Title

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Journal

Clinical Cancer Research, 27(11)

ISSN

1078-0432

Authors

Jha, Abhishek
Taïeb, David
Carrasquillo, Jorge A
et al.

Publication Date

2021-06-01

DOI

10.1158/1078-0432.ccr-20-3703

Peer reviewed

HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Clin Cancer Res. 2021 June 01; 27(11): 2989–2995. doi:10.1158/1078-0432.CCR-20-3703.

High-specific-activity ^{131}I-MIBG vs ^{177}Lu-DOTATATE targeted radionuclide therapy for metastatic pheochromocytoma and paraganglioma

Abhishek Jha[1], **David Taïeb**[2], **Jorge A. Carrasquillo**[3], **Daniel A. Pryma**[4], **Mayank Patel**[1], **Corina Millo**[5], **Wouter W. de Herder**[6], **Jaydira Del Rivero**[7], **Joakim Crona**[8], **Barry L. Shulkin**[9], **Irene Virgolini**[10], **Alice Chen**[11], **Bhagwant R. Mittal**[12], **Sandip Basu**[13], **Joseph S. Dillon**[14], **Thomas A. Hope**[15], **Carina Mari Aparici**[16], **Andrei H. Iagaru**[16], **Rodney J. Hicks**[17], **Anca M. Avram**[18], **Jonathan R. Strosberg**[19], **Ali Cahid Civelek**[20], **Frank I. Lin**[21], **Neeta Pandit-Taskar**[3,*], **Karel Pacak**[1,*]

[1]Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Dr., Bldg. 10, Room 1E-3140, Bethesda, MD, 20892, USA. [2]Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France. [3]Department of Radiology, Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA. and Dept of Radiology. Weil Cornell Medical College, NY. [4]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [5]Positron Emission Tomography Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA. [6]Section of Endocrinology, Department of Internal Medicine, ENETS Centre of Excellence, Erasmus MC Cancer Institute, Erasmus MC, Rotterdam, the Netherlands. [7]Developmental Therapeutics

Corresponding authors and request for reprints: Karel Pacak, M.D., Ph.D., D.Sc., FACE, Chief, Section on Medical Neuroendocrinology, Professor of Medicine, *Eunice Kennedy Shriver* NICHD, NIH, Building 10, CRC, 1E-3140, 10 Center Drive, MSC-1109, Bethesda, Maryland 20892-1109, karel@mail.nih.gov, Fax: 1-301-402-0884, Phone: 1-301-402-4594; **Neeta Pandit-Taskar, MD**, Attending Radiologist, Molecular Imaging &Therapy Svc, Dept of Radiology., *Member*, Memorial Hospital., Memorial Sloan Kettering Cancer Center, NY, *Professor*, Dept of Radiology, Weill Cornell Medical Center, NY, *Clinical Director*, Center for Targeted Radioimmunotherapy and Theranostics, Ludwig Center for Cancer Immunotherapy, MSK, Member Researcher, Parker Institute of Cancer Immunotherapy, MSK, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, pandit-n@mskcc.org, Fax: 1-212-717-3263, Phone: 1-212-639-3046.

*Neeta Pandit-Taskar and Karel Pacak equally share the senior authorship.

Financial Disclosure: This work was supported, in part, by the Intramural Research Program of the National Institutes of Health, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (grant number: Z1AHD008735) and was supported, in part, by the National Institutes of Health, National Cancer Institute Cancer Center Support Grant P30 CA008748.

Disclaimer: Daniel Pryma: Research Grant, Siemens AG, Research Grant, 511 Pharma, Research Grant, Progenics Pharmaceuticals, Inc, Research Consultant, Progenics Pharmaceuticals, Inc, Research Consultant, 511 Pharma, Research Consultant, Siemens AG, Research Consultant, Actinium Pharmaceuticals, Inc, Research Consultant, Bayer. Wouter W de Herder: honoraria from Ipsen, AAA, and Novartis. Irene Virgolini: Research Consultant, AAA and Ipsen Pharma. Joakim Crona: lecture honoraria from Novartis and educational honoraria from NET Connect (funded by IPSEN). Joseph Dillon: Research Grant, Progenics Pharmaceuticals, Inc. Andrei Iagaru receives institutional research support from GE Healthcare, AAA, Progenics Pharmaceuticals, and is a consultant to GE HealthCare, AAA, Progenics Pharmaceuticals, and ITM. Rodney J. Hicks: shareholder in Telix Pharmaceuticals with proceeds donated to his institution. Jonathan Strosberg: honoraria from Ipsen, Lexicon, and Novartis. N. Pandit-Taskar is a consultant, receives honoraria or serves on the advisory board for Actinium Pharma, Progenics, Medimmune/Astrazeneca, Illumina, Ymabs and conducted research supported by Imaginab, Janssen and Regeneron.

