Tc]Tc-DB4*) at the preclinical stage demonstrated high accumulation in PC3 xenografts of human prostate cancer in combination with its rapid excretion by the kidneys [23]. In the subsequent phase I of the clinical trial involving eight patients with prostate cancer, two individuals had a primary tumor and did not receive hormone therapy, and six patients had metastatic prostate cancer and received hormone therapy. After intravenous administration of *[^{99m}Tc]Tc-DB4*, the primary tumor node in the prostate was visualized on SPECT in all patients who did not receive systemic treatment, while in patients with metastatic prostate cancer, the accumulation was extremely low [24].

Another bombesin receptor agonist that was studied in a clinical trial was the molecule *AMBA* (*DOTA-Gly-4-aminobenzoyl-BBN (7-14*)), which is a BBN protein modified at the side ends of amino acids. The analysis of ten patients with IHC confirmed tumors of various localizations (prostate cancer, breast cancer, medullary thyroid cancer, uterine and colon tumors) and yielded visualization of the primary tumor, regional and distant metastases after the administration of the [^{68}*Ga]Ga- AMBA* to patients with prostate and breast cancer. At the same time, the results in patients with thyroid cancer and tumors of the colon and uterus were unsatisfactory (Table 1) [25].

Labeled peptides – bombesin antagonists. Despite the satisfactory data from clinical research (Table 1), it was noted that the use of bombesin analogs as a targeting module has a number of disadvantages, which include receptor activation and subsequent cascade reaction, mitogenic effect on tumor cells, significant side effects in the form of nausea and vomiting, abdominal cramps (which is apparently associated with the activation of GRPR not only in tumor cells, but also in neuroendocrine cells in the GI tract and in the pancreas), and rapid desensitization of receptors to the ligand. The identified disadvantages

allowed to consider alternative compounds that exhibit antagonism towards GRPR [19].

The results of preclinical trials performed by R. Cescato et al. demonstrated a greater advantage of GRPR antagonists compared to agonists in aiming at a target due to the neutralization of the receptor activation effects, including side effects [26].

SB3 molecule was developed for diagnostic and therapeutic purposes. Radiolabeling was carried out using isotopes ^{68}Ga and ^{111}In, ^{177}Lu was used for radiotherapy. According to the results of *in vivo* studies, *[^{111}In]In-SB3* and *[^{177}Lu]Lu-SB3* were rapidly catabolized and subsequently were not admitted to clinical trials. A clinical trial with the *[^{68}Ga]Ga-SB3* involved 17 patients with a disseminated process (eight patients with breast cancer and nine – with prostate cancer) and allowed to visualize breast tumors in four out of eight patients and prostate cancer in five out of nine patients. [27].

Another GRPR antagonist *[^{68}Ga]Ga-RM2* was studied in tumor models *in vivo* and demonstrated good tolerability, specificity and sensitivity to GRP receptors, optimal pharmacological properties, and a high degree of accumulation in tumor tissue. The subsequent clinical study involved 32 patients with IHC-confirmed prostate cancer recurrence with elevated levels of prostate-specific antigen, in whom standard diagnostic methods (computed tomography and magnetic resonance imaging) did not prove to be effective. According to the study, recurrence of tumors in the prostate gland was detected in 71.8% of cases (23 out of 32 cases) [28]. *[^{68}Ga]Ga-RM2* was also studied in 2022 in 41 patients with moderate and high-risk prostate cancer. The PET data after *[^{68}Ga]Ga-RM2* administration were comparable with the results of histologic examination of subsequent surgical material after prostatectomy performed in 32 patients and with the results of multivariate magnetic resonance imaging of 36 patients [29].

Another GRPR antagonist, the *RM26* molecule labeled with ^{68}Ga and ^{99m}Tc, demonstrated similar results. The first RM26 clinical trial was conducted in 2018 by J. Zhang et al., and included five healthy individuals and 28 patients diagnosed with prostate cancer (17 patients with diagnosed prostate tumors who did not receive treatment and 11 patients who underwent treatment). The *[^{68}Ga]Ga-RM26* administration did not have any side effects and was well tolerated. Visualization of the primary tumor was noted in 15 out of 17 patients, metastatic lymph nodes were observed in three out of eleven patients with previous treatment, and distant bone metastases were detected in eight out of eleven cases [30].

