



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
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ARTICLE TITLE	PRE-THERAPY FUNCTIONAL IMAGING AS A TOOL FOR PERSONALIZED TREATMENT SELECTION IN PHEOCHROMOCYTOMA AND PARAGANGLIOMA: A THERANOSTIC PERSPECTIVE
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DOI	https://doi.org/10.31435/ijitss.3(51).2026.6482
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RECEIVED	23 July 2026
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ACCEPTED	23 September 2026
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PUBLISHED	27 September 2026
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PRE-THERAPY FUNCTIONAL IMAGING AS A TOOL FOR PERSONALIZED TREATMENT SELECTION IN PHEOCHROMOCYTOMA AND PARAGANGLIOMA: A THERANOSTIC PERSPECTIVE

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ABSTRACT

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors with heterogeneous biological behavior, requiring individualized diagnostic and therapeutic strategies. This review aimed to evaluate the role of functional imaging, particularly [^{123}I]I-MIBG scintigraphy and [^{68}Ga]Ga-DOTATATE PET/CT, in guiding personalized treatment selection within a theranostic framework. A comprehensive literature review was performed using PubMed and other scientific databases, including clinical studies, systematic reviews, retrospective analyses, and international guidelines. The analysis focused on diagnostic performance, molecular imaging characteristics, genotype–phenotype associations, tumor heterogeneity, and the impact of imaging findings on radionuclide therapy selection.

[^{68}Ga]Ga-DOTATATE PET/CT demonstrated superior sensitivity, especially in metastatic PPGLs and SDHB-associated disease, and enabled identification of patients potentially eligible for peptide receptor radionuclide therapy (PRRT). Although less sensitive, [^{123}I]I-MIBG scintigraphy remains essential for selecting candidates for [^{131}I]I-MIBG therapy. Functional imaging revealed substantial interlesional heterogeneity, reflecting differences in receptor expression and tumor biology that may influence treatment response.

Functional imaging is a fundamental component of precision management in PPGLs. The integration of molecular imaging with therapeutic radionuclide approaches enables identification of the predominant molecular target and supports individualized treatment decisions. MIBG scintigraphy and [^{68}Ga]Ga-DOTATATE PET/CT should be considered complementary modalities within a comprehensive theranostic strategy.

KEYWORDS

Pheochromocytoma, Paraganglioma, Functional Imaging, Theranostics, Tumor Heterogeneity, Personalized Medicine.

CITATION

Slobozheniuk, L., Manila, Y., Bieniak, M., Skrobisz, A., Owczarek-Danowska, I. M., Zająć, D., Płóciennik, J., Ołdak, J., Korshak, O., & Abramchuk, O. (2026). Pre-therapy functional imaging as a tool for personalized treatment selection in pheochromocytoma and paraganglioma: A theranostic perspective. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.6482](https://doi.org/10.31435/ijitss.3(51).2026.6482)

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1. Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine neoplasms arising from chromaffin cells of the adrenal medulla and extra-adrenal paraganglia (Juhlin & Mete, 2024; Timmers et al., 2024). Although these tumors are generally characterized by relatively indolent biological behavior, a substantial proportion of patients develop metastatic or unresectable disease, which is associated with limited therapeutic options and considerable variability in clinical outcomes (Pacak et al., 2026; Taieb et al., 2019a).

Functional imaging has become an integral component of PPGL management. Beyond tumor localization and staging, it provides valuable insight into tumor biology and molecular characteristics that are directly relevant to therapeutic decision-making. Conventional radiopharmaceutical imaging with [^{123}I]I-MIBG evaluates norepinephrine transporter (NET) activity, whereas newer positron emission tomography (PET) tracers, such as [^{68}Ga]Ga-DOTATATE, target somatostatin receptor (SSTR) expression, particularly somatostatin receptor subtype 2 (SSTR2) (Carrasquillo et al., 2021; Taieb & Pacak, 2018).

