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Norepinephrine Transporter–Targeted Cancer Theranostics—New Horizons

Takahiro Higuchi, MD, PhD,† Konrad Klimek, MD,‡ Daniel Groener, MD, MHBA,‡ Xinyu Chen, PhD,§ and Rudolf A. Werner, MD‡||*

Abstract: In the evolving landscape of precision oncology, this review delineates the role of radiopharmaceuticals targeting the norepinephrine transporter (NET), with a particular focus on the current clinical application of ^{123}I-MIBG diagnostic imaging and ^{131}I-MIBG therapeutics, in particular for pheochromocytoma, neuroblastoma, or paraganglioma. We will also highlight recently introduced ^{18}F-labeled NET targeting imaging radiotracers, which would offer unparalleled resolution, enhanced tumor localization, and staging properties. Complementing these novel second-generation PET agents in a theranostic approach, astatine-211 meta-astatobenzylguanidine (^{211}At-MABG) would leverage the advantages of alpha-particles to selectively target and eradicate NET-expressing tumor cells with minimal off-target effects.

Key Words: norepinephrine transporter, neuroendocrine tumors, precision medicine, PET imaging, alpha-particle therapy, astatine, ^{18}F

(*Clin Nucl Med* 2025;50: 44–51)

In recent years, the field of oncology has witnessed a paradigm shift toward personalized and targeted cancer therapies, aiming to improve treatment efficacy while minimizing adverse effects on healthy tissues.[1] Among the emerging targets for such precision medicine approaches, the norepinephrine transporter (NET) has witnessed an expanded use.[2]

NET, primarily known for its role in the reuptake of norepinephrine at the synaptic cleft in the central and peripheral nervous systems, has also been recognized for its involvement in cancer biology.[3] Beyond its canonical function in neurotransmission, NET has been found to be dysregulated in certain cancers originated from neural crest tissues. The aberrant expression of NET in certain types of cancer cells offers a unique opportunity for targeted diagnosis and therapeutic interventions.[4] By exploiting the overexpression of NET in malignant tumor tissues, strategies to deliver therapeutic radiopharmaceuticals have been developed, which are analogues of norepinephrine structure, binding selectively to cancer cells while sparing normal tissues. Moreover, imaging agents targeting NET have enabled noninvasive visualization and quantification of NET expression in vivo, facilitating cancer diagnosis, staging, and treatment monitoring.[2,4]

In this review, we aim to provide an overview of the role of NET as a promising diagnostic and therapeutic radiopharmaceutical target in specific types of tumors. We will discuss current and recent advancements in NET-targeted radiotheranostics, highlighting novel radiopharmaceuticals aimed at enhancing precision oncology with NET-targeted agents in cancer management.

IMPORTANCE OF NET IN DIAGNOSING AND TREATING SPECIFIC CANCERS

As mentioned, NET plays a crucial role in the diagnosis and treatment of specific cancers, particularly those originating from neural crest tissues. Neural crest cells, a transient embryonic cell population, give rise to a diverse array of tissues and cell types during development, including the peripheral nervous system, adrenal medulla, and melanocytes. Aberrant development or differentiation of neural crest cells can result in the formation of tumors with neuroendocrine features. Three notable malignancies arising from neural crest tissues include the following. First, arising from chromaffin cells in the adrenal medulla, pheochromocytoma is a rare neuroendocrine tumor characterized by excessive catecholamine production.[5] These tumors often present with symptoms such as hypertension, palpitations, and diaphoresis due to episodic release of catecholamines. Although most pheochromocytomas are benign, approximately 10% are malignant and may metastasize to distant organs, leading to a poorer prognosis. Second, paragangliomas are typically benign tumors arising from paraganglia, that is, clusters of neuroendocrine cells associated with the autonomic nervous system.[6] They are found along the paravertebral axis in the head, neck, thorax, and abdomen.[7] Paragangliomas can produce catecholamines, leading to symptoms such as hypertension, palpitations, and sweating. Although most are benign and slow-growing, some may demonstrate aggressive behavior, particularly those with certain genetic mutations or larger sizes. Treatment often involves surgical resection, with careful consideration to avoid catecholamine-induced complications during the procedure.[8] Third, neuroblastoma is the most common extracranial solid tumor of childhood, originating from primitive neuroblasts derived from neural crest cells.[9] These tumors can arise anywhere along the sympathetic chain, with the most common sites being the adrenal glands and retroperitoneum. Neuroblastomas exhibit heterogeneous clinical behavior, ranging from spontaneous regression to aggressive metastatic disease. High-risk neuroblastomas are associated with a poor prognosis,

Received for publication August 28, 2024; revision accepted September 21, 2024.

