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Радиотераностика приходит на помощь

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АННОТАЦИЯ

Ситуация с пандемией COVID-19 не уменьшила интереса к радиотераностике, скорее, наоборот, запрос на визуализацию патологических процессов с помощью кросс-секционных и гибридных томографических исследований (рентеновской и магнитно-резонансной, однофотонной эмиссионной, позитронно-эмиссионной) только усилился. Фактически за последние 15 мес в мире наблюдается экспоненциальный рост инвестиций в новые радиофармацевтические препараты для радиотераностики. По мере выяснения молекулярных механизмов регуляции и исполнения метаболических процессов, расширяется перечень антител и лигандов, меченных «медицинскими» радиоактивными изотопами. Также расширяется спектр диагностических и лечебных радиоактивных изотопов, что в конечном итоге развивает ассортимент и доступность радиотераностики в центрах ядерной медицины во всем мире. Для развития радиотераностики необходимо объединение усилий физиков, радиофармацевтов, химиков, биологов, врачей и математиков. Использование и совершенствование персонализированной дозиметрии для планирования радионуклидной терапии также является приоритетным направлением. Международный фонд Oncidium, например, помогает в информационном плане и обмену опытом, а международное диагностическое исследование NOBLE позволяет повысить доступность и снизить стоимость PSMA-рецепторной сцинтиграфии. В целях интенсификации интеграционного обновления ядерной медицины создана ассоциация развития тераностики.

Ключевые слова: радиотераностика; рак предстательной железы; PSMA.

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Radiotheranostics is here to help

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ABSTRACT

The COVID-19 pandemic did not diminish interest in radiotheranostics. However, the demand for visualization of pathological processes using cross-sectional and hybrid imaging (CT, MRI, SPECT, and PET) is increased. Over the past 15 months, the world has seen an exponential increase in investment in new radiopharmaceuticals for radiotheranostics. The list of antibodies and ligands labeled with "medical" radioactive isotopes is expanding as the molecular mechanisms of regulation and implementation of metabolic processes become clearer. The range of diagnostic and therapeutic radioactive isotopes is also expanding, ultimately increasing the range and availability of radiotherapy in nuclear medicine centers worldwide. It is necessary to unite the efforts of physicists, radiopharmacists, chemists, biologists, doctors, and mathematicians to develop radio technology. Usage and improvement of personalized dosimetry for planning radionuclide therapy is also a priority. For example, the International Foundation Oncidium helps with information and exchange of experience, while the international diagnostic study NOBLE increases the availability and reduces the cost of PSMA receptor scintigraphy. An association for the development of theranostics was created to intensify the integration renewal of nuclear medicine.

Keywords: radiotheranostics; prostate cancer; PSMA.

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无线电技术起到了拯救作用

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简评

COVID-19大流行的情况并没有降低人们对无线电恐怖症的兴趣，相反，通过交叉段和混合层析成像技术对病理过程进行成像的请求（伦顿和磁共振，单光子发射，正电子发射）只增加了。事实上，在过去15个月里，世界上用于放射恐怖症的新型放射性药物的投资呈指数级增长。随着新陈代谢过程调节和执行的分子机制的澄清，由“医学”放射性同位素标记的抗体和配体清单正在扩大。诊断和治疗放射性同位素的范围也在不断扩大，最终发展了世界各地核医学中心放射治疗的范围和可用性。　放射恐怖学的发展需要物理学家、放射药剂师、化学家、生物学家、医生和数学家的共同努力。使用和改进个性化剂量测定来规划放射性核素治疗也是一个优先事项。 例如，国际文心 Oncidium帮助提供信息和交流经验，国际诊断研究 NOBLE 有助于提高 PSMA 受体闪烁扫描的可用性并降低成本。 为加强核医学一体化更新，成立了治疗诊断学发展协会。

关键词：放射学； 前列腺癌; PSMA。

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INTRODUCTION

Recent studies and nuclear medicine advancements showed the leading role of radiotheranostics in oncology. Whatever the term of this promising area (radiotherapy, theranostics, radiotargeting, radioligand, peptide-receptor, or radionuclide therapy), this is a new area of nuclear medicine, particularly, in the diagnosis and treatment of malignant tumors using radioactive isotopes (Fig. 1).

