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MOLECULAR IMAGING AND THERANOSTICS OF NEUROENDOCRINE TUMORS: THE ROLE OF SSTR-PET, RADIOPHARMACEUTICALS, AND RADIOMICS IN PERSONALIZED DIAGNOSTICS

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ABSTRACT

The review presents modern approaches to the molecular imaging of neuroendocrine tumors based on the use of somatostatin-receptor radiopharmaceuticals, hybrid PET technologies and radiomics methods. The diagnostic and prognostic possibilities of SSTR-PET/CT, FDG-PET are considered/CT and PET/MRI in the assessment of the biological behavior of NEO of various gradations. Special attention is paid to the molecular mechanisms of somatostatin receptor expression, the use of 68Ga and 64Cu-labeled radioligands, as well as the integration of AI algorithms and radiomic features into personalized theranostics. Modern biomarkers of PRRT efficacy, including NETest and transcriptome panels, have been analyzed. The presented data demonstrate the formation of a new paradigm for the molecular diagnosis of NEO, based on a combination of functional imaging and biological characteristics of the tumor.

KEYWORDS: neuroendocrine tumors; radiation diagnostics; SSTR-PET/CT; FDG-PET/CT; PET/MRI; radiomics; artificial intelligence; PRRT; radiopharmaceuticals; molecular imaging.

INTRODUCTION

Neuroendocrine tumors (NEOS) are a heterogeneous group of neoplasms originating from cells of the diffuse neuroendocrine system and characterized by a complex molecular organization, variable receptor expression, and varying degrees of biological aggressiveness. A special feature of NEO is the ability of tumor cells to synthesize biologically active substances, as well as the expression of specific molecular markers, primarily somatostatin receptors (SSTR1–5), which play a key role both in diagnosis and in targeted radionuclide therapy [2, 10, 26]. Modern concepts of the pathogenesis of NEO are increasingly based on the study of the molecular mechanisms of tumor transformation, including disruptions of cellular proliferation signaling pathways, changes in Ki-67 expression, activation of metabolic cascades, and tumor dedifferentiation processes [27, 33].

In recent decades, there has been a steady increase in the incidence of neuroendocrine tumors, which is associated not only with a real increase in the prevalence of the disease, but also with the development of highly sensitive molecular imaging techniques [44]. NEOS are most often localized in the gastroenteropancreatic system and lungs, but tumors can occur in almost any organ due to the widespread distribution of neuroendocrine cells in the body [8, 9]. Despite the relatively slow course of some highly differentiated NEOS, significant molecular and phenotypic heterogeneity of tumors determines pronounced differences in prognosis, sensitivity to therapy, and overall patient survival [20, 29].

The development of molecular medicine has significantly changed approaches to the diagnosis of NEO. While traditional imaging methods primarily evaluate anatomical changes, modern hybrid technologies allow analyzing the functional and molecular characteristics of a tumor in vivo. SSTR-PET methods have acquired the greatest importance in clinical practice./CT and FDG-PET/CT, providing assessment of the receptor status and metabolic activity of tumor cells [22, 30]. Highly differentiated NEOS are usually characterized by pronounced expression of somatostatin receptors and high accumulation of radiolabeled somatostatin analogues, whereas aggressive and dedifferentiated forms exhibit increased uptake of 18F-FDG, reflecting activation of glycolysis and a high level of cellular metabolism [20, 39].

A special place in modern oncology is occupied by the concept of theranostics, which combines molecular diagnostics and targeted radionuclide therapy within a single personalized treatment strategy. The use of paired radiopharmaceuticals such as 68Ga-DOTATATE and 177Lu-DOTATATE makes it possible not only to visualize SSTR expression, but also to carry out selective therapeutic effects on tumor cells [16, 24]. Additional opportunities are provided by the integration

of radiomics, artificial intelligence, and transcriptomic biomarkers, including NETest, which contributes to more accurate prediction of the response to PRRT and the formation of individualized patient management algorithms [25].
With the rapid development of molecular imaging and personalized oncology, there is an increasing need to systematize modern data on the diagnostic capabilities of hybrid PET technologies, new radiopharmaceuticals, and AI-associated image analysis methods. In this regard, the purpose of this review is to summarize modern molecular approaches to imaging neuroendocrine tumors and to evaluate their role in the diagnosis, staging, prognosis of the disease course and monitoring the effectiveness of theranostics.