Nothing to disclose: Abhishek Jha, David Taïeb, Jorge Carrasquillo, Mayank Patel, Corina Millo, Jaydira Del Rivero, Barry L. Shulkin, Alice Chen, Bhagwant R. Mittal, Sandip Basu, Carina Mari Aparici, Anca M. Avaram, Ali Cahid Civelek, Frank I. Lin, and Karel Pacak.

Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA. [8]Department of Medical Sciences, Uppsala University, Uppsala, Sweden. [9]Department of Diagnostic Imaging, St. Jude Children's Research Hospital, Memphis, TN, USA. [10]Department of Nuclear Medicine, Medical University of Innsbruck, Innsbruck, Austria. [11]Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA. [12]Department of Nuclear Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India. [13]Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe; Homi Bhabha National Institute, India. [14]Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA. [15]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California. [16]Divisions of Nuclear Medicine and Molecular Imaging, Stanford University School of Medicine, Stanford, California. [17]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia. [18]Division of Nuclear Medicine, Department of Radiology, University of Michigan, Ann Arbor, MI, USA [19]Gastrointestinal Department/Neuroendocrine Tumor Division, Moffitt Cancer Center, Tampa, FL, USA [20]Division of Nuclear Medicine and Molecular imaging, Department of Radiology and Radiological Sciences, Johns Hopkins Medicine, Baltimore, MD, USA [21]Molecular Imaging Program, National Cancer Institute, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA.

Abstract

Targeted radionuclide therapies using ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) and peptide receptor radionuclide therapy (^{177}Lu or ^{90}Y) represent several of the therapeutic options in the management of metastatic or inoperable pheochromocytoma and/or paraganglioma (PPGL). Recently, high-specific-activity-^{131}I-MIBG therapy was approved by the FDA and both ^{177}Lu-DOTATATE and ^{131}I-MIBG therapy were recommended by the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of metastatic PPGL. However, a clinical dilemma often arises in the selection of targeted radionuclide therapy, especially when a patient can be treated with either type of therapy based on eligibility by MIBG and somatostatostatin receptor imaging. In order to address this problem, we assembled a group of international experts including oncologists, endocrinologists, and nuclear medicine physicians, with substantial experience in treating neuroendocrine tumors with targeted radionuclide therapies in order to develop consensus and provide expert recommendations and perspectives on how to select between these two therapeutic options for metastatic PPGL. This manuscript aims to summarize the survival outcomes of the available targeted radionuclide therapies, discuss personalized treatment strategies based on functional imaging scans, address practical issues including regulatory approvals, and compare toxicities and risk factors across treatments. Further, it discusses the emerging targeted radionuclide therapies.

SUMMARY

The clinical decision making in the selection of patients for appropriate TRT should be personalized. Due to lack of controlled studies, we recommend a pragmatic approach based on expert consensus and opinion that is primarily based on the imaging results of MIBG and SSTRI scans. The agent with the highest uptake should be prioritized while considering the unique

toxicity profiles and relevant risk factors (age, marrow reserve, renal function, prior chemotherapy with alkylating agents or radiotherapies, and location and size of tumors). Additionally, practical aspects related to availability, insurance, and experience can influence the selection. Finally, multicentric randomized control trials comparing PRRT and HSA-^{131}I-MIBG therapy in progressive inoperable/metastatic PPGL patients should help to unravel this conundrum.

Keywords

MIBG; PRRT; ^{177}Lu-DOTATATE; ^{90}Y; ^{131}I; radionuclide therapy; somatostatin receptor; ^{68}Ga-DOTATATE; PET/CT; metastatic; pheochromocytoma; paraganglioma

Background

Targeted radionuclide therapies (TRTs) using ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) and peptide receptor radionuclide therapy (PRRT, ^{177}Lu or ^{90}Y) are available for metastatic or inoperable pheochromocytoma and/or paraganglioma (PPGL). It is unclear which therapy is preferable when tumors show uptake by both MIBG [generally ^{123}I-MIBG single-photon emission computed tomography/computed tomography (SPECT/CT) but potentially also ^{124}I-MIBG or ^{18}F- metafluorobenzylguanidine (^{18}F-MFBG) positron emission tomography/computed tomography (PET/CT)] and somatostatin receptor imaging (SSTRI, ^{111}In-pentetreotide or ^{68}Ga-DOTA-TATE/TOC/NOC PET/CT or ^{64}Cu-DOTATATE PET/CT). ^{131}I-MIBG is a safe and well-tolerated therapy, used since 1980s with objective, biochemical, and symptomatic responses in patients with PPGL (1). The recent Food and Drug Administration (FDA) approval of novel high-specific-activity (HSA)-^{131}I-MIBG therapy (Azedra®) in inoperable or metastatic PPGL has generated considerable interest (2). Similarly, the recent FDA approval of ^{177}Lu-DOTATATE (Lutathera®) for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) has led to an increasing interest in its use for other SSTR-expressing NETs including PPGLs (3-6). Availability of both of these TRTs presents a conundrum regarding the selection of the most appropriate option in patients who are candidates for TRTs. Therefore, we assembled experts in the field of oncology, endocrinology, and nuclear medicine to develop consensus and provide an expert opinion on how to select between these two therapeutic options for metastatic PPGL.