The situation with the coronavirus disease-2019 pandemic did not diminish the interest in radioteranostics. Contrarily, only the demand for visualization of pathological processes using ultrasound and tomographic studies, such as computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission CT (SPECT), and positron emission tomography (PET), as well as hybrid methods, has increased. The world saw the exponential growth of investments in new radiopharmaceuticals (RPHs) for radioteranostics over the past 15 months. This trend is due to both the availability of funds from promising investors and the realization of the enormous growth market potential of radioactive isotope-labeled molecules for therapy. The growing investments in radiotherapy are based on the advances achieved in this field over the past 10 years. The monetary capital growth estimation in this industry revealed that the nuclear medicine market in 2019 was $4.1 billion and this figure is expected to increase within 5 years to $5.2 billion at an average annual growth rate of 4.7% by 2024[1]. Key players see growing revenues from therapeutics as clearly superior to those from diagnostics. The increased attention to radionuclide technologies in the last 20 years is comparable to the growing interest in cancer immunotherapy in 1980–2000. At that time, the pharmaceutical industry preferred to watch the evolution of technologies through start-ups and small companies, most of which went bankrupt, whereas the rest perfected the technologies and made multibillion-dollar profits.

Currently, the range of radiotherapeutic drugs exceeds 300 items and has long surpassed the list of diagnostic RPHs, which require much fewer financial investments. For the past 50 years, the global RPH industry had an insufficient budget to develop such drugs in government agencies. Only "traditional" pharmaceutical companies had sufficient