Comparative studies have consistently demonstrated that [^{68}Ga]Ga-DOTATATE PET/CT provides higher diagnostic sensitivity than MIBG scintigraphy and several other functional imaging techniques, particularly in patients with metastatic disease or SDHB-associated PPGLs (Janssen et al., 2015; Maurice et al., 2012; Scheuba et al., 2025). Furthermore, multimodal imaging has revealed substantial intertumoral and intratumoral heterogeneity, indicating that no single imaging modality can comprehensively characterize the molecular phenotype of all lesions (Chang et al., 2016; Hedeer et al., 2025).

The concept of theranostics has emerged as a transformative strategy in modern oncology by integrating molecular imaging with targeted radionuclide therapy based on shared biological targets. In PPGLs, functional imaging biomarkers facilitate individualized treatment selection between [^{131}I]I-MIBG therapy and peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogues, such as [^{177}Lu]Lu-DOTATATE (Carrasquillo et al., 2021; Jha et al., 2021). Importantly, expression of somatostatin receptor

subtype 2 (SSTR2), particularly in SDH-deficient tumors, has been identified as one of the principal determinants of responsiveness to PRRT (García-Vioque et al., 2026; Leijon et al., 2019).

Growing evidence indicates that functional imaging findings may directly influence therapeutic decision-making. Patients demonstrating predominant MIBG uptake are more likely to benefit from norepinephrine transporter-targeted radionuclide therapy, whereas tumors exhibiting high SSTR expression are considered optimal candidates for PRRT (Jha et al., 2021; Prado-Wohlwend et al., 2022). Moreover, differences in the diagnostic performance of [^{68}Ga]Ga-DOTATATE PET/CT, [^{18}F]FDG PET/CT, magnetic resonance imaging (MRI), and MIBG scintigraphy further support an imaging-guided approach to personalized treatment stratification (Jha et al., 2024; Scheuba et al., 2025).

Despite these advances, the optimal integration of functional imaging into routine clinical decision-making remains an area of ongoing investigation. The extent to which pre-treatment molecular imaging can reliably predict therapeutic efficacy and guide individualized treatment selection has yet to be fully established.

The objective of this review is to analyze the current role of functional imaging in pheochromocytoma and paraganglioma (PPGL), with particular emphasis on its contribution to molecular characterization, treatment selection, and the implementation of personalized therapeutic strategies. This review aims to evaluate the diagnostic and predictive value of major functional imaging modalities, including [^{68}Ga]Ga-DOTATATE PET/CT, [^{123}I]I-MIBG scintigraphy, and [^{18}F]FDG PET/CT, in guiding radionuclide therapy and optimizing clinical management of patients with advanced PPGL.

The main research problems addressed in this review include:

Determining the comparative diagnostic performance of currently available functional imaging modalities in different clinical and molecular subgroups of PPGL, including metastatic disease, SDHB-associated tumors, and specific anatomical locations.

Evaluating the relationship between functional imaging phenotypes, tumor biology, molecular characteristics, and genetic background, with particular attention to somatostatin receptor expression and norepinephrine transporter activity.

Assessing the role of functional imaging in theranostic decision-making, including the selection of candidates for [^{131}I]I-MIBG therapy and peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTATATE.

Identifying current limitations of imaging-based treatment stratification and defining areas requiring further investigation for improving personalized management of PPGL.

2. Materials and Methods

This review evaluates the role of pre-treatment functional imaging in the management of pheochromocytoma and paraganglioma (PPGL). The primary objective was to assess the potential of functional imaging to guide personalized therapeutic decision-making in patients with PPGL.

A comprehensive literature search was performed using the PubMed database and other scientific sources. Only articles published in English in peer-reviewed international journals were considered. The review included original clinical studies, retrospective analyses, review articles, and international clinical practice guidelines.

The literature search focused on the following key areas: (1) the diagnostic performance of functional imaging for the detection, localization, and staging of PPGL; (2) comparisons among imaging modalities, including [^{68}Ga]Ga-DOTATATE PET/CT, [^{123}I]I-MIBG and [^{131}I]I-MIBG scintigraphy, [^{18}F]FDG PET/CT, magnetic resonance imaging (MRI), and computed tomography (CT); (3) the role of imaging in characterizing tumor phenotype and inpatient heterogeneity; (4) the contribution of functional imaging to selecting targeted radionuclide therapies; and (5) recent advances in theranostics and precision medicine for PPGL.