From the *Department of Nuclear Medicine and Comprehensive Heart Failure Center, University Hospital Würzburg, Würzburg, Germany; †Dentistry and Pharmaceutical Sciences, Faculty of Medicine, Okayama University, Okayama, Japan; ‡Clinic for Radiology and Nuclear Medicine, Department of Nuclear Medicine, Goethe University Frankfurt, University Hospital, Frankfurt, Germany; §Nuclear Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany; and ||Division of Nuclear Medicine and Molecular Imaging, The Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins School of Medicine, Baltimore, MD.

Conflicts of interest and sources of funding: R.A.W. received speaker honoraria from Novartis/AAA and PentixaPharm, and advisory board work for Novartis/AAA and Bayer. All other authors declare no conflict of interest. This project is partially supported by the Okayama University "RECTOR" Program, KAKENHI grant (22H03027) from the Japan Society for the Promotion of Science (T.H.), and the German Research Foundation (453989101, R.A.W., T.H.; 507803309, R.A.W.).

ChatGPT4.0 has been employed for editing tasks.

Correspondence to: Takahiro Higuchi, University Hospital Würzburg, Department of Nuclear Medicine, Oberdürrbacher Str. 6, 97080 Würzburg, Germany. E-mail: thiguchi@me.com.

ISSN: 1536-0229/25/5001–0044
DOI: 10.1097/RLU.0000000000005567

despite intensive multimodal therapy including chemotherapy, surgery, radiation therapy, and immunotherapy.[10]

^{123}I-MIBG FOR CANCER DIAGNOSIS

^{123}I-MIBG imaging has emerged as a valuable tool for diagnosing and localizing tumors with neuroendocrine features, especially those originating from neural crest tissues as mentioned above. MIBG, functioning as an analog of norepinephrine, is radiolabeled with iodine-123 and actively taken up by neuroendocrine tumors expressing the NET. Due to its structural resemblance to norepinephrine, MIBG is specifically recognized and transported into tumor cells via the NET[11,12] (Fig. 1). Utilizing SPECT imaging, ^{123}I-MIBG facilitates the localization of these tumors, aiding in differential diagnosis and treatment planning.

^{123}I-MIBG scintigraphy stands out as the leading functional imaging technique for identifying pheochromocytoma due to unmatched specificity and excellent sensitivity, along with widespread availability.[13] Its utility becomes especially pronounced in confirming diagnoses where other methods are unsuitable, for instance, when biopsies are risky due to possible severe complications like a hypertensive crisis. Furthermore, MIBG scintigraphy proves invaluable for determining the extent of the disease and assessing the response to treatment.

The diagnostic performance of ^{123}I-MIBG scintigraphy for pheochromocytoma and paraganglioma has been confirmed in a prospective multicenter study.[14] Including confirmed and suspected cases based on clinical symptoms and biochemical markers, this study demonstrated that ^{123}I-MIBG scintigraphy exhibits a sensitivity range of 82%–88% and a specificity range of 82%–84%. Notably, the sensitivity for pheochromocytoma and paraganglioma was found to be 88% and 67%, respectively, indicating a higher diagnostic accuracy for adrenal versus extra-adrenal tumors. The addition of SPECT imaging improved reader confidence but did not substantially alter the sensitivity and specificity outcomes. This study unequivocally validates the effectiveness of ^{123}I-MIBG as a reliable imaging modality for evaluating primary or metastatic pheochromocytoma or paraganglioma.

Although ^{123}I-MIBG scintigraphy is an established method for diagnosing and monitoring paragangliomas, not all tumors show the expected uptake due to variability in neuroendocrine marker expression.[15] Some paragangliomas, especially those with low neuroendocrine marker expression, may not be detected by this technique, which could result in false-negatives. This underscores the importance of a comprehensive diagnostic approach, combining ^{123}I-MIBG with other imaging methods like CT or MRI to improve detection rates. However, it is essential to interpret MIBG scintigraphy results within the broader clinical context, taking into account its limitations and integrating findings from other diagnostic modalities to form a complete picture of the patient's condition.[16]

Sharp et al[17] compared ^{123}I-MIBG scintigraphy and ^{18}F-FDG PET for neuroblastoma diagnosis. The study found that ^{18}F-FDG PET was more effective for stages 1 and 2 neuroblastomas, revealing extensive disease areas not seen on ^{123}I-MIBG. For stage 3, the 2 methods exhibited similar efficacy, but ^{123}I-MIBG proved superior for stage 4, particularly in identifying bone or marrow metastases. However, the effectiveness of ^{123}I-MIBG is compromised by the lower resolution of SPECT imaging, which can pose a significant drawback when examining small-sized pediatric patients. The sensitivity of ^{123}I-MIBG in detecting lesions is also a concern, as smaller lesions or those located in certain body regions may not be as clearly visualized compared with ^{18}F-FDG PET.[18]