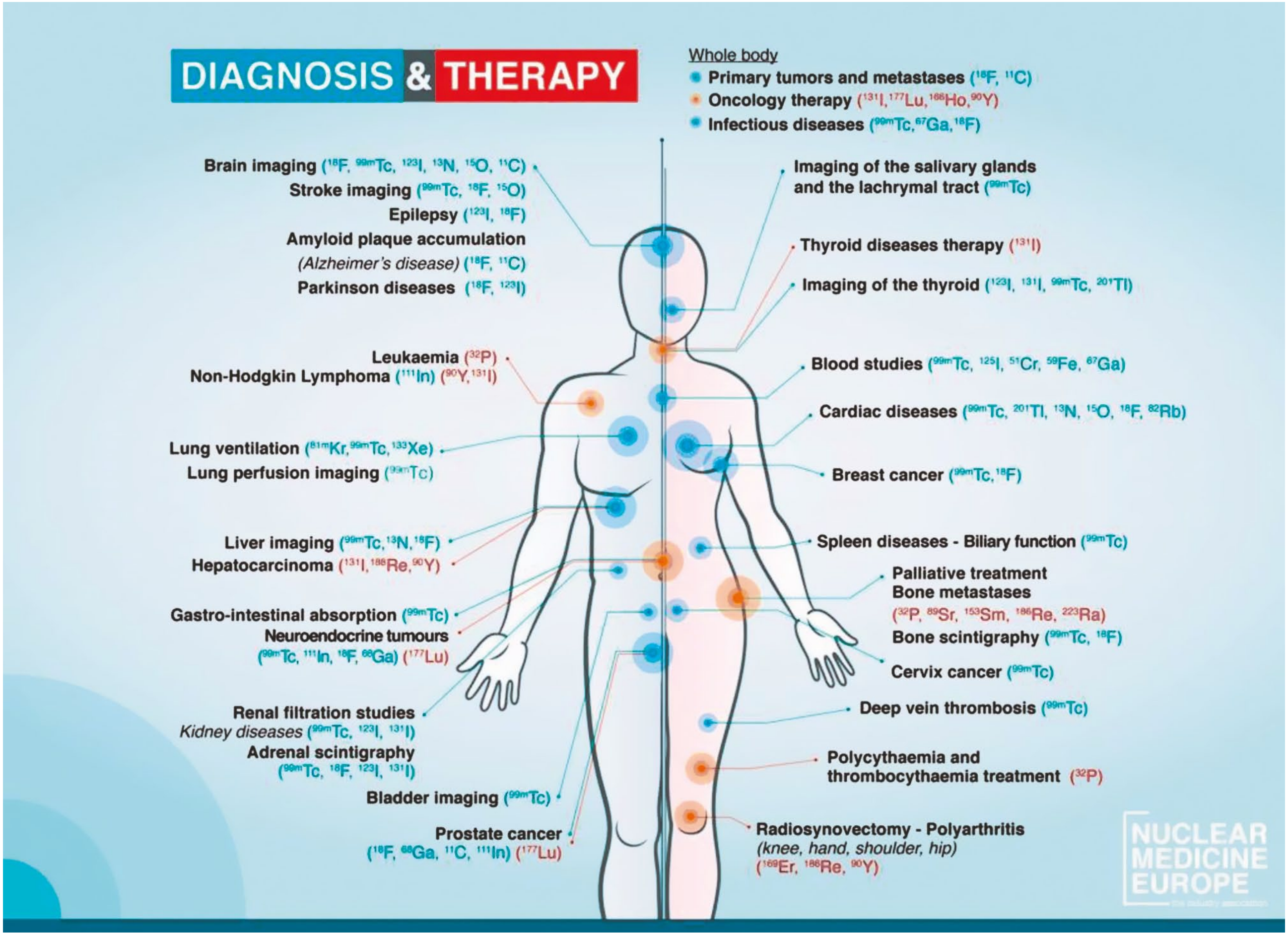

Fig. 1. Radioactive isotopes to diagnose and treat various diseases.

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[1] Nuclear Medicine/Radiopharmaceuticals Market by Type (Diagnostic [SPECT—Technetium, PET—F-18], Therapeutic [Beta Emitters—I-131, Alpha Emitters, Brachytherapy—Y-90]), Application (oncology and cardiology), Procedures—Global Forecast to 2026. Available at https://www.marketsandmarkets.com/Market-Reports/radiopharmaceuticals-market-417.html. Accessed on 07/10/2021.

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capital and infrastructure to develop and market RPHs. In addition to huge financial resources, they have access to the target audience, i.e., doctors (oncologists, radiologists, endocrinologists, etc.). The pharmaceutical companies, Bayer (Germany) and Novartis (Switzerland), were the first to engage in this area and brought therapeutic RPHs (^{223}Ra-Xofigo and ^{177}Lu-Lutathera, respectively) to the market, which were limited to generic patents, thus have not reached (at least so far) blockbuster levels (annual sales of over $1 billion). Nevertheless, the next generation of therapeutic RPHs, such as glutamate carboxypeptidase II or prostate-specific membrane antigen (PSMA), will be based on proprietary names. The first radioligand, ^{177}Lu-PSMA-617 for prostate cancer (Novartis), is expected to hit the global market next year. In addition to Novartis, which is actively investing in new radiotherapeutic drugs (for example, based on fibroblast activity protein inhibitor for radionuclide therapy of a large number of malignancies or CXCR4, a chemokine receptor-4, which is used in myeloma, lymphoma, aldosterone, esophageal cancer, and glioblastoma), a growing interest is noted in the industry worldwide from iTheranostics (Switzerland), Sofie Biosciences (USA), Aktis Oncology (USA), Astellas (Japan) and Actinium Pharma (USA) collaborations, Jubilant (India), Lantheus and Noria Therapeutics (USA), Bracco Blue Earth Diagnostics (Italy), Scintomics (Germany), Fusion Pharma (Canada), Ipsen (France), and, more recently, EZAG and Pentixapharm consortium (Germany). New names appear annually on the RPH market, such as Abscint (Belgium), Abdera Therapeutics (Canada), Precirix (Belgium), and RayzeBio (US).