Particular attention was given to studies involving patients with metastatic, unresectable, or recurrent PPGL, in whom therapeutic decision-making is especially challenging. Studies investigating genotype–phenotype associations, particularly those involving SDHB mutations, as well as somatostatin receptor expression, were also included because of their potential impact on imaging interpretation and treatment planning.

The selected publications were qualitatively analyzed, with particular emphasis on methodological quality, transparency, and clinical relevance, in order to provide a structured overview of the role of functional imaging in guiding personalized treatment strategies for PPGL.

3. Results

3.1. Diagnostic Performance of Functional Imaging

Functional imaging represents an essential component of the diagnostic work-up of pheochromocytoma and paraganglioma (PPGL). It is routinely used for tumor localization, disease staging, detection of metastatic lesions, and post-treatment surveillance. Unlike conventional anatomical imaging, functional imaging provides additional information regarding tumor biology, receptor expression, and molecular phenotype, all of which have direct implications for therapeutic decision-making (Carrasquillo et al., 2021; Janssen et al., 2015; Janssen et al., 2016a; Janssen et al., 2016b; Maurice et al., 2012; Scheuba et al., 2025).

Among the currently available imaging modalities, [^{68}Ga]Ga-DOTATATE PET/CT has demonstrated excellent diagnostic performance across a wide range of clinical settings. Numerous studies have reported particularly high sensitivity for detecting metastatic disease, skeletal metastases, and head and neck paragangliomas. This imaging modality appears to be especially valuable in patients with SDHB-associated PPGLs and in tumors exhibiting high somatostatin receptor expression. Its superior diagnostic performance is largely attributed to preserved or increased expression of somatostatin receptor subtype 2 (SSTR2) in these tumors (Janssen et al., 2015; Janssen et al., 2016a; Janssen et al., 2016b; Jha et al., 2024; Maurice et al., 2012; Scheuba et al., 2025; Shahrokhi et al., 2020).

In contrast, [^{123}I]I-MIBG scintigraphy generally demonstrates lower sensitivity for lesion detection, particularly in poorly differentiated or biologically aggressive tumors. Nevertheless, it remains clinically important because it identifies tumors with preserved norepinephrine transporter activity, thereby enabling the selection of patients who are most likely to benefit from [^{131}I]I-MIBG radionuclide therapy (Jha et al., 2021; Prado-Wohlwend et al., 2022; Shahrokhi et al., 2020).

Other imaging modalities, including [^{18}F]FDG PET/CT, [^{18}F]FDOPA PET/CT, MRI, and CT, also play complementary roles in specific clinical scenarios. [^{18}F]FDG PET/CT is particularly valuable in aggressive, dedifferentiated, or rapidly progressive disease, whereas MRI offers superior soft-tissue contrast and improves the detection of spinal and soft-tissue involvement. Evidence from long-term observational studies indicates that combining anatomical and functional imaging modalities enhances overall diagnostic accuracy and provides a more comprehensive assessment of disease extent (Jha et al., 2024; Mori et al., 2024; Scheuba et al., 2025).

3.2. Tumor Heterogeneity and Molecular Imaging Phenotypes

One of the most consistent findings across the reviewed studies is the marked biological heterogeneity of PPGLs. Different lesions within the same patient may exhibit distinct uptake patterns on [^{68}Ga]Ga-DOTATATE PET/CT, [^{18}F]FDG PET/CT, and MIBG scintigraphy. This heterogeneity likely reflects differences in receptor expression, tumor differentiation, and underlying molecular or genetic characteristics (Chang et al., 2016; Hedeer et al., 2025; Iravani et al., 2022; Pacak et al., 2026; Timmers et al., 2024;).