Phase I clinical trial of the *[^{99m}Tc]Tc-maSSS-PEG$_2$-RM26* was carried out at the Department of Radionuclide Therapy and Diagnostics of Cancer Research Institute of Tomsk NRMC in 2023. The study included six patients with prostate cancer and seven patients with breast cancer who did not receive specialized treatment. Images of the primary tumor were obtained in four out of six cases of prostate cancer, a correlation was noted with the prostate-specific antigen (PSA) level (optimal visualization was achieved in the patient with the highest PSA value) and the size of the tumor. In breast cancer patients, the effectiveness of primary tumor imaging was observed in all seven participants. Additionally, accumulation of the *[^{99m}Tc]Tc-maSSS-PEG$_2$-RM26* in metastatic regional lymph nodes was noted in three out of seven cases [31].

The antagonist of the gastrin-releasing peptide receptor *NeoBOMB1* is one of the solutions developed over the last decade. The first results of the study of the *[^{68}Ga]Ga -NeoBOMB1* including four prostate cancer patients demonstrated good tolerability and high levels of accumulation of radiopharmaceuticals in tumors, regional lymph nodes, and metastatic lesions of the liver and bones [32]. Another study focusing on *[^{68}Ga]Ga-NeoBOMB1* involved 19 patients with solid tumors of various localizations with overexpression of GRPR (tumors of the mammary and prostate glands, colorectal cancer, and lung cancer). The overexpression of GRPR was confirmed by the data of the IHC in all cases. The results of this clinical study demonstrated satisfactory tolerability of the *[^{68}Ga]Ga-NeoBOMB1*, as well as visualization of primary and metastatic tumors based on PET data [33].

Table 1

Clinical trials of bombesin analogs and antagonist peptides for radionuclide diagnosis of prostate cancer with GRPR overexpression

Analog GRPR	Radionuclide	Visualization method	Researcher, year
Bombesin analog peptides			
RP527	^{99m}Tc	SPECT	Van de Wiele, 2000
BBN	^{99m}Tc	SPECT	Scopinaro, 2003
AMBA	^{68}Ga	PET	Baum, 2007
DB4	^{99m}Tc	SPECT	Mather, 2014
Bombesin antagonist peptides			
SB3	^{68}Ga	PET	Maina, 2016

Table 1 (continued)

Analog GRPR	Radionuclide	Visualization method	Researcher, year
NeoBOMB1	^{68}Ga	PET	Nock, 2017 Djaileb, 2020
RM2	^{68}Ga	PET	Minamimoto, 2018
RM26	^{68}Ga ^{99m}Tc	PET SPECT	Zhang, 2018 Chernov, 2023

RADIONUCLIDE DIAGNOSIS OF BREAST CANCER WITH GRPR OVEREXPRESSION

Due to successful applications of labeled peptides that are bombesin analogs and its antagonists for prostate cancer, researchers concluded that this area should be studied in terms of targeted radionuclide imaging of breast tumors (Table 2).

Labeled peptides – bombesin analogs. In 2008, C. Van de Wiele et al. studied the *[^{99m}Tc]Tc-RP527* in 14 breast cancer patients, five of whom had negative expression of estrogen and progesterone receptors. The tumor process was visualized in all patients who had not previously received tamoxifen hormone therapy. In addition, metastasis to regional lymph nodes was also detected in all ER-positive patients. Imaging of tumors with a negative hormonal status was negative in all five patients [34].