All of these companies are very young and emerged at the nexus of nuclear medicine, radiopharmacy, and medical physics. Thus, Telix Pharmaceutical (Australia) develops cutting-edge radiotheranostical agents for prostate cancer (iPSMA, J591), glioblastoma, kidney, bladder, and ovarian cancers by combining ^{177}Lu-labeled peptide-based RPHs and monoclonal antibodies with ^{177}Lu and ^{131}I in its product portfolio.

Current approaches to neuroendocrine tumors and prostate cancer treatment are represented by both radiotargeting therapy in a single-mode, i.e., one RPH during all courses, and the use of “tandem” RHPs by combining the same base molecules with different radiolabels. An example is the sequential use of ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617. One of the first companies to specialize in ligand radiolabeling with ^{225}Ac alpha emitter was Fusion Pharmaceuticals (2014). The profile of Precision Molecular Inc. (the US, 2019) is radio targeting therapy for prostate cancer and other malignancies using ^{177}Lu and ^{225}Ac. Since 2020, Point Biopharma (USA) and RayzeBio (with a focus on similar ^{225}Ac-labeled ligands) have actively developed and used radiotheranostical drugs for neuroendocrine tumors and prostate cancer based on ^{177}Lu RPH.

Currently, over 60 radiotheranostical agents that target over 20 malignancies are in various stages of clinical trials; of these, 6 agents are in Phase III. Among the first 27 RPH names (9 for neuroendocrine tumors and 18 for prostate cancer), only a few (the most effective and safe ones) will enter the medical market.

Further development of radiotheranostics, especially in combination with existing anticancer therapy methods, will significantly expand the range of cancers with highly positive treatment responses. In oncology, radiotheranostics is an alternative to surgery (e.g., radioiodine therapy for thyrotoxicosis) or adjuvant treatment (as in thyroid cancer) in conjunction with surgery and hormonal therapy, or with distant radiotherapy, chemotherapy, and targeted drugs in other cases.

Accumulating an evidence-based clinical base will refine the indications for radioactive isotopes in the third, second, and first line of anticancer therapy. The concept of radiotheranostics generates much interest in personalized medicine, in which the patient is treated not according to a general, but to an individual plan, where specific targets and treatment mechanisms are determined using specific radiotheranostical agents (see Table 1). However, this is still a goal, for which a lot of logistical and regulatory issues will have to be resolved, allowing financial investments of pharmaceutical companies and private investors in the promising area of personalized medicine. Moreover, further informational and methodological work should be done with doctors, “non-nuclear” physicists, chemists, and public opinion.

RAPIDLY INCREASING DEVELOPMENT OF RADIOTHERANOSTICS WORLDWIDE

The international non-profit Oncidium[2] Foundation (headquartered in Belgium) was established in 2011 and operates globally to inform the public and professionals about radiotheranostics. The foundation aimed to promote and accelerate the development of radiotheranostics in oncology, making it more accessible to patients with cancer worldwide by updating information about the centers’ work. Hopefully, the number of such centers in the Russian Federation will increase.

The corresponding section of the website is continuously updated with information about new RPHs, evidence-based preclinical and clinical trials and practical application, mechanisms of action, efficiency and safety, and combinations with other technologies for cancer diagnosis and treatment. For example, the NOBLE Registry (a project of international collaboration) offers patients with prostate cancer access to SPECT or preferably to SPECT combined with CT (SPECT/CT) and PSMA, regardless of their place of residence and financial situation, particularly, if PET combined with PSMA

[2] Oncidium. Official website: https://www.oncidiumfoundation.org.