Although ^{123}I-MIBG scintigraphy holds invaluable clinical utility, there is a need to enhance its sensitivity, especially for detecting small lesions or tumors with minimal neuroendocrine expression. This is especially crucial for pediatric oncology, where SPECT resolution might not provide the necessary clarity for accurate diagnosis and staging.[18] Respective progress may be achieved through the adoption of technologies like PET, which offers higher spatial and temporal resolution.[19]

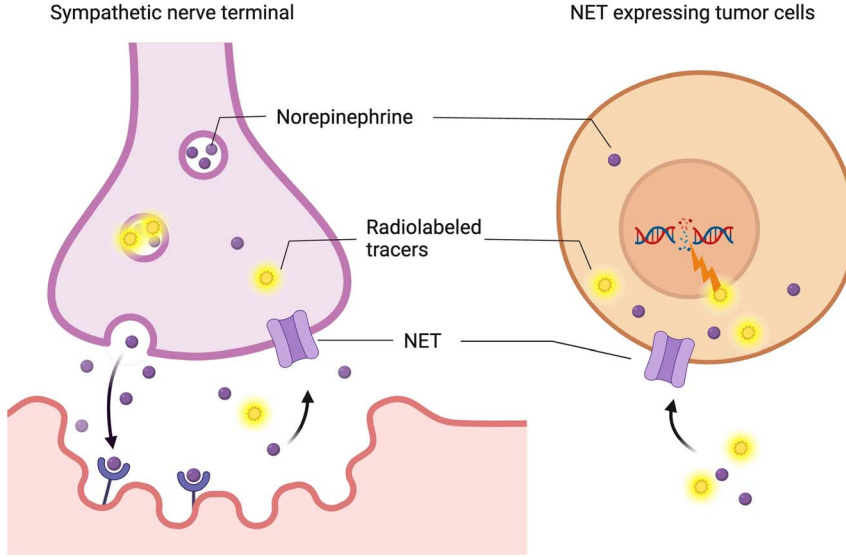

FIGURE 1. Norepinephrine, a critical neurotransmitter of sympathetic nerves, is released into synaptic clefts and subsequently reabsorbed by NETs situated on postsynaptic terminals for reuse. ^{123}I-MIBG, a radiolabeled analog of norepinephrine, is similarly internalized by nerve terminals through NET. This uptake mechanism facilitates the imaging of sympathetic nerve distributions and NET functioning. Furthermore, certain neuroendocrine tumors overexpress NET, allowing for targeted delivery of the radiopharmaceuticals into tumor cells. The use of beta-emitting radionuclides in these radiopharmaceuticals, such as ^{131}I-MIBG, confers the capacity for high cytotoxicity, enabling selective destruction of tumor cells that exhibit enhanced NET expression. Created with BioRender.com.

^{131}I-MIBG FOR CANCER TREATMENT

In addition to its diagnostic utility, ^{131}I-MIBG has demonstrated promise as a therapeutic option for NET-expressing tumors.[20] Iodine-131, a beta-emitting radioisotope, is conjugated to MIBG to deliver targeted radiation therapy to tumor cells while sparing surrounding healthy tissues. This targeted approach leverages the selective uptake of ^{131}I-MIBG by NET-expressing tumors, resulting in internal radiation therapy and improved patient outcomes. Therefore, ^{131}I-MIBG is effectively used as a first-line and neoadjuvant treatment for pheochromocytoma and paraganglioma.[21] Surgical resection is the preferred treatment; however, for tumors considered inoperable, ^{131}I-MIBG therapy has proven valuable in reducing tumor size, thus facilitating surgery.[22,23] The therapy has led to significant improvements in patients' functionality and quality of life, with no reported hypertensive crises or tumor lysis syndrome, indicating its safety.[21,24] In reported cases, patients treated with ^{131}I-MIBG were able to undergo surgery, highlighting the therapy's potential as a life-extending option.[25] The findings suggest that preoperative ^{131}I-MIBG therapy should be considered for reducing the size of unresectable tumors, enhancing operability and patient outcomes.

In a phase 2 trial, patients with advanced pheochromocytoma and paraganglioma were treated with high-specific-activity ^{131}I-MIBG (median 444 MBq/kg), a therapy aimed at those with few treatment options and typically poor prognoses.[26] The trial involved 74 patients, 68 of whom received therapeutic doses of high-dose specific activity ^{131}I-MIBG, resulting in 25% experiencing a significant and sustained reduction in antihypertensive medication use. Additionally, a majority experienced a tumor response, with 92% having partial responses or stable disease and a median overall survival of 36.7 months. Although the therapy showed promise, especially considering the lack of acute hypertensive events during treatment, challenges remain. The complex nature of pheochromocytoma and paraganglioma, variability in response, and the need for continued research to optimize treatment efficacy and manage disadvantages such as potential myelosuppression and fatigue highlight the importance of individualized patient care plans. In July 2018, the Food and Drug Administration approved iobenguane ^{131}I (https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-rare-adrenal-tumors), a specific form of ^{131}I-MIBG, marking it as the first Food and Drug Administration–approved radiopharmaceutical for treating paragangliomas and pheochromocytomas in patients aged 12 and older who have inoperable, metastatic tumors. Clinical trials are summarized in Table 1.[27–31]