Molecular imaging phenotypes frequently correlate with specific genomic subgroups. Tumors associated with SDHB mutations typically demonstrate high uptake on [^{68}Ga]Ga-DOTATATE PET/CT and/or [^{18}F]FDG PET/CT, whereas more differentiated tumors often retain MIBG avidity. These imaging characteristics may have important prognostic implications and contribute to individualized treatment selection (Hedeer et al., 2025; Janssen et al., 2015; Pacak et al., 2026; Timmers et al., 2024).

Interlesional heterogeneity may further complicate therapeutic planning. Some patients demonstrate positive findings across multiple imaging modalities, whereas others exhibit mixed imaging phenotypes, with certain metastatic lesions showing intense DOTATATE uptake while others are predominantly FDG-avid or MIBG-avid. Such findings likely reflect clonal evolution and variable degrees of tumor dedifferentiation within the same individual (Chang et al., 2016; Hedeer et al., 2025).

A multimodal imaging approach provides a more comprehensive assessment of tumor heterogeneity and supports more informed clinical decision-making. In many patients, no single imaging modality is sufficient to accurately characterize the entire disease burden or identify the most appropriate molecular target for therapy (Chang et al., 2016; Hedeer et al., 2025; Iravani et al., 2022).

3.3. Clinical Significance of Somatostatin Receptor Expression for PRRT

Somatostatin receptor imaging plays a pivotal role in identifying patients who are suitable candidates for peptide receptor radionuclide therapy (PRRT). Although somatostatin receptors are commonly expressed in PPGLs, both receptor density and subtype distribution vary considerably among patients and even among individual lesions within the same patient. This biological variability has a substantial impact on imaging findings and therapeutic response (García-Vioque et al., 2026; Leijon et al., 2019; Patel et al., 2021; Taieb & Pacak, 2018).

Among the five known somatostatin receptor subtypes, somatostatin receptor subtype 2 (SSTR2) is considered the most clinically relevant in PPGL. SSTR2 exhibits high affinity for radiolabeled somatostatin analogues, including [^{68}Ga]Ga-DOTATATE, which is widely used for PET/CT imaging, and [^{177}Lu]Lu-DOTATATE, the therapeutic agent used for PRRT. Consequently, intense uptake on [^{68}Ga]Ga-DOTATATE PET/CT not only confirms receptor expression but also indicates the presence of a suitable therapeutic target (García-Vioque et al., 2026; Patel et al., 2021; Taieb & Pacak, 2018).

However, receptor expression is not uniform across all PPGLs. Histopathological studies have demonstrated considerable variability in the expression of somatostatin receptor subtypes. While some tumors exhibit strong and diffuse SSTR2 expression, others show low or heterogeneous receptor expression. Consequently, tracer uptake on [^{68}Ga]Ga-DOTATATE PET/CT may vary substantially, resulting in less predictable responses to PRRT (Leijon et al., 2019).

Genetic background also influences receptor expression. PPGLs associated with SDHB mutations frequently demonstrate increased SSTR2 expression and intense uptake on somatostatin receptor imaging. Since SDHB-associated tumors are often metastatic and clinically aggressive, this finding is particularly important because it identifies a subgroup of patients who may derive substantial benefit from PRRT despite their unfavorable biological characteristics (García-Vioque et al., 2026; Janssen et al., 2015).

The intensity and distribution of [^{68}Ga]Ga-DOTATATE uptake can also be used to estimate the likelihood of therapeutic response. High and homogeneous tracer uptake across most tumor lesions suggests that an adequate radiation dose can be delivered during PRRT. Conversely, heterogeneous uptake or the presence of receptor-negative lesions may indicate incomplete treatment coverage and consequently reduced therapeutic efficacy (Iravani et al., 2022; Mori et al., 2024).

The relationship between somatostatin receptor expression and tumor differentiation is equally important. Well-differentiated tumors generally retain receptor expression and demonstrate high uptake on [^{68}Ga]Ga-DOTATATE PET/CT, whereas poorly differentiated or rapidly progressive lesions may lose receptor expression while exhibiting increased metabolic activity on [^{18}F]FDG PET/CT. In such cases, PRRT alone may be insufficient, and alternative or combination therapeutic strategies should be considered (Chang et al., 2016; Iravani et al., 2022).