Molecular phenotypes of NEO in SSTR-PET/CT and FDG-PET/CT imaging

Modern molecular imaging of neuroendocrine tumors is based on the assessment of the receptor and metabolic profile of the tumor, reflecting its biological behavior and degree of differentiation. One of the key molecular markers of NEO is the expression of somatostatin receptors, mainly of the SSTR2 subtype, which determines the effectiveness of SSTR-oriented imaging and the possibility of using theranostic approaches [2, 22]. As noted by Toumpanakis et al. [22], highly differentiated G1–G2 NEOS are characterized by a high density of SSTR on the surface of tumor cells, which ensures an intensive accumulation of radiolabeled somatostatin analogues and a high sensitivity of SSTR-PET/CT when detecting even small foci of tumor lesion. In clinical practice, this makes SSTR-PET the main method of molecular diagnosis of slow-growing neuroendocrine tumors and an important tool for selecting patients for PRRT.
In contrast, low-grade G3 NEOS show decreased expression of somatostatin receptors and increased metabolic activity associated with activation of glycolysis and dedifferentiation processes [20, 29]. The increased accumulation of 18F-FDG in FDG-PET/CT reflects a high level of cell proliferation, increased expression of GLUT transporters, and an aggressive molecular phenotype of the tumor. Prospective studies by Binderup et al. [20], as well as Bahri et al. [29] showed that SUVmax with FDG-PET is directly correlated with the Ki-67 index, an unfavorable prognosis and a decrease in overall patient survival. Thus, FDG-PET/CT is becoming not only an imaging method, but also an important molecular biomarker of NEO aggressiveness.
The concept of dual-tracer imaging, based on the combined use of SSTR-PET and FDG-PET, is of particular importance in modern molecular diagnostics [23]. The use of two molecular markers makes it possible to assess intra-tumor heterogeneity, identify dedifferentiation zones, and determine the predominant biological phenotype of a neuroendocrine tumor. Patients with high SSTR expression and low FDG accumulation are usually characterized by a more favorable disease course and a better response to PRRT, whereas the combination of high FDG activity and low receptor expression is associated with an aggressive clinical course and less effective radioligand therapy [19, 39].
Complementing these data, studies by Johnbeck et al. [28] and Zhou et al. [14] demonstrate the promise of new radiopharmaceuticals, including 64Cu-DOTATATE and SSTR antagonists, with improved pharmacokinetic characteristics and increased imaging sensitivity. The use of new molecular radioligands makes it possible to more accurately identify intermediate biological phenotypes of NEO and expands the possibilities of personalized theranostics.
Thus, modern SSTR and FDG PET imaging methods provide a comprehensive assessment of the molecular profile of neuroendocrine tumors, forming the basis for a personalized approach to diagnosis, prognosis, and choice of therapeutic tactics.

Hybrid molecular imaging: the diagnostic potential of PET/MRI in NEO

The development of hybrid PET/MRI technologies has become one of the most significant areas of modern molecular imaging of neuroendocrine tumors, since the combination of high-contrast anatomical imaging and functional molecular assessment makes it possible to more accurately characterize the biological features of a tumor [5-7]. Unlike traditional radiographic diagnostic methods, PET/MRI provides simultaneous assessment of the receptor status, tissue structure, and metabolic activity of tumor foci, which is especially important in the case of high molecular heterogeneity of the NEO.
One of the key advantages of PET/MRI is the possibility of a detailed assessment of the expression of somatostatin receptors in combination with highly sensitive soft tissue imaging. As studies by Gurevich et al. [2] show, the variability of SSTR expression in NEO of various localities and degrees of malignancy determines differences in the accumulation of radiopharmaceuticals and directly affects the diagnostic sensitivity of molecular imaging. The use of SSTR-PET/MRI makes it possible to more accurately identify highly differentiated G1–G2 tumors characterized by intense SSTR2 expression, as well as to assess the intracellular heterogeneity of the receptor profile, which is important for PRRT planning.
PET/MRI is of particular clinical value in the early detection of metastatic lesions of the liver, bones, and mesenteric lymph nodes, where the high contrast of MRI significantly increases the accuracy of staging compared with CT [37, 42]. The additional use of diffusion-weighted sequences (DWI) makes it possible to estimate the cell density of a tumor and indirectly reflect the degree of its biological aggressiveness. Combined with molecular PET imaging, this forms a multiparametric approach to in vivo tumor phenotype analysis.
The possibility of quantifying molecular parameters is also essential. Works by Phan et al. [38], as well as studies by Piwowarska-Bilska [37] and Gherghe et al. [42] demonstrate that SUV metrics and volumetric indicators of tumor receptor load can be used as molecular biomarkers of prognosis and effectiveness of therapy. Quantitative analysis of radioligand accumulation during PET/MRI makes it possible to assess the degree of SSTR expression, monitor changes in receptor status during treatment, and predict the likelihood of a response to PRRT.
Additional prospects for hybrid molecular imaging are related to the integration of radiomics and AI algorithms capable of extracting hidden quantitative signs of a tumor from PET/MRI. The analysis of textural characteristics, spatial heterogeneity of radiopharmaceutical accumulation, and diffusion parameters opens up opportunities for noninvasive assessment of the molecular heterogeneity of NEOS and the formation of personalized prediction models. Thus, PET/MRI