A recent meta-analysis aimed to evaluate the effectiveness and safety of ^{131}I-MIBG therapy in treating neuroblastoma.[32] By reviewing 26 clinical trials involving 883 patients, the study found that ^{131}I-MIBG therapy, both as a standalone treatment and in combination with other therapies, shows promise in clinical outcomes for this type of neuroendocrine tumor. The pooled data revealed an objective response rate of 39% for MIBG monotherapy, with stable and progressive disease rates at 31% and 22%, respectively, and a minor response rate of 15%. When combined with other treatments, the objective response rate slightly decreased to 28%. The analysis also reported 1-year and 5-year survival rates of 64% and 32%, respectively. However, the treatment is associated with high rates of thrombocytopenia (53% in monotherapy, 79% with combination therapy) and neutropenia (58% in monotherapy, 78% with combination therapy), indicating significant adverse effects. The conclusion suggests that ^{131}I-MIBG can be an effective option in neuroblastoma treatment strategies, recommending its individualized use based on clinical considerations.

Although ^{131}I-MIBG therapy has shown effectiveness, there are ongoing challenges to optimize treatment, including fine-tuning dosing protocols, mitigating side effects, and establishing reliable predictors for patient response. To enhance the therapy's overall efficacy, research is pivoting toward the investigation of more potent radionuclides, such as alpha-particles,[33] which may offer a more targeted and powerful treatment alternative.

TABLE 1. Summary of Clinical Trials of Radionuclide Therapy Targeting Norepinephrine Transporter

Number	Phase	Interventions	Disease	Enrollment	Study Completion	Location	Reference
JRCT2021220012	Phase 1	^{211}At-MABG	Pheochromocytoma Paraganglioma	18 participants	First enrollment November 2022	Japan	27
NCT03561259	Phase 2	^{131}I-MIBG	Neuroblastoma	60 participants	Estimated April 2025	United States	
NCT00874614	Phase 2	^{131}I-MIBG	Pheochromocytoma Paraganglioma	74 participants	Result posted October 2020	United States	28 29
NCT01590680	Compassionate use	^{131}I-MIBG	Neuroblastoma Pheochromocytoma Paraganglioma	NA	NA	United States	
NCT01838187	Expanded access	^{131}I-MIBG +/−Vorinostat	Neuroblastoma Pheochromocytoma Paraganglioma	NA	NA	United States	
NCT00028106	Phase 2	^{131}I-MIBG	Pheochromocytoma	32 participants	Completed (July 2017)	United States	
NCT00960739	Phase 2	^{131}I-MIBG	Neuroblastoma	30 participants	Completed (July 2016)	France	30
NCT01019850	Phase 1	^{131}I-MIBG	Neuroblastoma	27 participants	Completed (February 2015)	United States	
NCT01313936	Phase 1	^{131}I-MIBG	Neuroblastoma	32 participants	Completed (May 2014)	United States	
NCT00458952	Phase 1	^{131}I-MIBG	Pheochromocytoma Paraganglioma	24 participants	Completed (June 2011)	United States	31
NCT00659984	Phase 2	^{131}I-MIBG	Neuroblastoma	15 participants	Completed (November 2010)	United States	29
NCT01413503	Phase 2	^{131}I-MIBG	Pheochromocytoma Paraganglioma	50 participants	Completed (May 2009)	United States	

EMERGING DIAGNOSTIC APPROACHES: ^{18}F-LABELED PET TRACERS

The evolution from SPECT to PET marks a milestone in the field of nuclear medicine.[34] SPECT, which became a clinical tool in the 1970s, utilizes gamma cameras and lead collimators to detect gamma rays emitted by radiopharmaceuticals.[35] These collimators are double-edged swords; they are crucial for photon direction but also limit spatial resolution due to the inevitable sensitivity-resolution trade-off. Consequently, practical resolution of SPECT technology is often around 10 mm, which poses a significant limitation in scenarios such as pediatric oncology where detecting small lesions is critical.

PET, on the other hand, emerged in the 1980s as a substantial improvement, particularly in sensitivity and spatial resolution.[36] The technique's signature ability to detect coincident photon pairs from positron annihilation negates the need for lead collimators, thereby enhancing sensitivity and reducing the spatial resolution to approximately 4–5 mm.[19] This leap in sensitivity is not just quantitative but also qualitative, enabling dynamic imaging and real-time tracking of radiotracer kinetics, thus offering a dynamic functional assessment. The introduction of whole-body PET imaging significantly changed the clinical use of this technology.[36] Initially more focused on brain and heart research, the applicability broadened, especially in oncology for whole-body evaluations. The ability to conduct a comprehensive scan of the entire body in a single session may make whole-body PET a cornerstone for the detection and management of cancer.