HSA-^{131}I-MIBG therapy

Recently, a HSA-formulation consisting almost entirely of radiolabeled ^{131}I-MIBG (~2,500 mCi/mg) was developed for norepinephrine transporter expressing tumors resulting in fewer pharmacological (side) effects than lower specificity formulations of ^{131}I-MIBG (15-50 mCi/mg) in which only ~1:2000 MIBG molecules have ^{131}I (2,7).

HSA-^{131}I-MIBG is administered in PPGL patients with positive MIBG scans and either progressive or symptomatic inoperable/metastatic disease. The main therapeutic goals are disease stabilization and symptom control. Treatment is given following dosimetry assessment using HSA-^{131}I-MIBG imaging over three to five days. A standard treatment regimen consists of two doses of 500 mCi (or 8 mCi/kg if weight <62.5 kg) of HSA-^{131}I-

MIBG, each given over 30 minutes [60 minutes recommended for pediatric (≥12 years) patients] at least 90 days apart. Thyroid blockade with stable iodide is mandatory.

In a single-arm phase II trial, 68 PPGL patients were treated with up to two cycles of HSA-^{131}I-MIBG. The primary endpoint, reduction in baseline antihypertensive medication lasting ≥6 months, was reached in 25% of patients (2). Furthermore, an objective partial response (PR, 23%) or stable disease (SD, 69%) within 12 months was seen in 92% patients by RECIST 1.0; and 68% showed complete response (CR) or PR in serum chromogranin levels. The median overall survival (OS) was 36.7 months from the first treatment (2). Moreover, the PR rate increased from 6% at 3 months to 23% at 12 months among patients receiving at least one therapeutic dose, indicating that HSA-^{131}I-MIBG effects can evolve over many months (2).

The most common side effects were myelosuppression, nausea/vomiting, and fatigue (2). Seventy-two percent (49/68) of patients in the phase II HSA-^{131}I-MIBG trial experienced ≥grade 3 hematotoxicity (41% thrombocytopenia, 41% leukopenia, 38% neutropenia, and 21% anemia) and 25% (17/68) required hematologic supportive care (packed red blood cells, platelets, granulocyte colony stimulating factor, and/or erythropoietin-alfa therapy for limited time) (2). Other severe adverse events included pulmonary embolism in 3% (2/68), myelodysplastic syndrome (MDS) in 4% (3/68), and secondary malignancies in 3% (acute myeloid leukemia and acute lymphocytic leukemia in 1 patient each) (2). Less common side effects included headache, dizziness, and fatigue (16-27%) (2). No acute hypertensive event was noted during or after the administration of HSA-^{131}I-MIBG . Similarly, nephrotoxicity was not reported (2). Of note, some patients in this Phase II trial were pre-treated with most having received at least one prior cytotoxic systemic therapy (38% chemotherapy and 30% ^{131}I-MIBG and/or HSA-^{131}I-MIBG TRT) and few having received several prior lines of cytotoxic systemic therapies (2).

Peptide receptor radionuclide therapy

PRRT with ^{177}Lu-DOTATATE was FDA approved in 2018 for patients with well-differentiated inoperable/metastatic GEP-NETs following favorable progression free survival (PFS) and quality of life outcomes in a phase III study of patients with progressing midgut NETs and the results of ongoing studies in the Erasmus MC, Rotterdam, the Netherlands (3,8,9). ^{177}Lu-DOTATATE has been used to treat patients with inoperable/ metastatic PPGL although the published data are limited to small uncontrolled retrospective studies using various dose regimens and radiopharmaceuticals (^{177}Lu/^{90}Y-DOTATATE/ DOTATOC) (5,6). In a meta-analysis of 179 pooled patients treated with 1-11 cycles of PRRT (^{90}Y and/or ^{177}Lu), 90% (95% CI: 84-95%) had achieved PR or SD (5). Similarly, a meta-analysis performed by Satapathy et al, reported an objective response rate [proportion of CR, PR, and/or minor response (MR)] of 25.0% (95% CI: 19.0-32.0%) and a disease control rate (proportion of CR, PR, MR, and SD) of 84% (95% CI: 77.0-89.0%) in 201 pooled patients (progressive disease <20% of patients) treated with 1-10 cycles (40.5-219 mCi/cycle) of PRRT (^{90}Y or ^{177}Lu or both) with a clinical and biochemical response in 61% and 64% of reported patients, respectively (6). Of note, many of the studies in both the meta-analyses are common. Furthermore, in a retrospective study (included in above meta-

analyses) in 22 progressive metastatic PPGL patients, the PFS and OS were significantly longer for metastatic PGL patients with PRRT (^{90}Y/^{177}Lu) compared to ^{131}I-MIBG but no significant difference was seen when considering all PPGL patients (10). There is an ongoing phase II study at the NIH (NCT03206060) evaluating ^{177}Lu-DOTATATE for progressive metastatic/inoperable PPGL patients with defects in genes encoding for succinate dehydrogenase subunits and sporadic PPGLs. However, currently no study protocol compares the survival outcomes of ^{131}I-MIBG and ^{177}Lu-DOTATATE.