Overall, somatostatin receptor imaging identifies the molecular target, evaluates its distribution throughout the body, and determines whether an adequate radiation dose can be delivered to tumor tissue. Consequently, assessment of somatostatin receptor expression represents a fundamental step in personalized treatment planning for patients being considered for PRRT (Patel et al., 2021; Taieb & Pacak, 2018; te Beek et al., 2023).

3.4. Functional Imaging as a Guide for Treatment Selection

Unlike conventional anatomical imaging, functional imaging provides insight into the biological characteristics of PPGLs, including receptor expression, metabolic activity, and norepinephrine transporter function. These molecular features help identify the dominant therapeutic target and facilitate the selection of the most appropriate targeted treatment strategy (Carrasquillo et al., 2021; Higuchi et al., 2025; Jha et al., 2021; Prado-Wohlwend et al., 2022; Taieb et al., 2019b; Vyakaranam et al., 2019).

The choice between [^{131}I]I-MIBG therapy and PRRT with [^{177}Lu]Lu-DOTATATE is largely determined by the imaging phenotype, receptor expression profile, and tracer uptake characteristics. Tumors demonstrating high MIBG uptake generally retain norepinephrine transporter function and are therefore suitable candidates for [^{131}I]I-MIBG therapy. In contrast, tumors exhibiting intense uptake on [^{68}Ga]Ga-DOTATATE PET/CT usually express high levels of SSTR2 and are more likely to respond favorably to PRRT (Carrasquillo et al., 2021; Higuchi et al., 2025; Jha et al., 2021; Prado-Wohlwend et al., 2022; Taieb et al., 2019b; Vyakaranam et al., 2019).

In some patients, both MIBG and [^{68}Ga]Ga-DOTATATE imaging produce positive findings. In these situations, treatment selection should also consider several additional factors, including tracer uptake intensity,

total tumor burden, previous therapies, expected toxicity, and treatment availability. For example, patients with extensive skeletal metastases demonstrating strong somatostatin receptor expression are generally considered better candidates for PRRT, whereas those with predominantly MIBG-avid disease and limited receptor expression may benefit more from [^{131}I]I-MIBG therapy (Jha et al., 2021; Prado-Wohlwend et al., 2022).

Functional imaging may also provide valuable prognostic information. Tumors retaining receptor expression are typically better differentiated and more responsive to receptor-targeted radionuclide therapy, whereas predominant [^{18}F]FDG uptake is often associated with aggressive tumor biology and a less favorable prognosis (Chang et al., 2016; Pacak et al., 2026; Timmers et al., 2024).

Overall, functional imaging has become an indispensable component of treatment selection in patients with advanced PPGL. By identifying the predominant molecular target and characterizing tumor biology, it enables a personalized therapeutic approach and may ultimately improve clinical outcomes (Carrasquillo et al., 2021; Higuchi et al., 2025; Jha et al., 2021; Prado-Wohlwend et al., 2022; Taieb et al., 2019b; Vyakaranam et al., 2019).

3.5. Clinical Efficacy of Radionuclide Therapy

Patients with metastatic or unresectable PPGL treated with PRRT using [^{177}Lu]Lu-DOTATATE have demonstrated favorable clinical outcomes, including disease stabilization, symptom control, and prolonged progression-free survival in numerous studies (de Jong et al., 2002; Jaiswal et al., 2020; Tang et al., 2023; Vyakaranam et al., 2019; Zhang et al., 2023). These benefits are primarily attributable to the ability of PRRT to deliver targeted radiation directly to tumor cells expressing somatostatin receptors while minimizing radiation exposure to surrounding healthy tissues. Furthermore, patients with high and homogeneous uptake on pre-treatment somatostatin receptor imaging are more likely to receive an adequate and uniform radiation dose, thereby increasing the probability of a favorable therapeutic response (Mori et al., 2024; Patel et al., 2021; te Beek et al., 2023; Vyakaranam et al., 2019).