The superior capabilities of PET support a more personalized approach to patient care, fostering its preference over SPECT in many clinical contexts.[34] Efforts to improve SPECT continue; however, trajectory of PET is steeply innovative with advancements such as new radiotracer classes and the incorporation of multimodal systems like PET/MRI.[37] Digitalization of detectors, advancements in scintillator materials, and enhancements in image reconstruction algorithms collectively push performance of PET further.[19] The introduction of time-of-flight technology epitomizes the depth of PET's technological progression, offering even more detailed and informative imaging possibilities. This suite of intrinsic and technological strengths underscores why PET has become the modality of choice in numerous clinical scenarios.

The leap forward provided by ^{18}F-labeled PET tracers in nuclear medicine is a testament to the blend of clinical excellence and economic pragmatism, especially in the realm of oncological imaging.[38] ^{18}F-FDG has revolutionized whole-body scanning for staging and monitoring treatment responses. The advantage of ^{18}F includes a longer physical half-life of approximately 110 minutes, facilitating scheduling flexibility and the distribution of radiotracers over larger distances from the production site.[39] The widespread availability of PET imaging has, in turn, galvanized the pursuit of tracer diversity, with each new compound offering a nuanced view of different physiological and pathological states[36] (Fig. 2).

The initial promise was seen with ^{11}C-labeled compounds like ^{11}C-hydroxyephedrine, which showcased high affinity for the norepinephrine transport system and contributed significantly to both cardiac and oncological imaging.[40,41] Yet, its brief half-life of 20 minutes restricted its utility, confining it to facilities with an on-site cyclotron and a narrow imaging timeframe. The costs associated with the on-site cyclotron operations for PET radiotracer production represent a substantial financial investment. These specialized facilities are not only expensive to build and operate but also require highly trained personnel. This financial consideration has historically limited the adoption of PET imaging.[39]

However, the transition to ^{18}F-labeled tracers circumvents these economic constraints. The longer half-life of ^{18}F allows for the creation of a centralized distribution system, reducing the need for each imaging

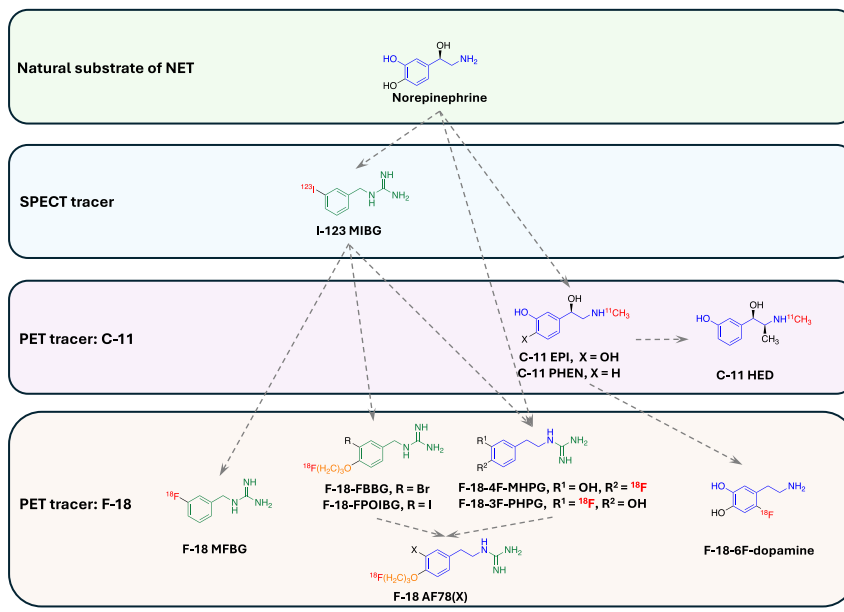

FIGURE 2. The diagram illustrates the branching evolution of NET radiotracers, showcasing the transition from SPECT to the technologically superior PET imaging, particularly emphasizing the introduction of ^{18}F-labeled tracers. These ^{18}F-labeled PET tracers confer both high-quality imaging and adaptable imaging protocols due to their extended half-life, coupled with economic efficiencies afforded by centralized production. The radiotracers are bifurcated into 2 core chemical structure groups: primary or secondary amines, and metabolically stable guanidines. The diagram shows how it branches into these categories, with shared core structures highlighted in blue and green, the common "tail" structures in orange, and the radionuclides marked in red, demonstrating the dynamic progression and diversification in the design of NET-targeted radiotracers.

center to bear the cost of a cyclotron. Such a system streamlines the process, significantly cutting down on the economic burden and expanding the reach of PET imaging across various healthcare settings. Advances in tracers such as ^{18}F-fluorodopamine,[42,43] followed by ^{18}F-LMI1195 (Flubrobenguane)[44–51] and ^{18}F meta-fluorobenzylguanidine (mFBG)[52] with their improved cardiac imaging contrast, and the introduction of compounds like ^{18}F-AF78 with high NET affinity, further optimize the utility and cost-effectiveness of the imaging process.[53–56] The centralized production and distribution of these tracers would enhance their economic viability, making PET imaging a more accessible and financially sustainable option for medical institutions[57] (Fig. 3).