PRRT therapy is usually administered in fixed dose cycles of 200 mCi/cycle of ^{177}Lu-DOTATATE infusion over 30-60 minutes with concomitant amino acid infusion for renal protection. Due to fixed dose therapy, dosimetry preparation/estimation is not routinely performed. Some centers have used dosimetric estimates, primarily to limit renal dose to 23 Gray and bone marrow to 2 Gray (11). Renal protection is provided by concomitant amino acid infusion. Some currently available commercial preparations contain many different amino acids which has a high rate of associated nausea and/or vomiting even with administration of anti-emetics, but the incidence can be substantially reduced by using a preparation that includes only $_{L}$-lysine and $_{L}$-arginine.

Based on its regulatory approval and commercial availability, ^{177}Lu-DOTATATE has displaced ^{90}Y-DOTATOC in recent years. Moreover, ^{177}Lu has longer half-life and gamma emission also which allows for imaging both for dosimetry, if desired, and post-therapy assessment (Table 1). A meta-analysis in PPGL, reported a pooled grade 3/4 thrombocytopenia, neutropenia, and lymphopenia in 9%, 3%, and 11% of the treated patients, respectively and nephrotoxicity in 4% patients (6). The therapy was discontinued for toxicity in only 4.9% (5/102) of patients (6). Reversible cardiac failure following catecholamine release (6.7%) and myelodysplastic syndrome (3.3%) has also been reported following ^{177}Lu-DOTATATE therapy (12). Further, development of catecholamine crises and tumor lysis syndrome were also observed following ^{177}Lu-DOTATATE (13).

Clinical decision-making process for the selection of HSA-^{131}I-MIBG vs ^{177}Lu-DOTATATE for PPGL

When a patient with metastatic/inoperable PPGL presents to the clinic for the evaluation of TRT, first and foremost step is to consider whether systemic therapy is indicated based on several factors: the disease course (progression vs stable disease), catecholamine/metanephrine secretion and related symptoms (e.g. controlled vs uncontrolled hypertension, arrhythmia, cardiovascular events, psychiatric symptoms), tumor location, and risk for complications (e.g. neurologic toxicity from vertebral metastases). Consideration of these factors is necessary because some patients with PPGL have indolent disease and are often safely followed with active surveillance and medical management of catecholamine excess (14-16). If the patient is potentially eligible for systemic therapy, particularly TRT, the second step is to evaluate MIBG and SSTRI scans to determine the degree and extent of uptake. It is of prime importance to ensure that the tumors can be targeted by TRT at a whole-body level by comparison of uptake in target lesions to total tumor burden noted on CT/magnetic resonance imaging and/or ^{18}F-fluorodeoxyglucose PET/CT (Figure 1).

The choice between ^{131}I-MIBG and ^{177}Lu-DOTATATE in many cases becomes obvious when lack of uptake is observed with one radiopharmaceutical and not the other as is frequently seen (Figure 2, **panel A and B**). The most important conundrum occurs when both ^{123}I-MIBG and SSTRI scans demonstrate similar uptake and extent of disease (Figure 2, **panel C**).

In such a scenario, where the imaging results of ^{123}I-MIBG and SSTRI scans allow TRT with either agent, the next step is to carefully consider the toxicity profile of each and patient's characteristics (age, marrow reserve, renal function, prior chemotherapy with alkylating agents or radiotherapies, and location and size of tumors). The most important factors to consider are bone marrow reserve and potential for acute catecholamine/hypertensive crisis. HSA-^{131}I-MIBG should be considered in patients with good bone marrow reserve [young patients, no history of prior extended radiotherapies to the bone marrow (spine or pelvis), fewer bone metastases] whereas ^{177}Lu-DOTATATE should be considered in patients with more marginal marrow reserve. Another important step is to evaluate cardiovascular status (electrocardiogram and echocardiogram) of these patients as elevated catecholamines and/or metanephrines can cause cardiac-related adverse events. In patients with elevated catecholamines and/or metanephrines, HSA-^{131}I-MIBG might be favored over ^{177}Lu-DOTATATE, as it is generally not associated with catecholamine crises (Table 1). There is no major preference between HSA-^{131}I-MIBG and ^{177}Lu-DOTATATE in patients with impaired renal functional and/or underlying risk factors for nephropathy (diabetes, essential hypertension, older age, prior nephrotoxic therapies or procedures), although parameters for renal function need to be monitored prior and during follow-up after the administration of both TRTs, and neither of the reagents have been adequately studied in patients with severe renal impairment (30mL/min) (Table 1). The impact of liver tumor burden on the choice between HSA-^{131}I-MIBG and ^{177}Lu-DOTATATE is equivocal: the median survival was similar for HSA-^{131}I-MIBG with or without lung/liver metastases, and baseline liver tumor burden did not have an impact on PFS in phase 3 NETTER-1 trial of ^{177}Lu-DOTATATE in GEP-NETs (2,17). In patients with a lower renal functional reserve, underlying renal disorders or those with suboptimal bone marrow reserve, dosimetry or low-dose TRT can be used for individualized TRT.