High-activity [^{131}I]I-MIBG therapy has also demonstrated meaningful clinical benefit in appropriately selected patients with MIBG-avid tumors. Its therapeutic efficacy depends largely on the results of pre-treatment functional imaging (Carrasquillo et al., 2021; Jha et al., 2021). Tumors retaining norepinephrine transporter function are more likely to accumulate sufficient therapeutic activity, resulting in improved disease control and symptom relief. Conversely, poor or heterogeneous MIBG uptake may lead to inadequate radiation delivery and reduced treatment efficacy (Carrasquillo et al., 2021; Higuchi et al., 2025; Jha et al., 2021; Prado-Wohlwend et al., 2022; Taieb et al., 2019a).

The effectiveness of radioligand therapy is influenced by several biological and physical factors, including receptor density, ligand affinity, tracer uptake, intratumoral retention time, and the absorbed radiation dose (te Beek et al., 2023).

Functional imaging provides valuable pre-treatment information regarding many of these parameters. High tracer uptake generally indicates abundant target expression, suggesting that therapeutic radiopharmaceuticals will accumulate efficiently within tumor tissue. In contrast, low or heterogeneous uptake may reflect limited target availability or uneven radiopharmaceutical distribution, potentially reducing therapeutic effectiveness (te Beek et al., 2023).

The physical properties of the radionuclide also contribute to treatment response. Different radionuclides vary in tissue penetration and radiation energy, influencing the depth and uniformity of radiation delivery. These characteristics are particularly relevant in patients with bulky disease or metastases of varying sizes, where achieving homogeneous radiation exposure may be challenging (de Jong et al., 2002; te Beek et al., 2023). In addition, intratumoral retention time is an important determinant of treatment efficacy. Even when initial tracer uptake is high, rapid tracer washout may reduce the absorbed radiation dose and diminish therapeutic benefit. Therefore, both tracer uptake intensity and retention kinetics should be considered when predicting treatment response (te Beek et al., 2023).

3.6. Future Perspectives

The role of precision medicine in the management of PPGL continues to expand. Advances in molecular imaging, radiomics, genomics, and artificial intelligence-based predictive models are expected to further improve individualized treatment planning and therapeutic outcomes in the coming years (Juhlin & Mete, 2024; Pacak et al., 2026; Timmers et al., 2024).

Current international guidelines recommend selecting imaging modalities according to tumor location, genetic background, disease stage, and intended therapeutic strategy. Consequently, multimodal imaging and theranostic approaches are increasingly being incorporated into routine clinical practice for patients with advanced PPGL (Juhlin & Mete, 2024; Taieb et al., 2019a).

3.7. Limitations of the Review

Despite the growing body of evidence supporting the role of functional imaging in the personalized management of PPGL, several limitations should be acknowledged. Most of the available evidence is derived from retrospective studies involving relatively small patient cohorts, which may limit the generalizability of the reported findings. In addition, considerable heterogeneity exists among published studies with respect to patient populations, imaging protocols, radiopharmaceuticals, treatment strategies, and outcome measures, making direct comparisons challenging.

Another important limitation is the lack of prospective, randomized clinical trials directly comparing different functional imaging-guided therapeutic approaches. Consequently, the current evidence is insufficient to establish standardized imaging-based treatment algorithms applicable across all clinical settings. Furthermore, because PPGLs are rare and biologically heterogeneous tumors, many published studies include highly selected patient populations, introducing the potential for selection bias.

Therefore, although current evidence strongly supports the integration of functional imaging into personalized treatment planning, further large-scale prospective multicenter studies are required to validate imaging biomarkers, optimize patient selection, and refine theranostic treatment strategies.