Among others, Flubrobenguane has already been used in a preclinical setting and clinical scenarios. For instance, Gaertner et al[50] applied this radiopharmaceutical to tumor-bearing multiple endocrine neoplasia mut/mut rats, representing a dedicated neuroendocrine tumor model. Of note, NET inhibition by desipramine injection resulted in diminished adrenal gland uptake, thereby confirming specificity. In addition, Flubrobenguane also provided favorable biodistribution. Rischpler et al[58] provided first clinical evidence by investigating 20 subjects with suspected primary or recurrent pheochromocytoma or paraganglioma, reporting on improved diagnostic read-out relative to the reference standard ^{123}I-MIBG. The same group also showed that Flubrobenguane can provide higher lesion-based SUV values when compared with healthy adrenal glands and liver parenchyma,[59] thereby facilitating lesion detection. Previous studies also included the use of ^{18}F-fluorodopamine. For instance, Ilias et al[60] performed a head-to-head comparison of this PET agent with the reference ^{131}I-MIBG in patients with pheochromocytoma and reported on positive findings with the ^{18}F-labeled compound in all patients, along with increased lesion detection rate (n = 90 exclusively by ^{18}F-fluorodopamine vs n = 10 only by ^{131}I-MIBG), indicative for a substantially improved read-out using PET technology. The same group also reported on ^{111}In-pentreotide as comparator and again, reported on increased sensitivity (90.2%) for ^{18}F-fluorodopamine (^{111}In-pentreotide, 22%; ^{123}I-MIBG, 76%).[43] This superior performance, however, seems to be limited to widespread disease, whereas for exclusively detecting nonmetastasized disease (ie, adrenal primary), PET and ^{123}I/^{131}I-MIBG provided comparable diagnostic capabilities.[61] Of note, for both pheochromocytoma and (abdominal) paraganglioma, the intake of 200 mg carbidopa further improves image contrast on ^{18}F-FDOPA PET.[62] A recent study also investigated the use of this ^{18}F-labeled NET-targeting PET agent relative to somatostatin receptor PET, and similar to findings with scintigraphy, ^{18}F-FDOPA, diagnostic accuracy was increased (98% vs 70%).[63]