Table 2

Clinical trials with bombesin analog peptides and antagonist peptides for radionuclide diagnosis of breast cancer with GRPR overexpression

Analog BBN	Radionuclide	Visualization method	Researcher, year
Bombesin analog peptides			
RP527	^{99m}Tc	SPECT	Van de Wiele, 2000 Van de Wiele, 2008
BBN	^{99m}Tc	SPECT	Scopinaro, 2002
AMBA	^{68}Ga	PET	Baum, 2007
Sestamibi	^{99m}Tc	SPECT	Urbano, 2020
Bombesin antagonist peptides			
SB3	^{68}Ga	PET	Maina, 2016
RM2	^{68}Ga	PET	Stoykow, 2016
RM26	^{68}Ga ^{99m}Tc	PET SPECT	Zhang, 2018 Chernov, 2023
NeoBOMB1	^{68}Ga	PET	Djaileb, 2020
DB15	^{99m}Tc	SPECT	Nock, 2021

A clinical study of *[^{99m}Tc]Tc-BBN* and *[^{99m}Tc]Tc-Sestamibi* with three breast cancer patients showed the high specificity of *[^{99m}Tc]Tc-BBN* and the possibility of using it to detect metastatic lymph nodes due to selective uptake by tumor cells and no uptake by nonspecific inflammatory cells [35, 36].

Labeled peptides – bombesin antagonists. Clinical trials focused on studying antagonists that have shown promising results in prostate cancer trials, as well as new molecules, are presented in Table 2.

A study of the *[^{68}Ga]^{68}Ga-RM2* conducted by C. Stoykow et al. in 2016 and included 15 patients with unilateral (n = 12) and bilateral (n = 3) breast cancer. Results demonstrated high accumulation of *[^{68}Ga]^{68}Ga-RM2* in the pathological sites in 73% of cases (in 13 out of 15 patients). In all patients, the diagnosis was confirmed by histologic examination of the biopsy material: 14 tumors were classified as invasive ductal carcinoma, three – as invasive lobular carcinoma, and one – as mucinous carcinoma. At the same time, lobular carcinoma was also detected during the study, but was not visualized using standard PET with 18F-fluorodeoxyglucose. In addition, the use of the *[^{68}Ga]^{68}Ga-RM2* showed its accumulation in axillary lymph node metastases with a diameter of < 5 mm. Visualization of lymphatic metastases using ^{18}F -fluorodeoxyglucose may be difficult due to the metabolic activity of nonspecific cells (macrophages, adipocytes, etc.) [37, 38].

Another molecule with antagonist properties was assessed in a prospective clinical trial involving 35 breast cancer patients. The administration of *[^{68}Ga]Ga-NOTA-RM26* demonstrated a positive correlation between its accumulation in tumor tissue expressing GRPR and estrogen receptors (estrogen-independent tumors were visualized worse). The authors considered the dependence of the accumulation of *[^{68}Ga]Ga-NOTA-RM26* on the phase of the menstrual cycle as another important result of the study. In this case the maximum value of SUV was observed in the secretory phase of the menstrual cycle, which can lead to distortion of the results and should be taken into account when planning further studies [39].

The *DB15* peptide labeled with technetium-99m is one of the latest advances. According to the results of preclinical *in vivo* studies, the *[^{99m}Tc]Tc-DB15* made it possible to accurately visualize primary tumors and metastatic cancer and had optimal pharmacological characteristics [40]. Two patients with advanced breast cancer participated in the first clinical trial of the *[^{99m}Tc]Tc-DB15*. No adverse effects were observed after *[^{99m}Tc]Tc-DB15* administration. According to the SPECT results, distant metastases were visualized in bones, lungs, and pleura. However, accumulation was not observed in intra-abdominal metastatic sites, which were later confirmed using

standard diagnostic methods (PET with FDG and histologic examination) [41].

CONCLUSION

The rapid development of radionuclide diagnosis demonstrates its unquestionable advantages over standard diagnostic procedures, significantly increasing the diagnostic value and reducing the cost of research. The requirements for optimizing the diagnosis of malignancies (in particular, breast cancer) contribute to expanding the scope of research to seek additional molecular targets, one of which is gastrin-releasing peptide receptors.

The results of preclinical and clinical trials have demonstrated the advantage of radiopharmaceuticals based on bombesin antagonist peptides compared with agonist peptides in the visualization of primary malignant breast tumors, as well as regional and distant metastases. At the same time, radioactively labeled GRPR antagonists showed a higher cumulative effect directly in the tumor tissue expressing this target, rapid elimination from the pancreas and other tissues with physiologically normal GRPR levels. The positive characteristics of bombesin receptor antagonists may contribute to the introduction of this method into clinical practice and consider GRPR not only as a diagnostic, but also as a therapeutic target.

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