is gradually becoming not only an imaging method, but also a platform for complex molecular analysis of neuroendocrine tumors, combining anatomical, functional and biological characteristics of the tumor process.

Radiomics, radiogenomics and AI in the molecular stratification of NEO

The modern development of molecular medicine and digital technologies has led to the formation of a new direction in the diagnosis of neuroendocrine tumors — the integration of radiomics, radiogenomics and artificial intelligence algorithms into the analysis of molecular images. Unlike traditional visual interpretation, radiomics allows you to extract from PET/CT and PET/MRI have a large number of quantitative parameters reflecting the hidden features of the tumor structure, receptor status, and metabolic activity. This approach makes it possible to noninvasively assess the molecular phenotype of NEO and to more accurately stratify patients according to the biological aggressiveness of the disease.

One of the most significant areas of radiomics is the analysis of tumor textural characteristics, SUV parameters, and spatial heterogeneity of radiopharmaceutical accumulation. Studies by Kratochwil et al. [43] have shown that the intensity of accumulation of [68Ga] DOTATOC in SSTR-PET correlates with the probability of response to PRRT, which allows us to consider quantitative parameters of molecular imaging as predictors of the effectiveness of therapy. At the same time, FDG-PET indicators reflect the level of metabolic activity and tumor dedifferentiation processes associated with an unfavorable prognosis [20, 39]. Thus, radiomic features become important molecular biomarkers characterizing the biological behavior of NEO.

Radiogenomics, a field that studies the relationship between the characteristics of medical images and the genetic characteristics of a tumor, is of additional importance. Current data indicate the existence of a correlation between the parameters of molecular imaging, the Ki-67 index, the level of expression of somatostatin receptors and the molecular mechanisms of tumor progression [27, 33]. High FDG activity is often associated with dedifferentiation and activation of aggressive metabolic pathways, whereas a pronounced accumulation of SSTR radioligands reflects a preserved neuroendocrine phenotype and a higher probability of response to PRRT. The integration of radiogenomic data makes it possible to form complex models for predicting the course of the disease and sensitivity to treatment.

Artificial intelligence algorithms that provide automated analysis of large amounts of visualization data play an essential role in the development of molecular diagnostics. The use of AI models makes it possible to identify hidden patterns that are inaccessible with the standard interpretation of images, as well as to reduce the subjectivity of the assessment of the tumor process. As noted by Slashchuk et al. [12], the transition to quantitative digital platforms contributes to the standardization of the assessment of NEOAND to increase the reproducibility of the results. Currently, AI is actively used for automatic tumor segmentation, assessment of intracellular heterogeneity, and prediction of response to PRRT.

Additional prospects are associated with the combination of radiomic features and liquid molecular biomarkers, including transcriptome panels and NETest [25]. The combined analysis of molecular imaging and circulating biomarkers makes it possible to more accurately assess the activity of the tumor process and monitor the effectiveness of treatment over time.

Together, the development of radiomics, radiogenomics, and AI forms a new paradigm for the molecular stratification of neuroendocrine tumors, providing the basis for highly accurate personalized theranostics and individualized choice of therapeutic tactics.