4. Discussion

The findings of this review support the concept of theranostics, whereby functional imaging serves not only as a diagnostic tool but also as a means of guiding personalized radionuclide therapy. Current evidence indicates that pre-treatment molecular imaging provides clinically relevant information on tumor biology, receptor expression, metabolic activity, and molecular phenotype, all of which play a central role in therapeutic decision-making (Carrasquillo et al., 2021; Chang et al., 2016; Janssen et al., 2015; Janssen et al., 2016a; Janssen et al., 2016b; Jha et al., 2024; Maurice et al., 2012; Scheuba et al., 2025).

Available clinical evidence consistently demonstrates the excellent diagnostic performance of [⁶⁸Ga]Ga-DOTATATE PET/CT across multiple PPGL subgroups, with particularly high sensitivity in patients with metastatic disease, SDHB-associated tumors, head and neck paragangliomas, and skeletal metastases (Janssen et al., 2015; Janssen et al., 2016a; Janssen et al., 2016b; Jha et al., 2024; Maurice et al., 2012; Scheuba et al., 2025).

Since SSTR2 also represents the molecular target for [¹⁷⁷Lu]Lu-DOTATATE therapy, functional imaging establishes a direct link between diagnosis and treatment, thereby providing the biological foundation for the theranostic approach (García-Vioque et al., 2026; Leijon et al., 2019; Patel et al., 2021; Taieb & Pacak, 2018).

Although [¹²³I]I-MIBG scintigraphy generally demonstrates lower diagnostic sensitivity, particularly in metastatic or poorly differentiated tumors, it remains an indispensable component of treatment planning because it identifies patients who are suitable candidates for [¹³¹I]I-MIBG therapy (Janssen et al., 2016a; Janssen et al., 2016b; Jha et al., 2021; Prado-Wohlwend et al., 2022; Taieb et al., 2019a).

These observations emphasize that the most clinically valuable imaging modality is not necessarily the one with the highest diagnostic sensitivity, but rather the one that provides the most relevant information for selecting the optimal therapeutic strategy.

Tumor heterogeneity represents another key challenge in the management of PPGL. These tumors are biologically heterogeneous, and functional imaging frequently reflects this complexity. Different lesions within the same patient may demonstrate distinct uptake patterns on [⁶⁸Ga]Ga-DOTATATE PET/CT, [¹⁸F]FDG PET/CT, and MIBG scintigraphy, reflecting differences in receptor expression, tumor differentiation, and clonal evolution (Chang et al., 2016; Hedeer et al., 2025; Iravani et al., 2022; Taieb et al., 2019b). This interlesional heterogeneity may explain why some patients experience durable responses to radionuclide therapy, whereas others exhibit mixed or only partial therapeutic responses.

The relationship between genotype and imaging phenotype has become increasingly important in the era of precision medicine. SDHB-associated tumors frequently demonstrate intense uptake on [⁶⁸Ga]Ga-DOTATATE PET/CT and/or [¹⁸F]FDG PET/CT, and are commonly associated with metastatic disease and a more aggressive clinical course (García-Vioque et al., 2026; Hedeer et al., 2025; Janssen et al., 2015; Timmers et al., 2024). In contrast, more differentiated tumors often retain MIBG avidity. These observations suggest that genetic alterations indirectly influence treatment selection by shaping the molecular imaging phenotype. Consequently, imaging heterogeneity should be regarded as an integral component of personalized treatment planning in PPGL.

PRRT has demonstrated encouraging clinical outcomes in appropriately selected patients with progressive PPGL. Several studies have reported durable disease control, improvement of clinical symptoms, and prolonged progression-free survival following treatment (de Jong et al., 2002; Jaiswal et al., 2020; Tang et al., 2023; Zhang et al., 2023).

Some comparative analyses have suggested superior disease control and longer progression-free survival with PRRT than with [¹³¹I]-MIBG therapy. However, these findings should be interpreted cautiously because the available evidence is derived predominantly from retrospective studies with heterogeneous patient populations and differences in treatment selection (Jaiswal et al., 2020; Prado-Wohlwend et al., 2022).