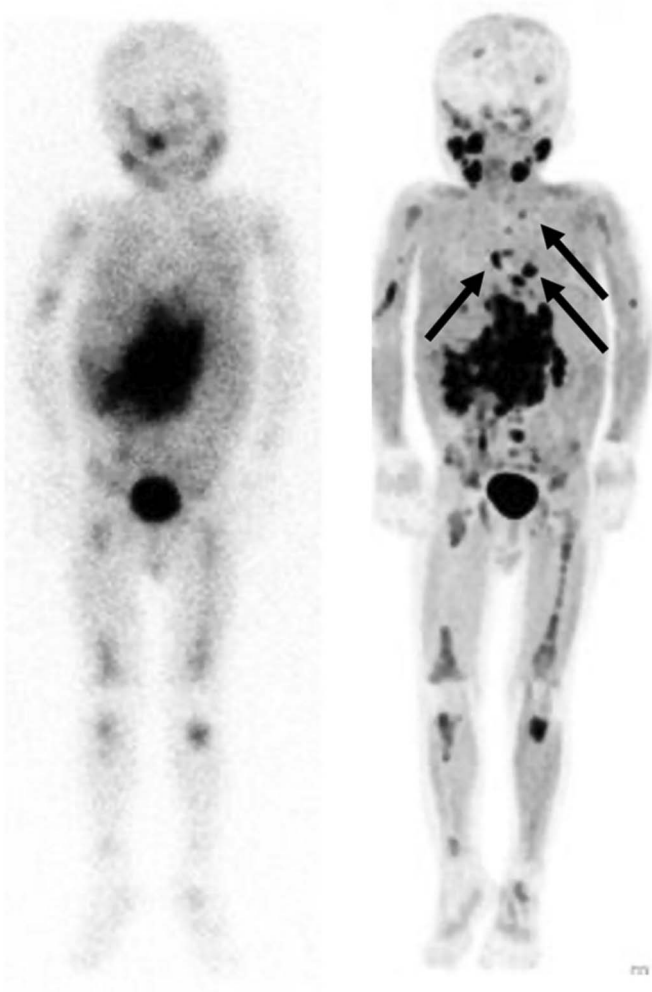

FIGURE 3. Images of a 4-year-old boy with high-risk neuroblastoma. The left panel displays a whole-body scan using ^{123}I-MIBG, whereas the right panel shows the MIP from ^{18}F-mFBG PET. Both imaging techniques reveal the pathological uptake characteristic of primary abdominal neuroblastoma as well as widespread osteomedullary neuroblastoma involvement. However, the ^{18}F-mFBG PET presents these findings with greater clarity and higher resolution. Additionally, ^{18}F-mFBG PET identifies extramediastinal lymph node metastases, as indicated by the arrows.[57] Copyright 2024, Springer Nature.

POTENTIAL THERAPEUTIC INNOVATION: ALPHA-PARTICLE THERAPY WITH ^{211}AT-MABG

Beta-emitting radionuclides like ^{131}I, ^{177}Lu, and ^{90}Y have been established as effective in clinical settings for tumor treatment through beta-particle therapy.[64] Of note, paraganglioma and pheochromocytoma provide increased somatostatin receptor expression on their tumor cell surface, thereby rendering peptide receptor radionuclide therapy suitable in those subjects.[65] For instance, a meta-analysis provided encouraging results with more than 89% achieving stable disease or partial response when treated with somatostatin receptor-targeted radionuclide therapy.[66] Nonetheless, patients experiencing progressive disease should be offered novel theranostic strategies, such as NET-directed radioligand therapies, preferably with radionuclides having increased potency relative to -beta-emitters.

Alpha-particle therapy can offer distinct advantages over beta-particle therapy, primarily due to differences in their radiation characteristics.[67] Alpha-particles, being 2 protons and 2 neutrons bound together, are much larger and carry more energy than beta-particles, which are electrons or positrons.[68,69] This difference leads to a higher linear energy transfer for alpha-particles, allowing them to deliver a concentrated dose of radiation over a very short range, usually only a few cell diameters. Consequently, alpha-particle therapy can target tumor cells more precisely and induce potent and localized cytotoxic effects, resulting in significant DNA damage that is particularly effective at killing cancer cells. One prominent example of alpha therapy is actinium-225 (^{225}Ac), which shows promise due to its suitable decay properties for use in targeted alpha therapy, especially when conjugated with peptides or antibodies.[70] However, the supply of alpha-emitters like ^{225}Ac is a challenge, mainly

because of their production in nuclear reactors, which are complex and costly facilities with stringent regulatory hurdles. Although the demand for ^{225}Ac is high due to its potential, its limited availability hinders widespread clinical application.[71]

In contrast, astatine-211 (^{211}At) offers unique advantages in the development of organic small molecule radiopharmaceuticals.[72] As a member of the halogen group, astatine shares chemical similarities with iodine, which allows it to form more compact compounds that are akin to the molecules used in established therapies, such as ^{131}I-MIBG[73] into molecules like meta-astatobenzylguanidine (MABG).[74] Furthermore, ^{211}At can be produced using cyclotrons, making it more accessible for research institutions and some hospitals, compared with the heavy ^{225}Ac, which requires a nuclear reactor for production as mentioned above.[75] However, employing ^{211}At comes with financial implications; the medium-sized cyclotrons needed for its production involve significant capital and operational expenses.[76] Despite these costs, the potential of ^{211}At for alpha-particle therapy is highly promising due to the localized and highly damaging effects of its alpha emission. Its production via cyclotrons presents an operational advantage, allowing for wider distribution and research application of ^{211}At-based therapies.[76] One characteristic of ^{211}At needs to be mentioned here: its short half-life of approximately 7.2 hours presents challenges in delivering an optimal radiation dose to the tumor while maintaining a low background level in nontargeted tissues. This rapid decay requires precise timing in the synthesis, delivery, and administration of the radiopharmaceutical to ensure that a sufficient dose accumulates at the tumor site before the radionuclide significantly decays. Balancing the high therapeutic potential of ^{211}At against the logistical hurdles is an ongoing concern in the field, driving innovation in radiotracer design and administration protocols to maximize tumor uptake quickly and efficiently.

Preclinical studies have demonstrated the potential of ^{211}At-MABG as an effective treatment for malignant pheochromocytoma.[77] In animal models, specifically PC12 tumor-bearing mice, ^{211}At-MABG has shown significant promises in reducing tumor volume with minimal side effects. Even at lower dosages, ^{211}At-MABG treatment resulted in substantial inhibition of tumor growth compared with controls, with mice experiencing temporary weight loss but recovering quickly. These findings suggest that ^{211}At-MABG has a strong and selective therapeutic effect, making it a promising candidate for the treatment of malignant pheochromocytoma. Additionally, dosimetry studies using mouse models have indicated that the absorbed doses of ^{211}At-MABG in organs expressing the NET, such as adrenal glands, heart wall, and liver, were higher than those from free ^{211}At.[78] This suggests a higher specificity of ^{211}At-MABG for target tissues, a crucial aspect for reducing side effects in potential clinical use.