Insurance coverage for selection of imaging modality as well as TRT is an important consideration. Reimbursement conditions for both MIBG and PRRT vary across, and sometimes within, countries. Currently in the United States HSA-^{131}I-MIBG is the only FDA-approved radiopharmaceutical specifically for PPGL patients although ^{131}I-MIBG therapy has often been reimbursed or supported by third-party payers. ^{177}Lu-DOTATATE, while approved by FDA for GEP-NETs, is not approved for treatment of PPGL, although National Comprehensive Cancer Network (NCCN) guidelines also include ^{177}Lu-DOTATATE as an option for this population. There are concerns about the insurance coverage or availability despite the FDA approvals of ^{123}I-MIBG for the imaging and ^{131}I-HSA-MIBG in practice which may vary by region and insurance carrier. Therefore, once the decision for TRT is reached, both ^{123}I-MIBG and SSTRI should either be performed or the patient should be referred to an institution which has capability of imaging and therapy with these radionuclide agents.

In cases of heterogeneous disease with mismatched MIBG/SSTR avid lesions, the disease coverage may potentially be achieved by combining these therapeutic agents in sequential order, with the first therapy agent being the radiopharmaceutical demonstrating the highest focal uptake in the highest number of lesions (surrogate of total tumor burden) (11) or in a combined regimen ("cocktail") as demonstrated in a very small prospective cohort (n=10) of patients (18). However, both the approaches have not yet been rigorously tested and should be explored in future. Further, if any progressive lesions lack uptake by both of the above imaging scans, then they can be targeted by additional external beam radiation (11). If there is multifocal non-avid disease, these patients are often better served with other systemic treatment options, most commonly cytotoxic chemotherapy. Also, conventional ^{131}I-MIBG TRT should be considered in cases where HSA-^{131}I-MIBG cannot be administered due to logistical reasons. In some jurisdictions, the cost of HSA-^{131}I-MIBG is prohibitive in the absence of reimbursement and mandates consideration of conventional ^{131}I-MIBG.

Emerging or future perspectives in TRTs for PPGL

A special consideration for ^{90}Y-based PRRT should be made in patients with large-sized tumors, as the maximum emitted energy and path length for ^{90}Y is greater compared to ^{177}Lu and ^{131}I (Table 1) (18,19). Combinations of ^{131}I-MIBG and ^{90}Y-based PRRT are being evaluated to determine if these can improve targeting of variable-sized tumors and minimize toxicity (NCT03044977). Whether one should precede the other and the optimal combination may be decided on disease burden and avidity on scans.

Recently, PRRT with alpha emitter (^{225}Ac, ^{213}Bi, ^{212}Pb, etc.) has emerged and the initial results of a prospective evaluation in 32 patients of metastatic GEP-NETs showed promising results after 2 cycles with median cumulative activity of 0.84 mCi (range: 0.60-1.2 mCi) of ^{225}Ac-DOTATATE (20). These patients were either stable after completion of ^{177}Lu-DOTATATE (n=14) or progressive on prior ^{177}Lu-DOTATATE (n=18) therapy (20). The interim RECIST 1.1 analysis was available for 24/32 patients (n=12 progressive, n=12 stable after ^{177}Lu-DOTATATE) 8 weeks after the second cycle of ^{225}Ac-DOTATATE, and demonstrated an overall PR of 62.5% [15/24; 58.3% (7/12) in progressive cohort], MR of 25% [6/24; 16.7% (2/12) in progressive cohort], and SD of 12.5% [3/24; 25% (3/12) in progressive cohort], respectively (20). None of the patients showed grade 3/4 toxicity, progression of disease, or death within the median follow-up duration of 8 months (20). Further, in another retrospective study of ^{177}Lu-DOTATATE therapy in 15 patients with metastatic/inoperable PPGL, ^{225}Ac-based PRRT (n=2 patients) and ^{131}I-MIBG (n=1 patient) was administered on a compassionate basis to patients who progressed after 3 cycles of ^{177}Lu-DOTATATE while the remaining patients completed 6 cycles of ^{177}Lu-DOTATATE (21). It is important to note that ^{177}Lu-DOTATATE remains the only PRRT approved for treatment of NETs, and that ^{90}Y-, ^{225}Ac-, and other alpha particle-based PRRT are only available on clinical trials or compassionate use protocols.