Table 1. The concept of radiotheranostics for prostate cancer

Stage	Diagnosis (molecular imaging)		Surgery	Dosimetry	Radionuclide therapy	Follow-up
Aim	Tumor staging, PSMA receptor expression in tumor cells, treatment efficiency monitoring		Intraoperative radionavigation	Radiokinetics, radionuclide therapy planning	Treatment	Tumor recurrence detection and localization
Visualization	SPECT/CT	PET/CT or PET/MRI	Gamma probe	SPECT	SPECT**	SPECT/CT, PET/CT, PET/MRI
RPHs	**$^{99}{}_{m}$Tc-HYNIC-PSMA**	^{68}Ga-PSMA-11* ^{18}F-PSMA-1007	**$^{99}{}_{m}$Tc-HYNIC-PSMA, $^{99}{}_{m}$Tc-nanocolloid**	^{177}Lu-PSMA (617, I&T, J591)		**$^{99}{}_{m}$Tc-HYNIC-PSMA**, ^{68}Ga-PSMA-11*, ^{18}F-PSMA-1007
Additional methods	TRUS, MSCT/MRI, puncturing, OS, and PSA					

Note. * More preferable (theranostic pair with ^{177}Lu-PSMA); ** whole body posttreatment scintigraphy (SPECT for all, SPECT/CT if indicated). SPECT: single-photon emission computed tomography; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; TRUS: transrectal ultrasound; MSCT: multispiral computed tomography; OS: osteoscintigraphy; PSA: prostate-specific antigen.

is unavailable. The simplicity and convenience of SPECT/CT with PSMA (a technetium generator is always at hand) is much higher than PET combined with CT (PET/CT), and the cost is significantly lower, whereas virtual digital registration is possible if SPECT is not performed in hybrid mode using CT. The NOBLE Registry compares SPECT/CT and PET/CT results with PSMA, clarifying accuracy parameters, benefits, limitations, and indications. However, the foundation cannot solve all problems alone, thus 18 nuclear medicine and radiotherapy experts from 11 countries came for assistance, including the Russian Federation representatives, i.e., P.O. Rumyantsev and Ye.V. Kargapoltseva. The Scientific Board of Oncidium Foundation and the NOBLE Registry Steering Committee, consisting of respected leaders of nuclear medicine and I, are honored to be a member. The Scientific Board ensures international communication and radiotheranostic improvements, considering the development of new RPHs and Next-Generation Imaging.

In 2021, the Theranostics Development Association was registered in the Russian Federation[3].

Radiotheranostics provide an opportunity to update approaches to personalized diagnosis, treatment, and rehabilitation of patients with cancer. Therefore, many organizational, methodological, economic, and regulatory issues arise. According to foreign colleagues, the cost of a new-generation radionuclide therapy session per patient ranges between $15,000 and $50,000, excluding the cost for diagnostic examination using SPECT and/or PET, which are necessary for dosimetry-based treatment planning and monitoring.

The toxicity and frequency of radionuclide therapy are much lower than that of chemotherapy or radiation therapy; however, this information is often unknown to doctors who are unfamiliar and inexperienced with this area of medicine. Clinical practice shows that the patient has maximum compliance with a high benefit/convenience ratio of the treatment option.

CONCLUSIONS

Therefore, "nuclear" oncologists greatly enhance the potential of multidisciplinary teams in advanced clinics worldwide. Physicians improve both the treatment outcomes by increasing the radiation dose and the quality of life by minimizing the dose to surrounding tissues in patients with early tumor stages. This is commonly done through regression (not cure), tumor stabilization, or palliative care in advanced stages by a dose reduction for non-tumor tissues. The use and improvement of personalized dosimetry for radionuclide therapy planning are prioritized to ensure the delivery of the optimal dose in tumor tissues and minimize the effects of ionizing radiation on normal tissues for an effective and safe treatment for each patient.

ADDITIONAL INFORMATION

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[3] Theranostics Development Association. Official website: http://theranostics.pro.

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