Moving forward with the clinical application of ^{211}At, Japan is poised to conduct the world's first clinical trial of 18 patients with malignant pheochromocytoma for targeted alpha therapy using ^{211}At-MABG at Fukushima Medical University, with primary outcome parameters including maximum tolerable dose and toxicity.[79] This study has determined that patients undergoing targeted alpha therapy with ^{211}At-MABG do not require admission to a radiotherapy room and that the therapy can be administered on an outpatient basis. Radiation exposure to patients, the general public, and caregivers adheres to the safety standards set by the ICRP and IAEA. The guidelines also encompass protocols for patient and family precautions, safety management for the use of ^{211}At-MABG, mandatory education and training for medical personnel, and procedures for the disposal of medical radioactive waste.[79] Although these guidelines are tailored to Japan's medical environment and legal regulations, the principles for radiation protection and evaluation methodologies are internationally relevant and could serve as a benchmark for future clinical trials and therapeutic applications worldwide.

NOREPINEPHRINE TRANSPORTER THERANOSTICS—POTENTIAL SYNERGETIC EFFECTS OF SECOND-GENERATION DIAGNOSTIC PET AGENTS AND TARGETED ALPHA THERAPY

The burgeoning field of cancer theranostics is poised to be revolutionized by the synergistic integration of next-generation diagnostic and therapeutic modalities, particularly ^{18}F-labeled PET tracers and alpha-particle therapy. This innovative convergence promises to enhance the precision and efficacy of cancer management, offering a dual advantage: the highly sensitive detection of NET-expressing tumors and their subsequent targeted destruction.

The synergy of these technologies becomes apparent when considering the lifecycle of cancer treatment. ^{18}F-PET tracers first delineate the extent of disease, guiding the application of ^{211}At-MABG to the identified malignancies. The subsequent targeted alpha therapy works to eradicate the NET-expressing tumors, with the potential for real-time monitoring of therapeutic response using the same ^{18}F-PET tracers. Furthermore, the utilization of these 2 modalities may combine their individual strengths. The sensitivity and resolution of ^{18}F-PET imaging ensure accurate treatment planning and due to the potential of delayed scan protocols, dosimetry for ^{211}At-MABG therapy, potentially improving outcomes and reducing the risk of recurrence. Simultaneously, the effective tumor control by ^{211}At-MABG could lower the burden of disease, further enhancing the diagnostic clarity of PET imaging.

As we stand on the cusp of clinical trials, such as those soon underway in Japan, the prospect of combining ^{18}F-PET imaging with ^{211}At-MABG treatment holds immense potential. This integrated approach could redefine the therapeutic landscape for patients with malignancies such as pheochromocytoma, neuroblastoma, and other NET-expressing tumors.[78,79] It also underscores the need for continued interdisciplinary collaboration and innovation within the fields of nuclear medicine and oncology to fully harness the capabilities of these advanced diagnostic and therapeutic tools.

CONCLUSIONS

The field of precision oncology is witnessing significant advancements through the integration of radiopharmaceuticals targeting the NET. These advancements, particularly the clinical applications of ^{123}I-MIBG for diagnostic imaging and ^{131}I-MIBG for therapeutic purposes, have shown significant promise in managing certain type of tumors such as pheochromocytoma, neuroblastoma, and paraganglioma. The emergence of ^{18}F-labeled NET-targeting imaging radiotracers represents a notable enhancement in tumor localization and staging, offering superior resolution and precision.

The theranostic approach combining diagnostic imaging with therapeutic interventions would be further advanced by the introduction of ^{211}At-MABG. This alpha-particle therapy might harness the potent and localized cytotoxic effects of alpha radiation to effectively target and eradicate NET-expressing tumor cells while minimizing off-target effects. Preclinical studies and forthcoming clinical trials, particularly in Japan, highlight the potential of ^{211}At-MABG as a powerful treatment option for malignant pheochromocytoma and other NET-expressing tumors.

The future of NET-targeted theranostics lies in the synergistic use of second-generation ^{18}F-labeled PET agents and alpha-particle therapy. This integration promises to enhance the precision and efficacy of cancer treatment, offering dual advantages in both diagnosis and therapeutic monitoring. As clinical trials advance and new radiopharmaceuticals are developed, the potential for improved patient outcomes through personalized and targeted cancer therapies continues to expand. Continued interdisciplinary collaboration and innovation are essential to fully harness the capabilities of these advanced diagnostic and therapeutic tools, paving the way for a new era in precision oncology.

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