Newer radiolabeled SSTR antagonists such as ^{177}Lu-Satoreotide tetraxetan (^{177}Lu-OPS201) are also undergoing evaluation in NETs, including metastatic PPGL (NCT02592707). It is still unclear whether the superior SSTR binding of antagonist drugs will result in improved therapeutic index compared to somatostatin analog based PRRT.

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Translational Relevance

Clinical decision making in the selection of appropriate targeted radiotherapy [^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) and peptide receptor radionuclide therapy (^{177}Lu/^{90}Y)] for patients is a clinical dilemma. The decision should be personalized based on the clinical presentation and MIBG and somatostatin receptor imaging. The agent that shows greater tumor targeting with more favorable toxicity profile and associated risk factors should be chosen for therapy. Heterogeneous disease with mismatched MIBG and somatostatin receptor avid lesions, poses additional challenge in decision making regarding choice of therapeutic agent. A combined or sequential regimen can be considered in such a situation. Additional external beam radiation for targeting any progressive lesions lacking uptake by both of the imaging modalities should be considered. Our perspective based on expert opinion and consensus provides a stepwise approach to selection of targeted systemic radiotherapy for patients with metastatic or inoperable pheochromocytoma and/or paraganglioma. In patients with large-sized or variable-sized tumors, ^{90}Y-based PRRT alone or in combinations (tandem- or duo-approaches) with other targeted radiotherapies can be entertained.

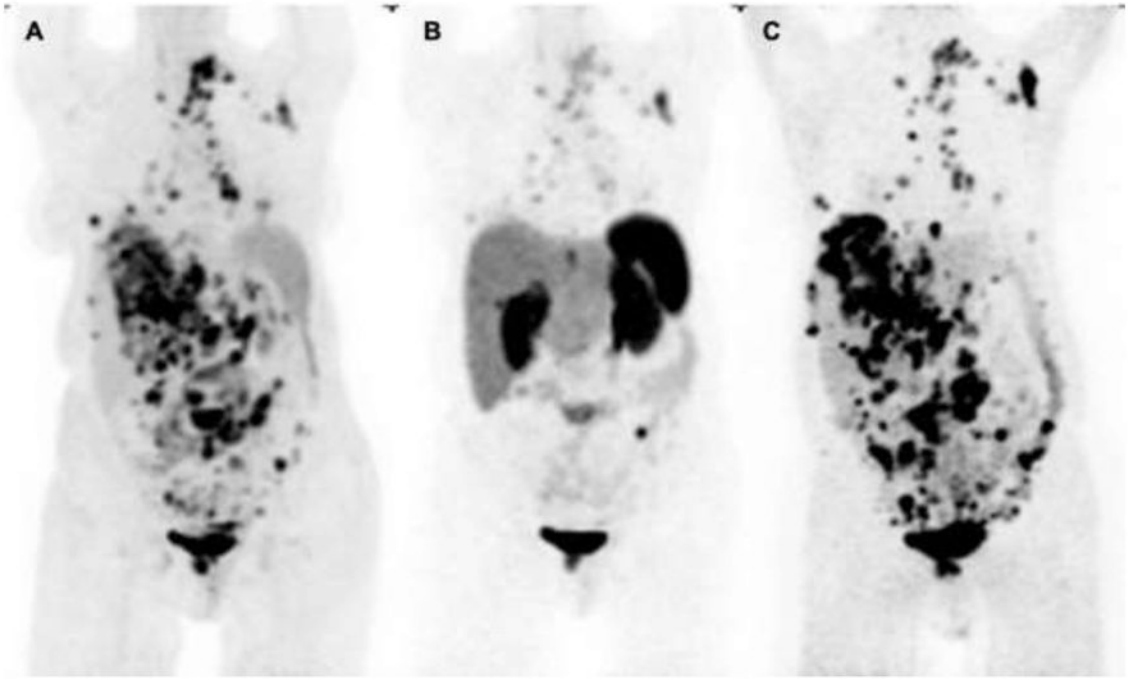

Figure 1. Selection of HSA-^{131}I-MIBG over PRRT for metastatic PPGL based on superior norepinephrine transporter expression imaged by ^{124}I-MIBG PET/CT and compared with ^{18}F-fluorodeoxyglucose PET/CT

The anterior maximum intensity projection images of (A) ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET/CT), (B) somatostatin receptor imaging by ^{68}Ga-DOTA(0)-Tyr(3)-octreotate (^{68}Ga-DOTATATE) PET/CT, and (C) norepinephrine transporter imaging by ^{124}I-metaiodobenzylguanidine (^{124}I-MIBG) PET/CT in a case of widely metastatic PPGL. ^{124}I-MIBG demonstrates more disease sites than ^{18}F-FDG as well as having significantly more intense and numerous lesion uptake than ^{68}Ga-DOTATATE, making MIBG therapy the preferred option for treatment in this case. Advantages of comparing PET to PET and ability to do prospective dosimetry are potential advantages of ^{124}I-MIBG over ^{123}I-MIBG although this technique is not widely available.