Treatment selection is rarely straightforward. In some patients, both MIBG and somatostatin receptor imaging demonstrate positive findings. In such cases, therapeutic decisions should consider additional clinical factors, including total tumor burden, tracer uptake intensity, previous treatments, expected toxicity, patient comorbidities, and local treatment availability or institutional expertise (Carrasquillo et al., 2021; Prado-Wohlwend et al., 2022). Patients with mixed imaging phenotypes may ultimately benefit from sequential or combined radionuclide treatment strategies; however, robust clinical evidence supporting these approaches remains limited.

The biological basis of radionuclide therapy further supports the use of functional imaging in treatment planning. The therapeutic efficacy of radioligand therapy depends not only on target expression but also on receptor density, ligand affinity, tracer uptake, intratumoral retention time, and the absorbed radiation dose delivered to the tumor (te Beek et al., 2023). Functional imaging provides valuable surrogate information regarding many of these parameters and therefore contributes to estimating the likelihood of therapeutic response while simultaneously identifying factors associated with treatment-related toxicity. Individualized treatment planning, including patient-specific dosimetry, assessment of tumor burden, and evaluation of radiation exposure to normal organs, may further optimize treatment outcomes while minimizing adverse effects.

Despite the promising evidence, several important limitations should be acknowledged. Most published studies are retrospective, include relatively small patient cohorts, and apply heterogeneous imaging protocols, therapeutic strategies, and outcome measures. Direct head-to-head comparisons between radionuclide therapies remain scarce, and high-quality prospective clinical trials are still lacking. Furthermore, standardized evidence-based algorithms for imaging-guided treatment selection have not yet been fully established (Pacak et al., 2026; Scheuba et al., 2025; Shahrokhi et al., 2020).

Future research should focus on integrating molecular imaging with genomic profiling, radiomics, and artificial intelligence-based predictive models to improve patient stratification and optimize individualized treatment strategies. Continued development of novel radiopharmaceuticals together with a deeper understanding of PPGL biology is expected to further expand therapeutic opportunities and improve clinical outcomes (Higuchi et al., 2025; Juhlin & Mete, 2024; Pacak et al., 2026; Taieb et al., 2019a; Timmers et al., 2024).

Overall, functional imaging has evolved beyond its traditional diagnostic role and now represents a cornerstone of precision medicine in patients with advanced PPGL. An individualized multimodal approach integrating molecular imaging, genetic background, and clinical characteristics provides the foundation for personalized treatment selection and has the potential to improve outcomes in this biologically heterogeneous disease.

5. Conclusions

This review highlights the critical role of functional imaging in the contemporary management of pheochromocytoma and paraganglioma (PPGL), extending beyond diagnosis to enable personalized therapeutic decision-making. Among currently available imaging modalities, [⁶⁸Ga]-DOTATATE PET/CT demonstrates the highest overall diagnostic performance, particularly in patients with metastatic disease, bone metastases, head and neck paragangliomas, and SDHB-associated tumors. In addition, it enables the identification of patients who may benefit from peptide receptor radionuclide therapy (PRRT) with [¹⁷⁷Lu]-DOTATATE. Although [¹²³I]-MIBG scintigraphy has lower sensitivity, it remains clinically valuable for selecting candidates for [¹³¹I]-MIBG therapy.

A key conclusion of this review is that the functional imaging phenotype reflects underlying tumor biology, molecular characteristics, and genetic background. Tumor heterogeneity, both among different

patients and between individual lesions within the same patient, plays a crucial role in determining prognosis and therapeutic response. The integration of somatostatin receptor imaging, MIBG imaging, and metabolic assessment with [¹⁸F]-FDG PET/CT provides a more comprehensive approach for clinical decision-making. Pre-treatment functional imaging can identify the predominant molecular target, predict treatment efficacy, and support the optimization of personalized therapeutic strategies in advanced PPGL. Therefore, functional imaging serves not only as a diagnostic tool but also as a key component guiding individualized management of these rare and complex tumors.

Funding Statement: This research received no external funding.

Ethics Approval Statement: Not applicable. Ethical approval was not required for this review study.

Conflict of Interest Statement: The authors declare no conflict of interest.

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