Radiological diagnosis of rare NEOALIZATIONS (thymus, lungs, primary extra-intestinal foci)

Rare localities of neuroendocrine tumors, including the thymus and lungs, require a particularly accurate radiological approach, since their clinical and morphological similarity to other mediastinal formations makes early differential diagnosis difficult, and it is nuclear medicine methods such as SSTR imaging that have proven effective in detecting these atypical foci [10]. Synthesis of PET data/CT and morphological techniques make it possible to reliably distinguish thymic NEOS from tim and carcinomas, especially in cases of paraneoplastic syndromes or atypical clinical debut, which is confirmed by radionuclide imaging studies in patients with various types of NEOS [1]. Evaluation of somatostatin receptors plays an important role in pulmonary and extra-intestinal NEOS, since these tumors can exhibit variable SSTR expression and high heterogeneity, which requires a combination of functional and topical diagnostics for proper localization of the primary focus [2]. Together, the use of SSTR-PET, FDG-PET and high-contrast anatomical methods forms the basis of a modern diagnostic algorithm, providing more accurate staging and determining optimal treatment routes for patients with rare neuroendocrine localization [4].

Criteria for visualization monitoring of the effectiveness of PRRT and biotherapy (biomarkers, new absorption indices)

Modern monitoring of the effectiveness of PRRT and biotherapy in neuroendocrine tumors is increasingly based on a comprehensive analysis of functional and morphological parameters, since traditional response assessment methods often do not reflect the true biological dynamics of the tumor process, especially in slow-growing GEP-NEOS [1, 39]. Given the limitations of RECIST in conditions of pronounced NET heterogeneity, the importance of quantitative PET indicators is growing, including SUV metrics and volumetric indices of SSTR-positive tumor load, which demonstrate a relationship with the prognosis and probability of response to PRRT, which is confirmed by data on the predictive role of SSTR expression and metabolic activity in FDG-PET [19, 20, 43]. Against this background, there is an increasing interest in radiomics, a high–performance extraction of textural features from images that makes it possible to identify subvisual markers of aggression and the phenomenon of "dedifferentiation", which previously could not be assessed using standard imaging and which have shown promise in NET patients observed in Russian and foreign centers [2, 24]. The addition of multiparametric biomarkers to imaging parameters, such as NETest and PPQ transcriptome panels, forms a new PRRT efficiency stratification model that combines molecular and radiological data and opens the way to personalized theranostics [16, 17].

Thus, the integration of modern molecular imaging techniques with highly informative liquid biomarkers forms a new standard for PRRT monitoring and biotherapy, allowing for much more accurate determination of the true biological dynamics of neuroendocrine tumors. An integrated approach, including radiomics, hybrid PET technologies and multilevel genomic tests, creates the basis for a personalized assessment of treatment effectiveness and a more informed adjustment of therapeutic tactics.

CONCLUSION

Modern diagnostics of neuroendocrine tumors is gradually moving beyond the framework of traditional radiation imaging and is increasingly based on the principles of molecular medicine and personalized oncology. The development of SSTR-oriented PET imaging, hybrid PET/MRI technologies, and new radiopharmaceuticals has significantly improved the accuracy of detection, staging, and monitoring of NEO, as well as brought us closer to a deeper understanding of the biological features of the tumor process.

The presented data demonstrate that molecular imaging reflects not only the anatomical spread of a tumor, but also its receptor profile, metabolic activity, and degree of aggressiveness. High expression of somatostatin receptors in highly differentiated NEOS determines the effectiveness of SSTR-PET and the possibility of PRRT, while increased accumulation of 18F-FDG is associated with tumor dedifferentiation, activation of metabolic pathways, and an unfavorable prognosis. Thus, the combination of SSTR and FDG PET forms the basis of the modern dual-tracer imaging concept, which makes it possible to more accurately stratify patients and predict the course of the disease.

Of particular importance in modern theranostics is the integration of molecular imaging with radiomics, artificial intelligence, and liquid biomarkers, including transcriptome panels and NETest. The use of quantitative radiomic parameters and AI algorithms opens up opportunities for noninvasive assessment of the molecular heterogeneity of NEO, prediction of response to PRRT, and the development of individualized treatment regimens.

In the future, further development of molecular oncology, radiogenomics and new targeted radioligands will contribute to the formation of a highly accurate personalized model for managing patients with NEO. The expansion of the use of theranostic approaches that combine diagnosis and targeted therapy into a single system strengthens the role of molecular imaging as one of the key tools of modern neuroendocrine oncology.

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Contribution of the authors
The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

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