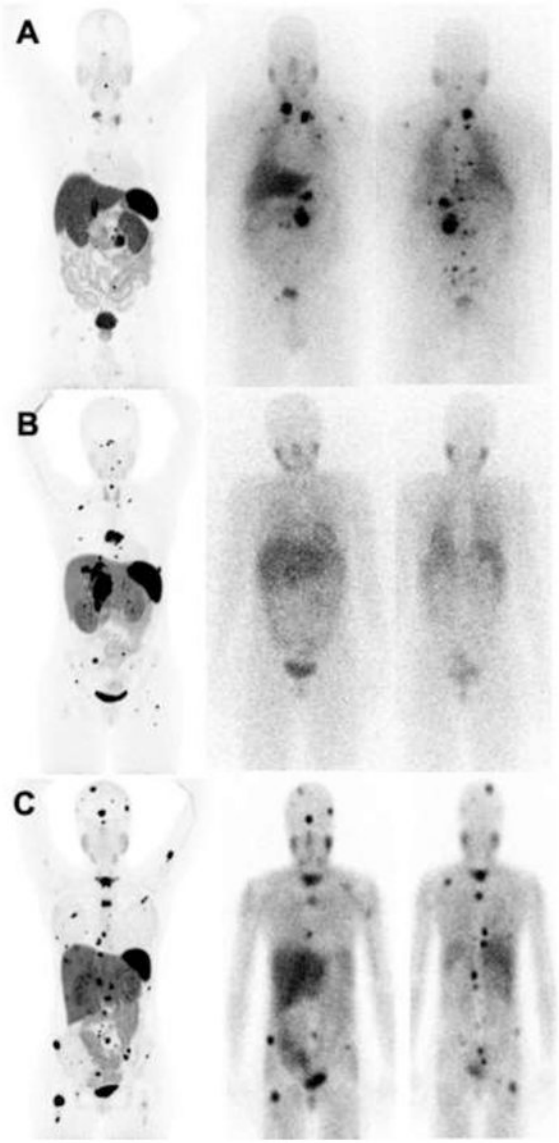

Figure 2. Selection of HSA-^{131}I-MIBG vs PRRT for metastatic pheochromocytoma/ paraganglioma based on expression of somatostatin receptor and norepinephrine transporter

Panel (A) demonstrates superior detection of tumors by norepinephrine transporter imaging by ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG, anterior and posterior planar images on the right) compared to somatostatin receptor imaging by ^{68}Ga-DOTA(0)-Tyr(3)-octreotate (^{68}Ga-DOTATATE) positron emission tomography-computed tomography (PET/CT) [maximum intensity projection (MIP) image on the left] in a 64-year-old man revealing a recurrent tumor in the left adrenalectomy bed along with retroperitoneal lesions, left supraclavicular lymph node and multiple scattered bony metastatic disease including cervical bone metastasis. Panel (B) demonstrates the superior detection of tumors by ^{68}Ga-DOTATATE PET/CT (MIP image on the left) compared to ^{123}I-MIBG (anterior and posterior planar images on the right) in a 33-year-old woman revealing an extensive recurrent tumor in the right adrenalectomy bed at the level of right mid kidney along with

metastatic disease in both lungs, scattered bone metastases in vertebral bodies, axial, and proximal appendicular skeleton. The planar images of ^{123}I-MIBG only reveals mild uptake of recurrent tumor in the right adrenalectomy bed. Panel (C) demonstrates the similar pattern of tumor detection by both ^{68}Ga-DOTATATE PET/CT (MIP image on the left) and ^{123}I-MIBG (anterior and posterior planar images on the right) in a 27-year-old female patient revealing metastatic liver lesions and multiple scattered bony metastatic disease. While interpreting the scans, it is critical to account for the inherent differences between single photon emission imaging (^{123}I-MIBG scintigraphy) and PET (^{68}Ga-DOTATATE) imaging as contrast recovery, sensitivity, and spatial resolution are far superior for PET imaging. Therefore, some of the smaller lesions seen on ^{68}Ga-DOTATATE MIP may not be visible on planar images of ^{123}I-MIBG scintigraphy despite adequate MIBG uptake. This should not be confused for greater uptake or a higher likelihood of response to therapy. ^{124}I-MIBG and ^{18}F-MFBG for PET that are under development should help simplify the comparison between MIBG and SSTRI scans in a given patient.

Table 1.

Targeted radionuclide therapies in pheochromocytoma/paraganglioma

	HSA-^{131}I- MIBG	^{177}Lu-DOTATATE	^{90}Y-based PRRT[a]
FDA approval for pheochromocytoma/ paraganglioma	Yes	No, currently only approved for gastroenteropancreatic neuroendocrine tumors	No
EMA approval for pheochromocytoma/ paraganglioma	No[b]	No, currently only approved for gastroenteropancreatic neuroendocrine tumors	No[c]
Approval of companion imaging modality for pheochromocytoma/paraganglioma	^{123}I-MIBG is FDA approved	^{68}Ga-DOTATATE is not FDA approved	^{68}Ga-DOTATATE is not FDA approved
Insurance coverage for metastatic pheochromocytoma/paraganglioma	Yes	Not usually	No
[d]**Cost of therapy (US dollars)**	~ 300,000	~ 200,000[e]	Commercial formulation currently unavailable
Dose [millicurie(mCi)/cycle]	500 (or 8 mCi/kg)	200	75-120
Number of cycles	2	4	2-4
Duration between cycles (months)	3	2	1.5-3
Special challenges	• Requirement of lead lined room or lead shields in room • Personnel training for radiation safety. • Requires in-patient stay. • Pre-treatment dosimetry. • Given that this has been recently approved, the number of centers currently doing this therapy is limited.	• Reimbursement by the insurance companies by prior approval. • Requirement of 4-hour co-infusion of amino acids.	• Availability • Requirement of 4-hour co-infusion of amino acids.
Physical properties			
• **Half-life (days)**	8.1	6.7	2.7
• **Maximum energy of emitted particle (mega electron-volt)**	0.81	0.5	2.3
• **Mean-maximum path length (millimeter)**	0.3-2.4	0.3-2.2	2.5-11.9
• **Gamma-radiation for post-therapy SPECT/CT imaging (mega electron-volt)**	0.364 (81% abundance)	0.113 (6% abundance), 0.208 (11% abundance)	No but utilizes the bremsstrahlung x-ray for SPECT/CT imaging and

	HSA-^{131}I- MIBG	^{177}Lu-DOTATATE	^{90}Y-based PRRT[a]
			internal pair production for PET/CT imaging
Preference based on clinical characteristics			
• **Age at therapy**	Preferred in young adults	Preferred in older patients	-
• **Size of tumor (centimeter)**	Small or medium-sized tumors (2.0-3.0)	Small or medium-sized tumors (<2.0)	Large-sized tumors (>3.0-5.0)
• **Prior radiotherapies or chemotherapies**	-	Preferred	-
• **Baseline cytopenias or low bone marrow reserve:** – **Hemoglobin (8-12 gram/deciliter)** – **Red blood cell count (3000000-4000000/ microliter)** – **White blood cell count (2000-4000/ microliter)** – **Platelet count (70,000-150,000/ microliter)**	-	Preferred	-
• **Lower renal function:** – **Estimated glomerular filtration rate (30-60 milliliter/ minute)**	Equivocal	Equivocal	-
• **Elevated plasma catecholamines and/or metanephrines (>5x upper reference limit)**	Preferred	-	-
• **Elevated alkaline phosphatase (>120 international units/liter)**	Equivocal	Equivocal	-
Preference based on risk for development of toxicities based on underlying risk or location of metastases			
• **Bone metastases**			
• **Low**	Preferred	-	
• **High**	-	Preferred	-
• **Lung metastases**	Equivocal	Equivocal	-
• **Hepatic metastases**	Equivocal	Equivocal	-
• **Underlying risk factors for nephrotoxicity (long-standing and poorly controlled**	Equivocal	Equivocal	-

	HSA-^{131}I- MIBG	^{177}Lu-DOTATATE	^{90}Y-based PRRT[a]
hypertension and diabetes mellitus)			

[a] ^{90}Y-based PRRT can be an alternative to ^{177}Lu-DOTATATE in certain cases.

[b] **Conventional ^{131}I-MIBG formulation is approved in many countries** (https://www.ema.europa.eu/en/documents/psusa/iodine-131i-iobenguane-list-nationally-authorised-medicinal-products-psusa/00001764/201505_en.pdf)

[c] **Awarded orphan drug status for ^{90}Y-Edotreotide between 2008–2018 by the European Medicines Agency** (https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308589)

[d] Calculated as a total of 2 cycles of 500 mCi of high-specific-activity ^{131}I-MIBG and 4 cycles of 200 mCi of ^{177}Lu-DOTATATE.

[e] Lower (~15000$) in centers which synthesize it in-house.